

CARBON-CARBON BOND FORMATION VIA CARBONYL-CARBENE COMPLEXES

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Abstract - The synthetic potential of carbonyl carbene complexes is demonstrated upon their reactions with alkynes. Both the electrophilicity of the carbene carbon atom and the facile substitution of carbon monoxide are used for selective carbon carbon bond formation. Nucleophilic alkynes (ynamines) add to the carbene carbon atom and then undergo insertion into the metal carbene bond. Chromium(0) is effective as a template in the annulation of carbene ligands bearing aromatic or vinylic side chains: Metal-assisted carbene transfer or both carbene and carbonyl transfer to alkynes are observed to yield indenenes or 1,4-hydroquinones. The hydroquinone formation occurs regioselectively with respect to the alkyne incorporation and the annulation of diarylcarbene ligands. The synthetic utility of this reaction is exemplified by the synthesis of vitamins K and E.

INTRODUCTION

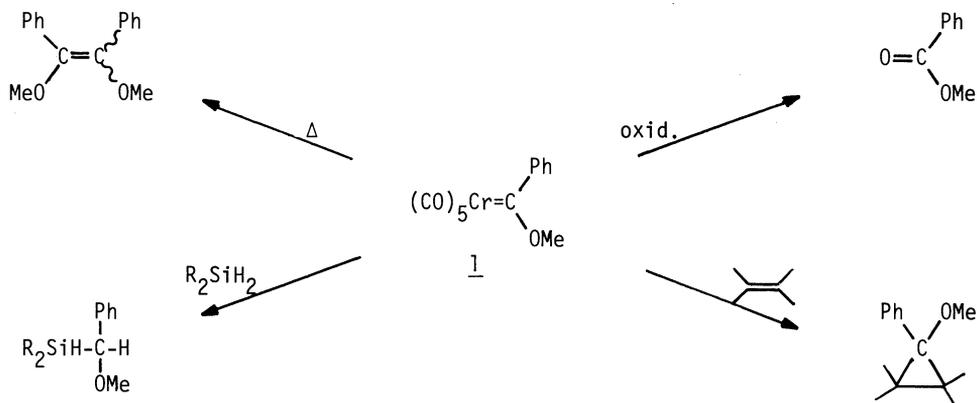
In the recent past a great deal of interest in co-ordination chemistry has shifted from synthesis to reactivity. The reactivity of a substrate co-ordinated to a metal may be influenced in two important ways: Firstly, the electronic properties of the substrate are changed dependent on its donor-acceptor ability. And secondly, the metal can be regarded as a template which holds the substrates in fixed positions within the co-ordination sphere, thus facilitating an interligand bond formation. We have studied interligand bond formations using low-valent transition metals in an octahedral configuration. The low oxidation state is crucial for the affinity for binding C_1 and C_2 carbon ligands such as CO, $:CR_2$, C=C or C≡C species which represent attractive building blocks in organic synthesis. The octahedral geometry is favorable for connecting more than two ligands. Our interest has focused on the linkage of alkyne, carbene and carbonyl ligands promoted by a group VIb metal template. The co-ordination of these three different ligands can be effected by starting with the hexacarbonyl complex, by modification of one carbonyl ligand into a carbene ligand and then by replacement of another carbonyl ligand by the alkyne. We have concentrated our interest on the chromium triad because the carbonyl carbene complexes are easily accessible via well-established routes and the chemistry of these compounds has been studied in most detail (1).

REACTIVITY PATTERN OF CARBONYL CARBENE COMPLEXES

Early work on the pentacarbonyl[methoxy(phenyl)carbene] complex 1 - aimed at the release of the carbene ligand (scheme 1) - has shown that the carbene ligand undergoes dimerization leading to a mixture of E- and Z-alkenes (2). Insertion of the carbene ligand was observed to occur into silicon hydrogen bonds (3,4). Oxidative decomposition resulted in ester formation (5). And finally, carbene transfer to activated alkenes yielded cyclopropanes (6,7).

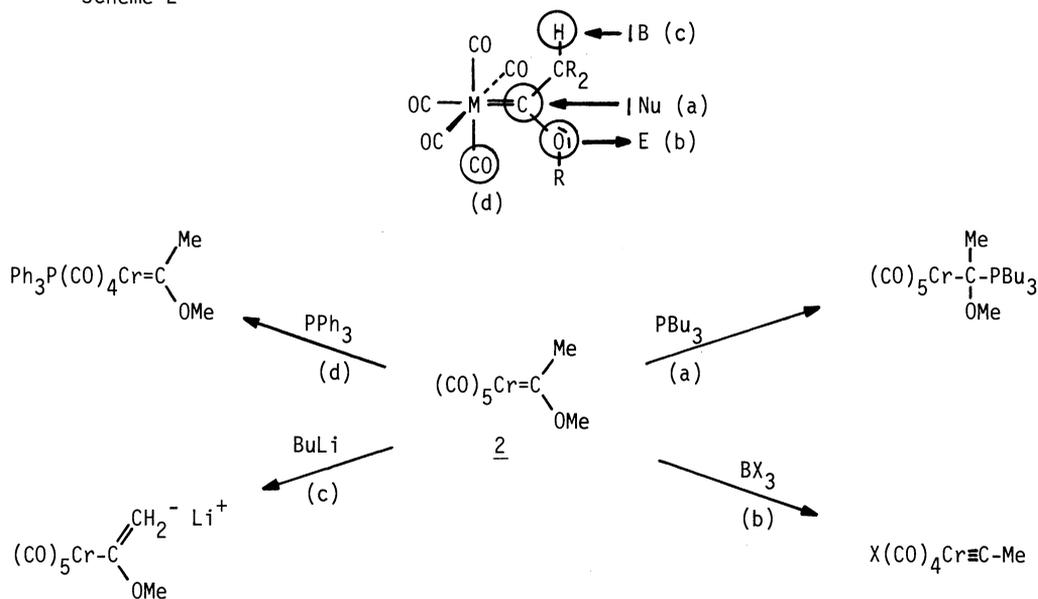
More extended studies revealed that no free carbenes are involved in these reactions (8,9). Thus it became obvious that the metal plays a crucial role even in the "organic" chemistry of carbene complexes.

Scheme 1



The reactivity pattern of carbonyl carbene complexes is governed by four pathways as exemplified for the methoxy(methyl)carbene complex 2 (scheme 2).

Scheme 2

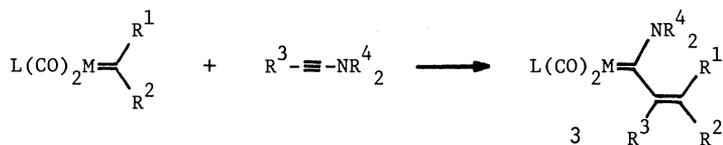


- (a) Nucleophilic addition occurs at the co-ordinated carbene carbon atom. For instance, trialkylphosphines are added to yield ylide complexes (10). Based on MO calculations the electrophilicity of the carbene carbon atom is thought to arise from frontier orbital control instead of charge control (11). The tendency for nucleophilic attack varies with the carbene substituents and increases in the order $(\text{CO})_5\text{M}=\text{C}(\text{Ph})\text{NR}_2 < (\text{CO})_5\text{M}=\text{C}(\text{Ph})\text{OMe} < (\text{CO})_5\text{M}=\text{CPh}_2$.
- (b) Electrophilic attack occurs at the alkoxy carbene substituent. By this route the alkoxy group can be removed and the carbene ligand is modified into a carbyne ligand (12).
- (c) Hydrogen atoms attached to the α -carbon atom of the carbene side chain are remarkably acidic (13). Thus, upon treatment with strong bases carbene anions - which are better regarded as vinyl chromium anions - are formed. Subsequent reaction with carbon electrophiles leads to a wide range of carbon carbon bond formations (14).
- (d) As is well-known in metal carbonyl chemistry, a carbonyl ligand can be released from the metal on heating or by photochemical procedures. The vacant co-ordination site may be occupied by other π -acceptor ligands such as less basic phosphines (15).

Routes (a) and (d) have proved to be most useful for reactions with alkynes and will be emphasized in this review.

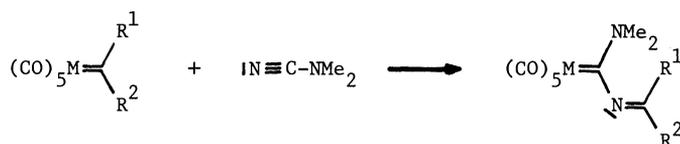
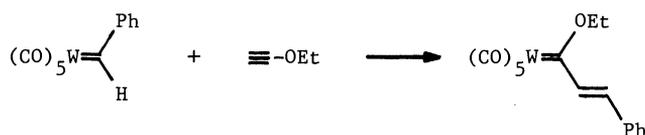
INSERTION OF YNAMINES INTO THE METAL CARBENE BOND

As a first type of reaction between carbonyl carbene complexes and alkynes we have studied the behaviour of nucleophilic alkynes such as ynamines. Alkenyl(amino)carbene complexes 3 are obtained as a result of a formal insertion of the alkyne into the metal carbene bond (16,17). The insertion of nucleophilic triple bond species has been shown to be a general feature of groups VIb and VIIb metal carbene complexes. Similar reactions have been reported later for ethoxyacetylene (18) and dimethylcyanamide (19) as well.



L = (CO)₃, π-Me-C₅H₄; M = Cr, Mo, W, Mn;

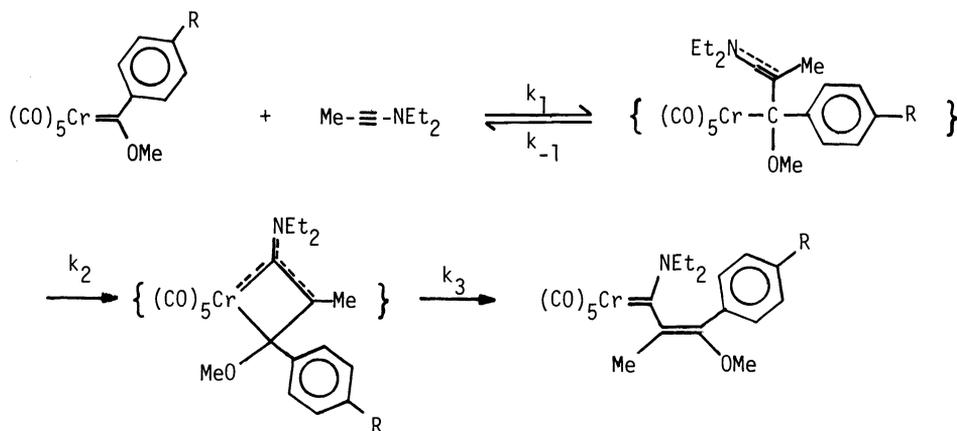
R¹ = alkyl, aryl; R² = alkoxy, aryl; R³ = H, alkyl; R⁴ = alkyl;



M = Cr, W;

Obviously, the primary product formed by addition of the β-ynamine carbon atom to the carbene carbon atom undergoes a rearrangement reaction which is believed to involve a four-membered metallacycle intermediate. This mechanistic scheme (scheme 3) is consistent with kinetic studies which have been carried out with a series of aryl(methoxy)carbene complexes of chromium and tungsten and which have established a first order reaction both in carbene complex and in alkyne characterized by low activation enthalpies and strongly negative activation entropies (20).

Scheme 3



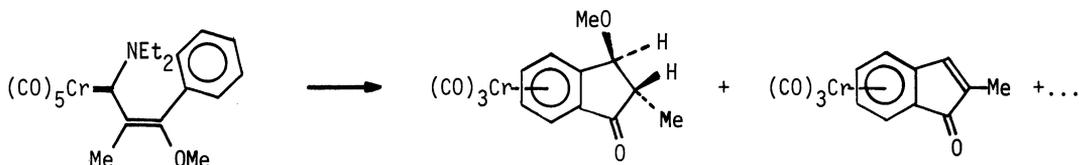
R = H, Me, CF₃, Br; R = H: ΔH[‡] = 33.5 kJmol⁻¹, ΔS[‡] = -142 Jmol⁻¹K⁻¹;

The C=C bond of the product is formed with high stereoselectivity (20,21). We have observed E/Z ratios from 5/1 up to 50/1 or even only the formation of the E-isomer. The ring-opening of the metallacycle is believed to be responsible for the stereoselectivity. Steric interaction between the dialkylamino group and the aryl ring prevents adoption of a planar conformation by the carbene ligand. ¹H NMR studies reveal that the alkenyl group is twisted

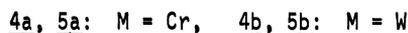
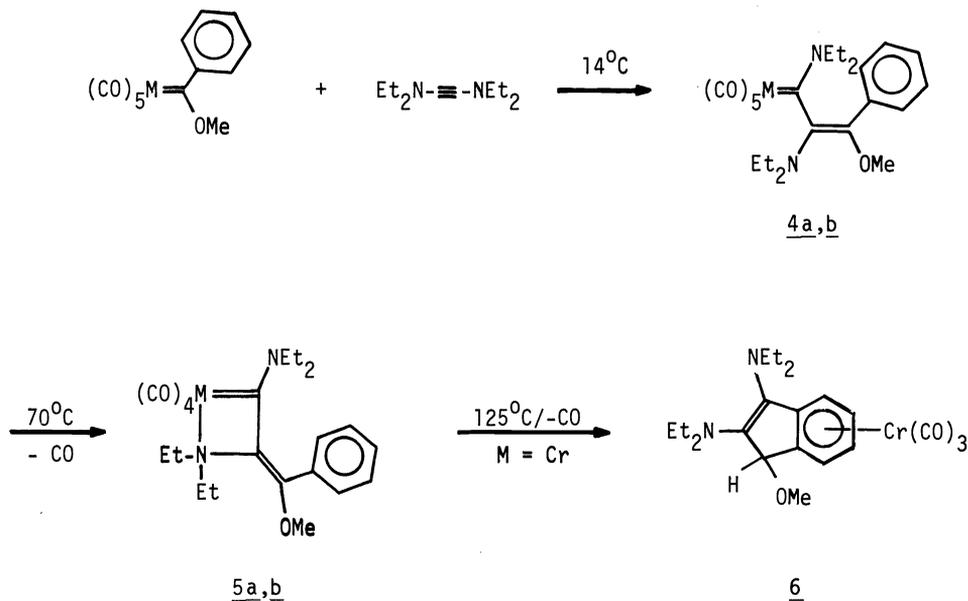
around the carbene alkenyl bond leading to chiral conformations similar to those of biphenyl compounds. For the styryl complex, no interconversion of both atropisomers is observed up to 140°C. If, however, the aryl ring is replaced by the less crowded methyl group, a rapid rotation occurs at temperatures above -25°C (16).

FORMATION OF INDENES

Chromium co-ordinated *E*-styrylcarbenes can be transformed into indene and indane ligands (21). Starting from the pentacarbonyl complexes, however, the cyclization is not a clean process. Indanone and indenone complexes are formed in yields not exceeding 20% or 25%, respectively.

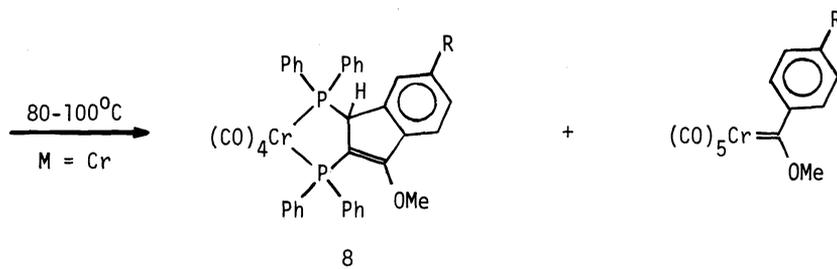
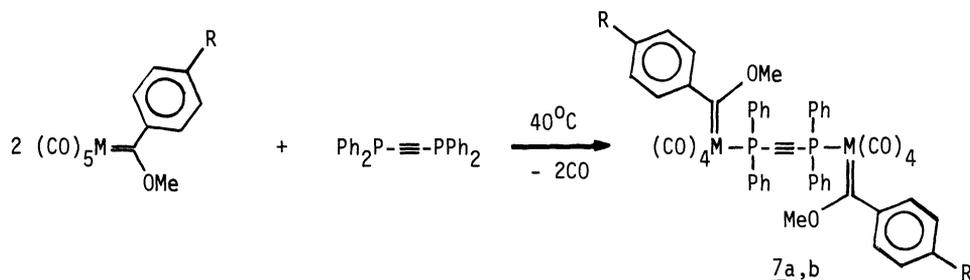


We felt that the cyclization process might be improved, if the mobility within the carbene side chain could be reduced. Thus we modified the monodentate carbene ligand into a chelating carbene ligand. Like ynamines, yndiamines undergo insertion into the chromium carbene bond as well. If the reaction mixture is kept at 14°C, the pentacarbonyl[amino(aminoalkenyl)-carbene] complex 4 can be isolated in good yield. Warming up to 70°C induces the dissociation of a *cis* CO ligand and the alkenyl-bonded amino group is co-ordinated to the metal. A chelating carbene ligand is formed as part of a non-planar four-membered metallacycle 5 (22). Using temperature-dependent ¹³C NMR techniques, the activation enthalpy for the inversion of the twisted conformation is estimated to be about 210 kJmol⁻¹. Even though the carbene ligand is not rigid, the co-ordination of the amino group favors a conformation necessary for linking the carbene carbon atom and the *ortho* position of the phenyl ring. Above 125°C an annulation of the arene occurs leading to a co-ordinated bis(amino)indene ligand which may be described as a formal 1,3-addition product of the yndiamine to the phenylcarbene ligand (23). The structure of complex 6 has been established by X-ray diffraction.



It is noteworthy that the indene formation is restricted to the chromium compound 5a. The homologous tungsten complex 5b which is synthesized by an analogous route does not undergo annulation.

Similar indene ligands are formed upon reaction of chromium aryl(methoxy)carbene complexes with bis(diphenylphosphino)acetylene. The mechanism, however, seems to be quite different. Compared with aminoacetylenes phosphinoalkynes are less nucleophilic; moreover, phosphines are excellent π -acceptor ligands with a pronounced tendency for co-ordination to low-valent metals. Accordingly, substitution of a CO ligand for the phosphino group occurs in the first step. It is interesting that binuclear alkyne-bridged biscarbene complexes 7 are formed even if the alkyne is used in excess. The *cis*-configuration is prevalent at each metal center. Whereas the binuclear tungsten compounds 7b remain unchanged upon heating up to 150°C, the homologous chromium complexes 7a are cleaved even under milder conditions. Along with the starting carbene complex a bis(phosphino)indene ligand is formed which is co-ordinated to the metal via both phosphorous atoms (24). An enol ether structure in the five-membered ring has been established for the 6-methyl derivative 8 by X-ray analysis. The indene complex formation may be carried out in a one flask reaction at 80–100°C as well. Using an excess of alkyne the yields rise to 75–85%.

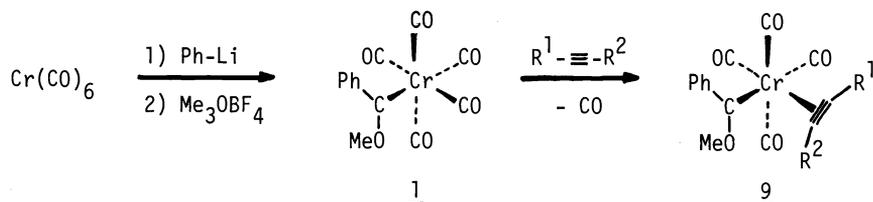


7a: M = Cr, 7b: M = W, R = H, Me, CF₃

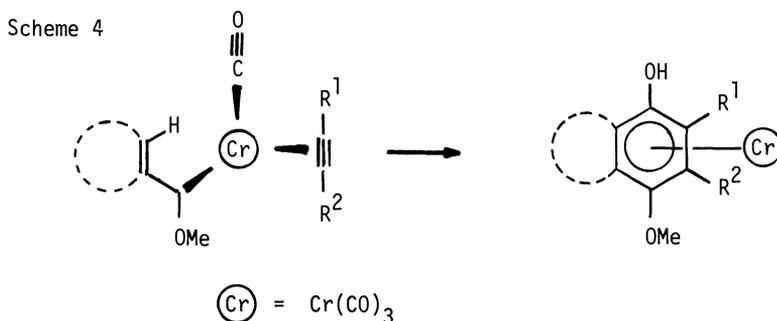
COCYCLIZATION OF ALKYNE, CARBENE AND CARBONYL LIGANDS

The reactions discussed so far are characterized by a carbon carbon bond formation between the alkyne and the carbene ligand. To make use of the carbonyl ligand as well the point of attack of the alkyne at the metal turned out to be of crucial importance: Instead of adding to the carbene carbon atom the alkyne must be bonded directly to the metal. A facial co-ordination of alkyne, carbene and carbonyl ligands is essential for the cocyclization. This process requires a vacant co-ordination site at the metal which may be provided by the loss of a CO ligand. In metal carbonyl chemistry the ease of CO elimination depends on the amount of back-donation and is effected by either thermal or photochemical means. The CO elimination in pentacarbonyl complexes is related to the donor-acceptor capacity of the carbene ligand and is favored in the order $:C(Ph)NR_2 < :C(Ph)OR < :CPh_2$. The carbonyl ligands in these compounds are distinguished as 4 *cis*-CO ligands and 1 *trans* CO ligand. With respect to the relative donor-acceptor properties of carbene and carbonyl ligands, a preference for the elimination of a *cis* CO group is expected. This idea has been proved by CO exchange studies (25).

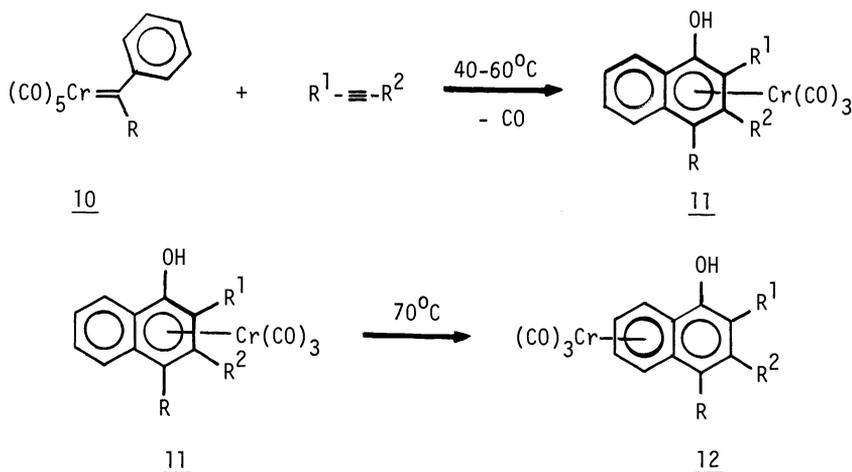
A plausible synthesis of a facial alkyne carbene carbonyl complex starts with the metal hexacarbonyl. Subsequent addition of a lithium nucleophile and an electrophile (e.g. Meerwein's salt) results in the modification of one carbonyl ligand into a carbene ligand. Finally, a *cis* CO ligand will be replaced by the alkyne.



The alkyne carbene carbonyl complex 9 is a highly reactive species which so far has eluded isolation. It undergoes a clean cyclization reaction to yield an aromatic six-membered ring which is π -bonded to the metal (scheme 4).



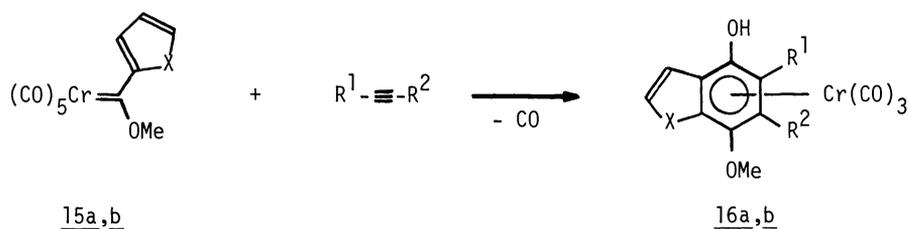
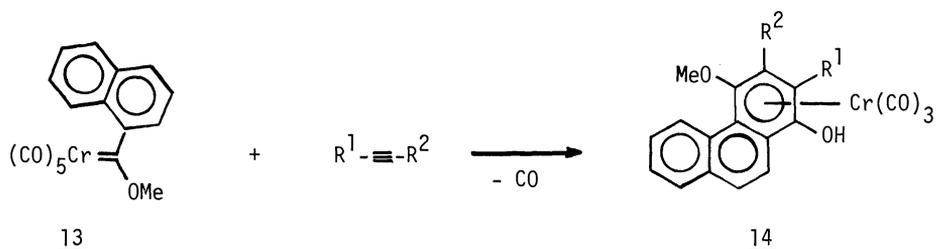
Starting from a pentacarbonyl(phenylcarbene)chromium complex 10 and an alkyne, a 1-naphthol ligand is formed. The alkyne is incorporated into the 2 and 3 positions of the naphthol skeleton. The phenylcarbene ligand ends up in the unsubstituted ring and the 4-position while the naphthol functionality has its origin in the former CO ligand. The cyclization occurs readily under mild conditions (40–60°C). Donor solvents are required for a clean reaction indicating that co-ordinatively unsaturated intermediates are involved. Under kinetic control the metal is co-ordinated to the newly formed aromatic ring. Heating for longer periods induces the migration of the metal to the less substituted ring yielding the thermodynamically more stable 5-10- η -compounds 12 (26).



We have tested so far a variety of aliphatic and aromatic alkynes. The naphthol formation is compatible with non-conjugated enynes (27) and carbonyl groups (26) which makes it attractive for the synthesis of more complex structures. The isolated yields range usually from 60 to 90%. Limitations were found for electron-deficient alkynes such as hexafluoro-2-butyne and for nucleophilic alkynes which add competitively primarily to the carbene carbon atom. Concerning the co-ordination sphere of the metal, effective acceptor ligands are required.

Accordingly, best results have been obtained if pentacarbonyl or tetracarbonyl(phosphine)-carbene complexes were used. Even a variation in the donor-acceptor ability of one ligand may cause striking effects on the yield. For instance, regarding the reaction of tetracarbonyl(phosphine)carbene complexes with toluene the yield decreases to 1/6 if the tri(p-fluorophenyl)phosphine ligand is replaced by tri-n-butylphosphine.

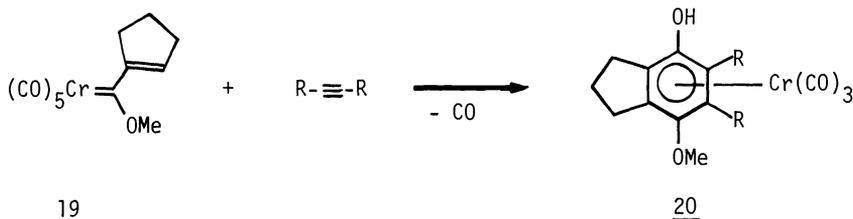
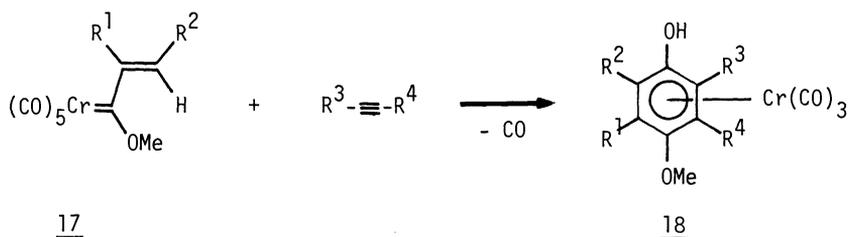
The annulation can be extended from phenylcarbene ligands to fused aromatic or heterocyclic systems 13 or 15 (28). Naphthylcarbene ligands are converted into phenanthrene derivatives 14. Benzofurans 16a and benzothiophenes 16b are obtained upon reaction with furyl and thienyl carbene complexes.



15a, 16a: X = O

15b, 16b: X = S

In a similar way vinyl carbene complexes can be used to produce mononuclear aromatic compounds. Thus alkenyl(alkoxy)carbene ligands are incorporated into 1,4-benzohydroquinone derivatives 18 (29) and indanes 20 have been prepared from cyclopentenylcarbene complexes 19 (28).

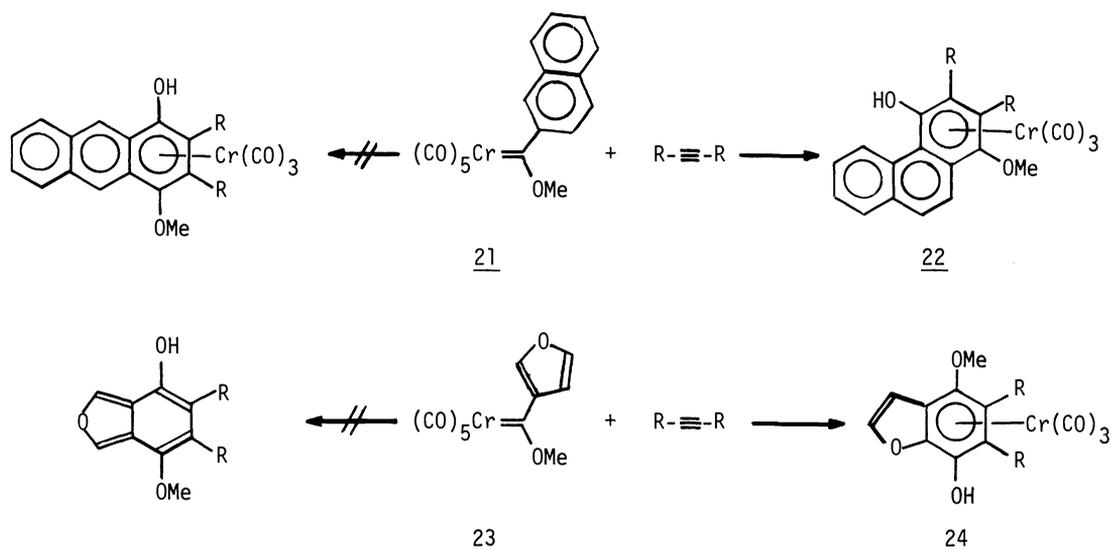


REGIOSELECTIVITY STUDIES

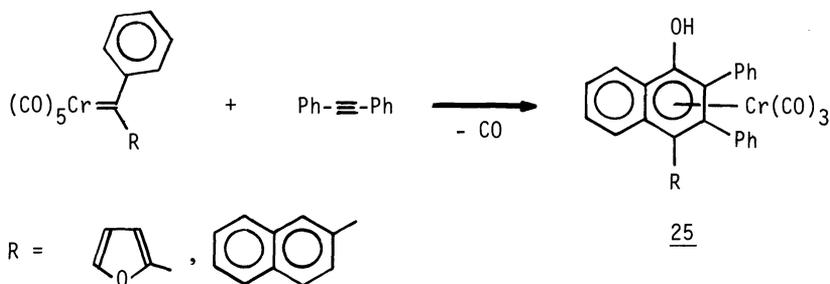
The value of the cyclization reaction for the synthesis of more complex structures, e.g. in natural product synthesis, depends on its regioselectivity. The regioselectivity refers to

- a carbene substituent which offers 2 possibilities for the annulation (28),
- a competitive annulation as expected for diarylcarbene ligands (28) and
- the incorporation of unsymmetrical alkynes into the arene ring (26,30,31).

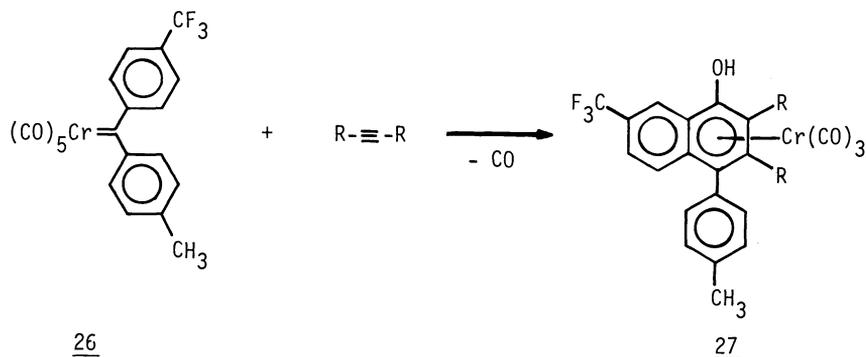
Regarding the 2-naphthylcarbene complex 21 an annulation can a priori occur in the 1 or in the 3 position. Upon reaction with tolane, however, only the phenanthrene complex 22 arising from ring-closure in the 1 position is isolated. No anthracene derivative could be observed. Similarly, the 3-furylcarbene ligand is annulated to yield the benzofuran complex 24. The cyclization in 4 position which might be expected to lead to an orthoquinoid isobenzofuran skeleton cannot compete successfully with the formation of the aromatic system.



A strong preference for the annulation of the phenyl ring has been observed in competition studies of diarylcarbene complexes containing phenyl, 2-furyl and 2-naphthyl substituents. After the usual work-up using chromatographic techniques, naphthol derivatives 25 have been isolated as the only products.

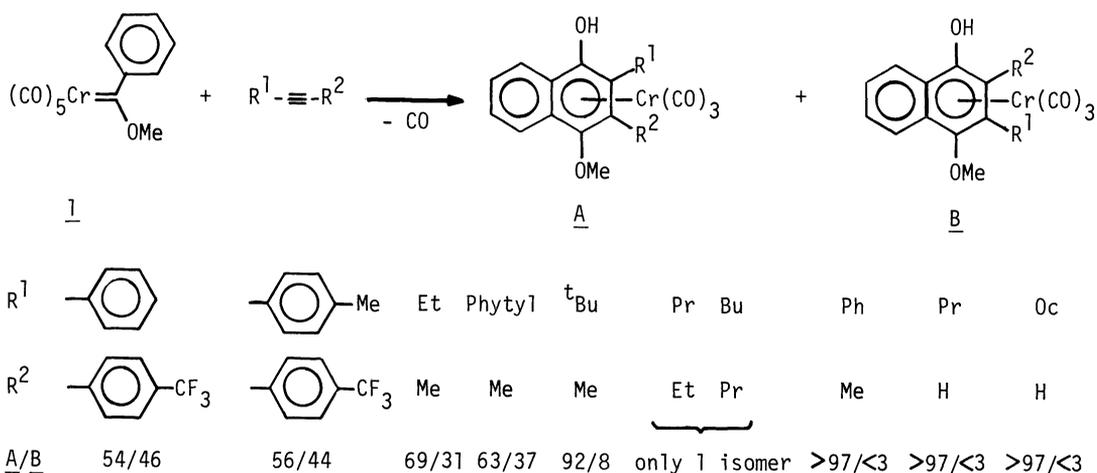


Since electronic or steric effects may be responsible for the regioselectivity in these examples, we included a diphenylcarbene complex in which the carbene substituents have similar steric requirements but differ in their electronic properties. Starting from the p-tolyl-p-trifluoromethylphenylcarbene complex 26 a single product is isolated which is shown to be the 4-p-tolyl naphthol derivative 27; this indicates that the acceptor-substituted phenyl ring is preferentially annulated.



The regioselectivity referred to the alkyne incorporation depends strongly on the alkyne. In the methoxy(phenyl)carbene series the selectivity is found to increase in the order diarylalkynes < 2-alkynes < longer chain dialkylalkynes and 1-alkynes (scheme 5).

Scheme 5



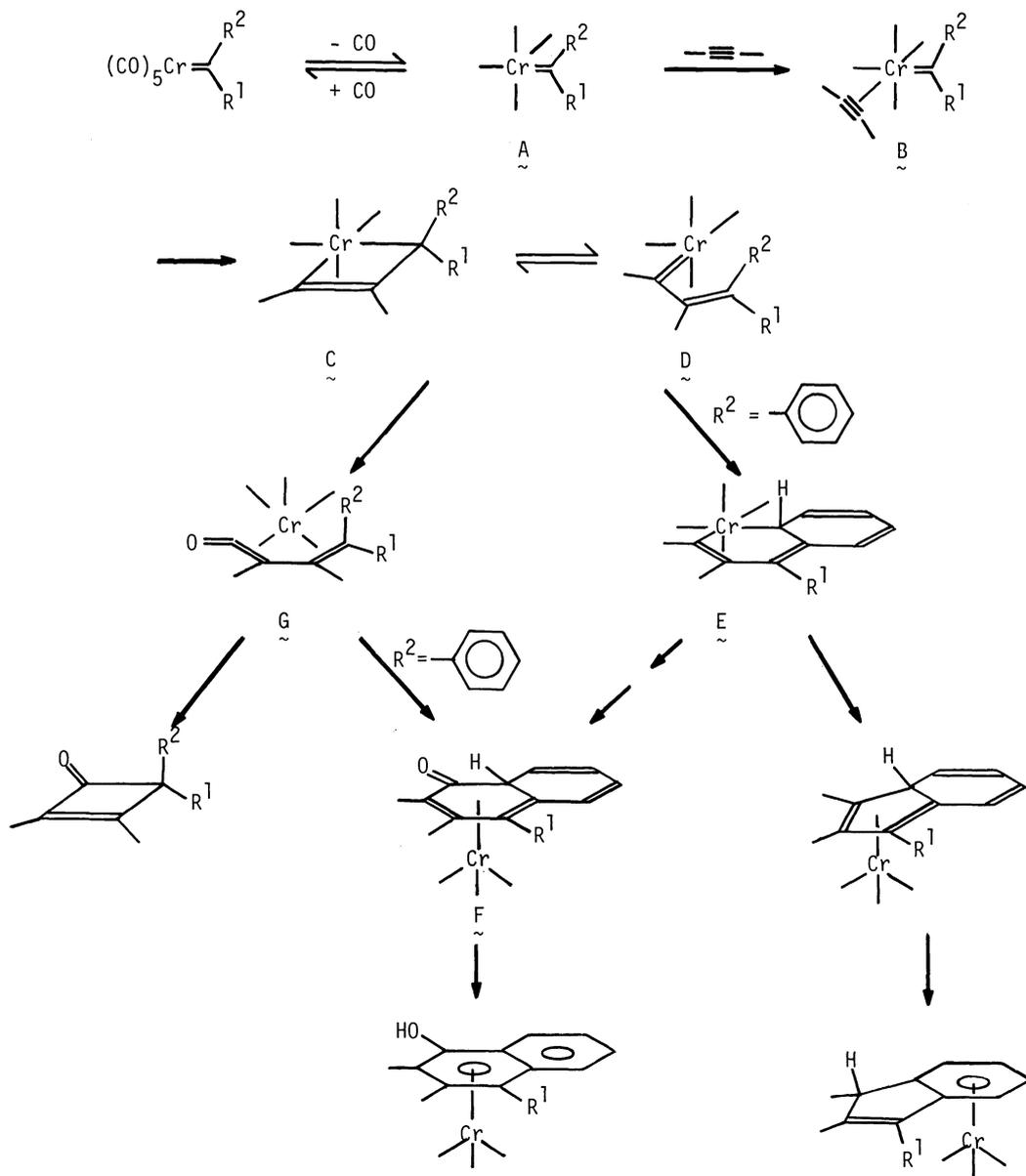
Tolane derivatives which are selectively substituted in para positions yield both regioisomers in nearly equal amounts. 2-Alkynes lead to the formation of A and B in an approximately 2/1 ratio. In the predominant isomer A, the longer carbon chain ends up nearer the hydroxyl group. Obviously, the length of the alkyl side chain has no influence; however, the isomer ratio depends on α -substitution (c.f. 4,4-dimethyl-2-pentyne). Surprisingly, for dialkylalkynes bearing longer carbon side chains, only 1 isomer is observed, the regiochemistry of which is not yet elucidated. A similar regiospecific incorporation is found to occur with 1-phenyl-1-propyne and a series of aliphatic 1-alkynes leading to 2-alkyl naphthol derivatives. These results indicate that the regioselectivity is mainly governed by steric factors which favor a bond formation between the carbene carbon and the less crowded alkyne carbon atom.

MECHANISTIC CONSIDERATIONS

Early experiments have shown that the cyclization reaction is blocked in the presence of excess carbon monoxide, suggesting CO elimination in the first step. Support for this idea is provided by a more sophisticated kinetic study (32). The activation parameters (for the reaction of $(\text{CO})_5\text{Cr}=\text{C}(\text{Ph})\text{OMe}$ with toluene: $\Delta H^\ddagger = 108 \pm 2 \text{ kJmol}^{-1}$ and $\Delta S^\ddagger = 26 \pm 6 \text{ Jmol}^{-1}\text{K}^{-1}$) are similar to those known for other dissociative substitution reactions of carbonyl carbene complexes. The loss of carbon monoxide produces a co-ordinatively unsaturated intermediate A for which the alkyne and the cleaved CO ligand can compete. The rate of the co-ordination of the alkyne increases with increasing electron density in the $\text{C}\equiv\text{C}$ bond: In di-n-butyl ether saturated with carbon monoxide the co-ordination of 1-phenyl-1-propyne is about 5 times faster than the co-ordination of toluene. Based on earlier CO substitution reactions (15,25) the

alkyne is assumed to occupy a position *cis* to the carbene ligand. Thus a complex B is formed in which the chromium holds the alkyne, the carbene and a carbonyl ligand in a *fac*ial configuration. A plausible mechanism for the subsequent cyclization involves a carbon carbon bond formation between the alkyne and the carbene ligand, yielding a chromacyclobutene C which may undergo a ring opening to give a co-ordinatively unsaturated alkenylcarbene species D (scheme 6). Oxidative addition of the phenyl group R^c followed by σ - π -rearrangement of E and re-aromatization of the six-membered ring is expected to give indenenes. The formation of naphthols may be rationalized in terms of 2 alternative pathways. A chromacyclobutene E may undergo CO insertion yielding a cyclohexadienone system F which isomerizes to the naphthol complex. An alternative mechanism (33) for which some experimental support has been provided involves an intramolecular carbonylation of the alkenylcarbene carbon atom in D to form a vinyl ketene intermediate G. This step has precedents in several examples in the manganese and iron series. For instance, tetracarbonyl(vinylcarbene)iron complexes have been converted into iron co-ordinated vinyl ketenes (34). Recently, similar compounds have been isolated from the reaction of tetracarbonyl[ethoxy(phenyl)carbene]iron with alkynes (35). The chromium vinyl ketene intermediate G for which a *s-cis* conformation is favored by a diene-like co-ordination to the metal is expected to produce cyclobutenones by 1,4-cyclization. If, however, a conjugated unsaturated system group R^c such as a phenyl ring is present, a 1,6-cyclization may lead to the naphthol system via the cyclohexadienone intermediate F.

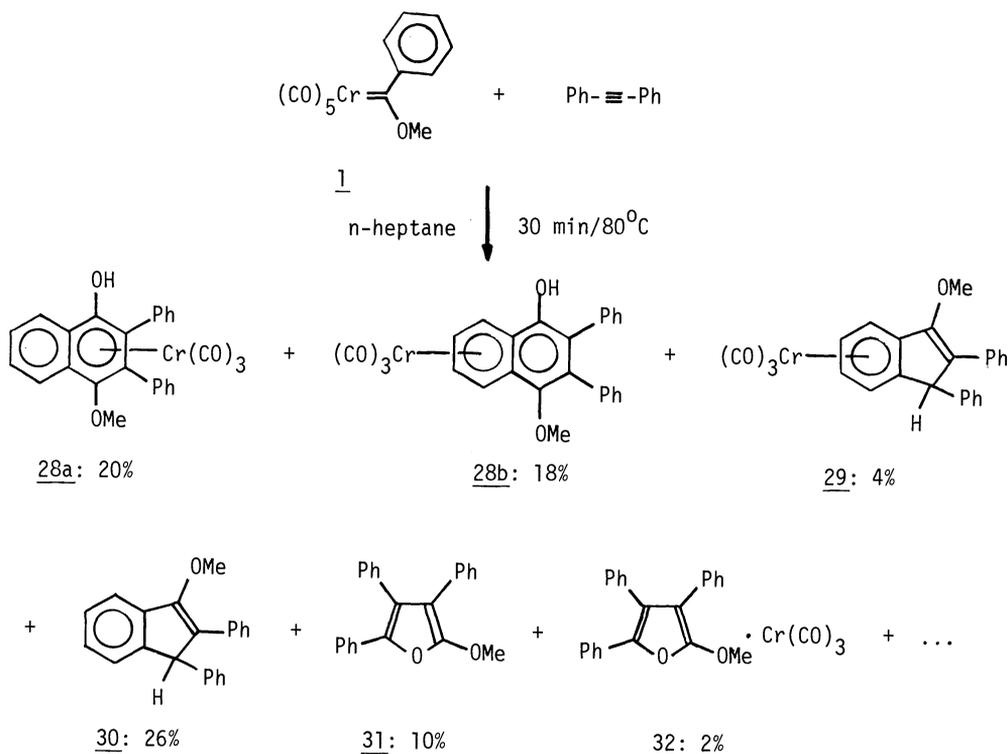
Scheme 6



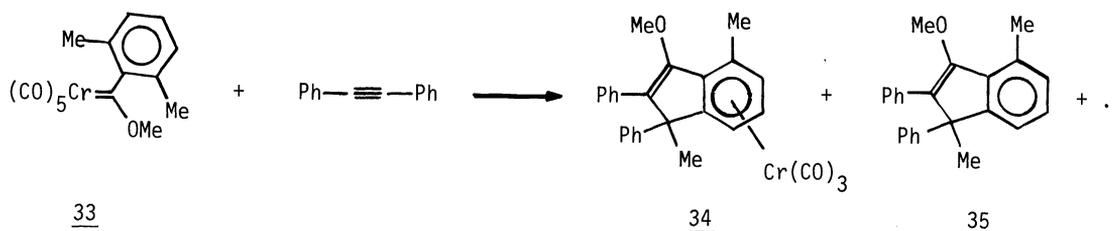
In this mechanistic scheme the chromacyclobutene **C** and the vinyl ketene **G** are to be regarded as key intermediates. A selective formation of the metallacycle, involving the connection of the alkyne and the carbene ligand and a selective ring-opening could account for the regioselectivity of both the alkyne incorporation and the annulation of diarylcarbene ligands.

The involvement of co-ordinatively unsaturated intermediates makes clear that donor solvents are required for a clean reaction. Best results have been obtained using ethereal solvents such as tert.butyl methyl ether or tetrahydrofuran. If non co-ordinating solvents are used, the product selectivity decreases. For instance, reaction of the carbene complex **1** and toluene in n-heptane causes the yield of naphthol complexes **28** to decrease to 40%, while indene and furan derivatives **29** - **32** are also formed in comparable amounts (36) (scheme 7).

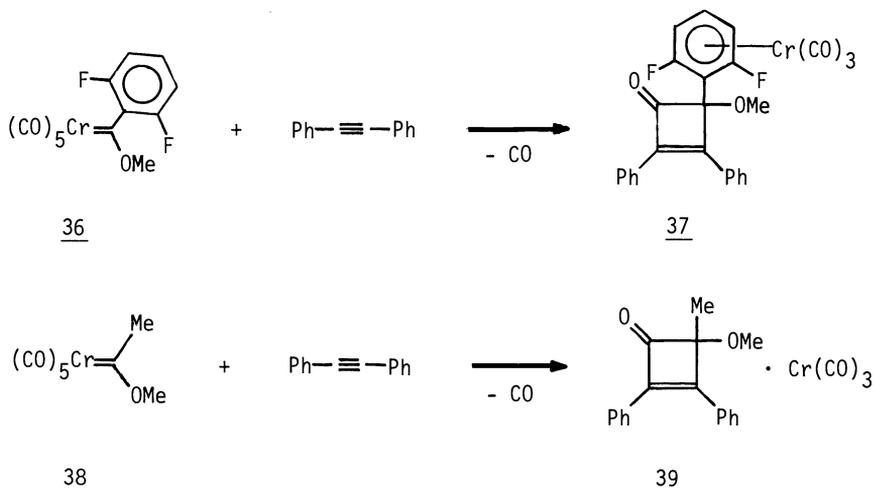
Scheme 7



To gain further insight into the reaction mechanism we extended our studies to *ortho*-disubstituted phenylcarbene complexes. We found that methyl substitution in **33** is not effective in preventing carbene annulation. Instead of naphthol formation only the alkyne and the carbene ligand are linked together without incorporation of a CO group. Methyl migration occurs to yield indenenes as has been shown for **34** by X-ray analysis (37).

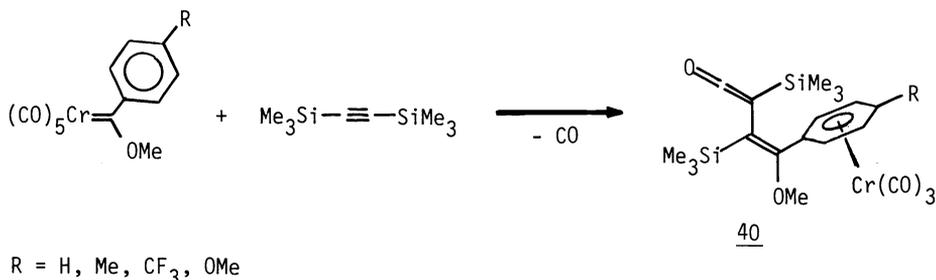


The annulation is suppressed by strong blocking groups such as in *ortho*-difluorophenylcarbene ligands or by using alkylcarbene complexes **38**. In these cases cyclobutenones **37** and **39** are formed which may be co-ordinated to chromium via arene substituents originating either from the carbene ligand or from the alkyne (38,39).



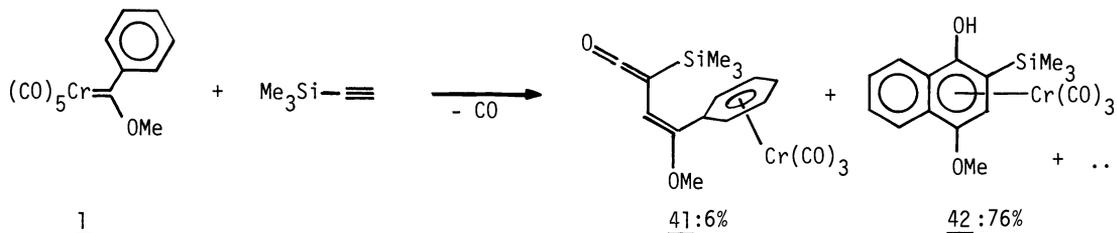
STABLE VINYL KETENES

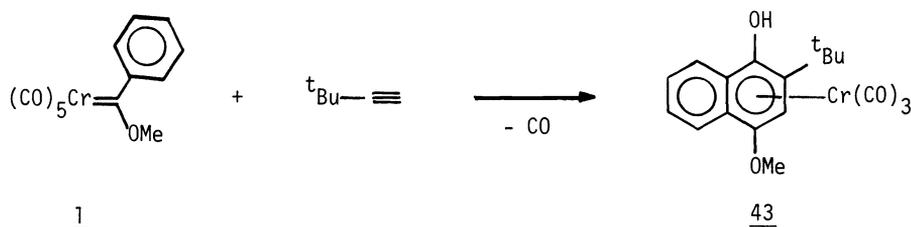
Since these results appeared consistent with the intermediacy of vinyl ketenes we tried to provide further support for this idea. Thus the conversion of the *s-cis*-conformation into the *s-trans*-form was attempted to prevent a subsequent cyclization. The *s-trans*-form will be favored by steric crowding at the central carbon carbon bond. Silyl groups are expected to stabilize the vinyl ketene system; thus, we reacted bis(trimethylsilyl)acetylene with a series of alkoxy(aryl)carbene complexes. Indeed, vinyl ketene complexes 40 were formed which may be regarded as formal head to tail carbonylation-olefination products of the alkyne (33,40).



An X-ray structure determination of the phenyl compound 40 (R = H) established that (a) the alkene C=C bond adopts the *Z*-configuration and (b) the alkene and the ketene parts are separated by a pure C-C single bond (151 pm) and form a dihedral angle of 77° in the solid state, thus excluding any electronic interaction (41).

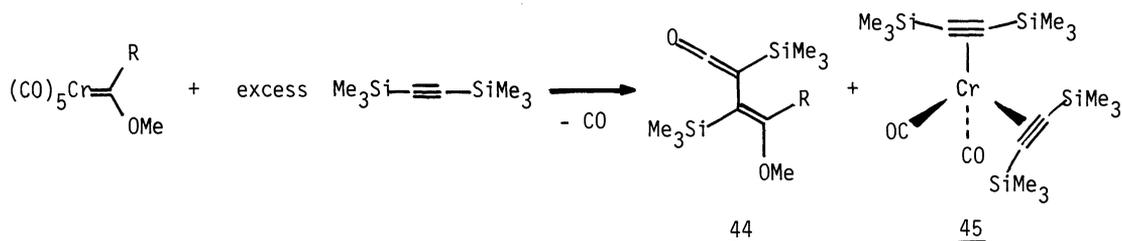
The isolation of chromium derived vinyl ketenes must be attributed to both steric and electronic properties of the trimethylsilyl group. A competition between the formation of the vinyl ketene and the naphthol complex is observed with trimethylsilylacetylene (33). Along with a small amount of the vinyl ketene compound 41 the 2-silyl-naphthol complex 42 is formed as the major product. If the trimethylsilyl group is replaced by the even more crowded tert.butyl group, only the naphthol complex 43 can be isolated (30).





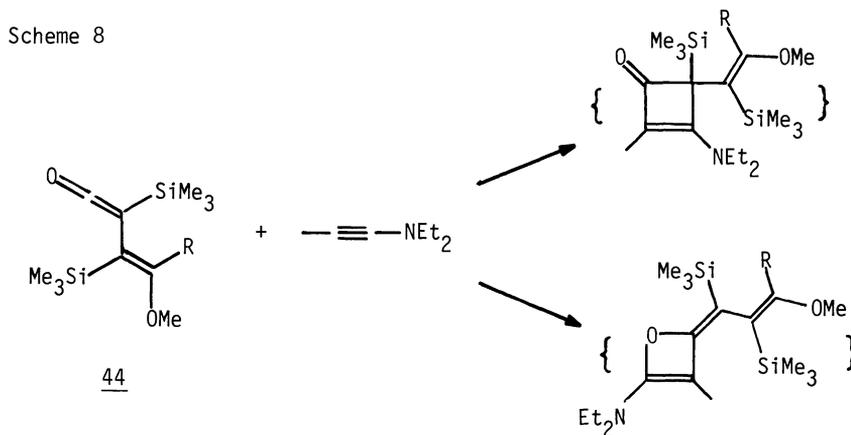
It should be noted that quite recently further support for the involvement of vinyl ketenes in reactions of carbonyl carbene chromium complexes with alkynes has been provided by trapping experiments (42).

Obviously, the diene-like co-ordinated vinyl ketene (G, scheme 6) can be replaced by an excess of alkyne. Using a two-fold excess of bis(trimethylsilyl)acetylene the metal-free vinyl ketenes 44 are obtained as stable compounds. The chromium is recovered as a purple bis(alkyne) dicarbonyl complex 45 which is extremely sensitive to oxidation (43).

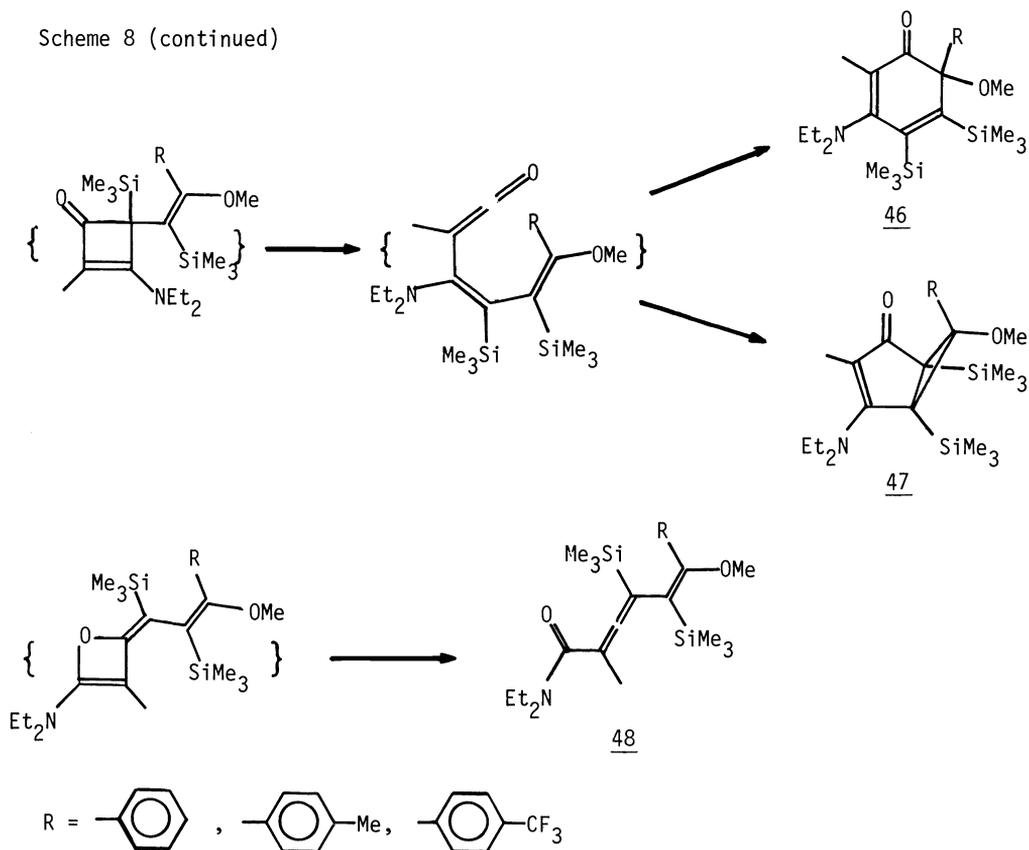


The properties of alkynes as variable electron donor ligands have been studied recently by ^{13}C NMR spectroscopy (44). For 45 a downfield shift of 197.8 ppm is observed for the co-ordinated alkyne carbon atoms; this indicates that the alkyne ligands act as 4-electron donors giving the metal the rare d^8 configuration. The effect of co-ordination is restricted to the alkyne bond. The observed ^{29}Si shift (-7.4 ppm) is similar to that reported for $(\text{CO})_4\text{Fe}(\text{Me}_3\text{Si-C}\equiv\text{C-SiMe}_3)$ (45) bearing a 2-electron alkyne ligand.

Spectroscopic studies demonstrated that the vinyl ketene system is not significantly influenced by the arene co-ordination to chromium. The reactivity is governed by the ketene functionality. Due to silyl substitution the addition of nucleophiles such as alcohols and amines is a rather slow process. For instance, ester formation from 44 requires heating for several hours in refluxing methanol (46). Cycloaddition reactions seem to be restricted to strong nucleophiles. While enol ethers and enamines proved to be unreactive, a competitive addition of the alkyne across the C=C and the C=O bonds is observed to occur with ynamines (47) (scheme 8). The cyclobutenone formed by addition across the C=C bond undergoes ring-opening to the dienyl ketene. Cyclohexadienones 46 are expected to arise from a 1,6-ring-closure whereas a stereospecific 1,5-ring-closure leads to *endo*-R-[3.1.0]bicyclohexenones 47 (48). On the other hand, ynamine addition across the C=O bond followed by ring-opening of the alkylidene oxetene intermediate yields allenic amides 48.



Scheme 8 (continued)



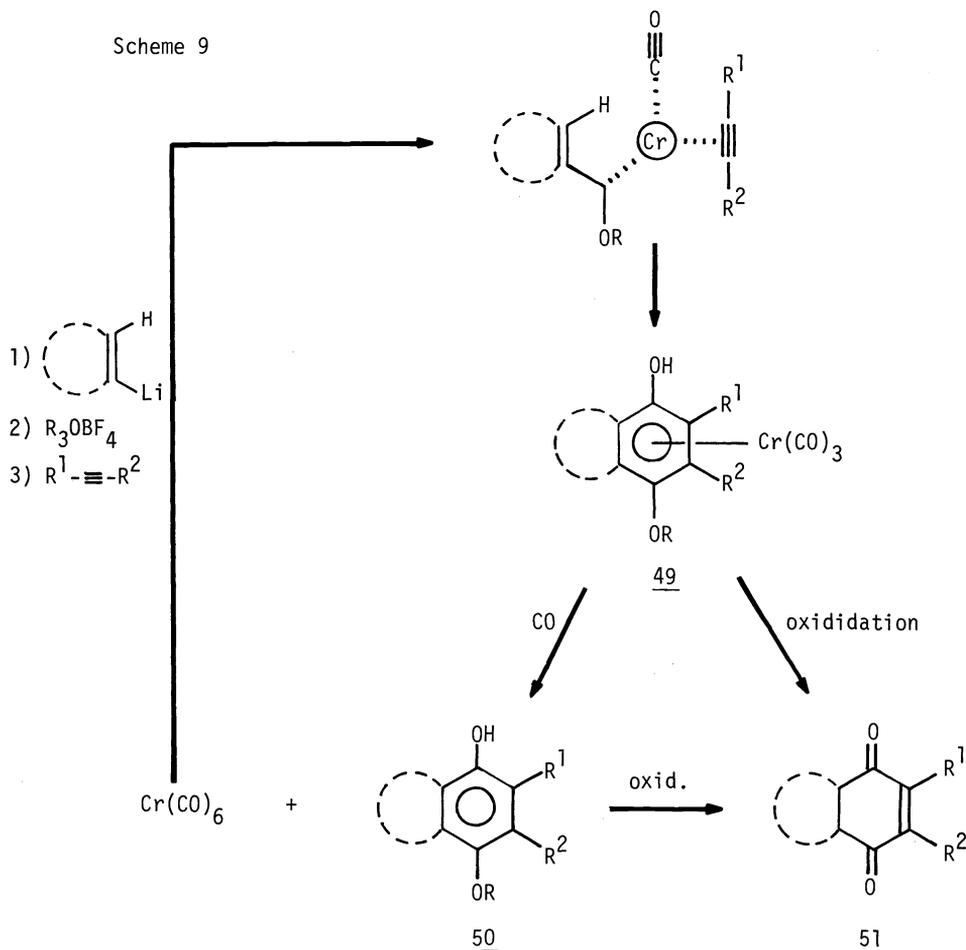
SYNTHESIS OF VITAMINS K AND E

The clean and high yield alkyne-carbene-carbonyl cyclization prompted us to extend the reaction to naturally occurring quinones and hydroquinones; among them, we have focused on vitamins K and E. The customary syntheses of these compounds dating back to the basic work of Fieser (49) and Karrer (50) are based on the condensation of isoprenoid alcohols or halides with 1,4-hydroquinones. Acidic conditions are required for this process which implies that an isomerization of the allylic C=C bond cannot be avoided. However, the *Z*-isomer of vitamin K₁(20) for instance, has proved to be biologically nearly inactive (51).

It is a prerequisite for the use of metal complexes in organic synthesis that the ligands can be released from the metal by mild and reasonable procedures. To cleave the arene-metal bond both ligand substitution and oxidation reactions have met with considerable success. Regarding hydroquinone chromium complexes 49 the substitution of the arene ring for carbon monoxide occurs under mild conditions in practically quantitative yield (36, 52). By this route the metal can be recycled to yield hexacarbonylchromium which serves as a starting material for the carbene complex. Alternatively, the cleavage of the arene-metal bond is effected by oxidation. Cerium(IV), iron(III) or silver(I) compounds, bromine and nitric acid have been used as oxidizing agents. Along with chromium(III) 1,4-quinones 51 are directly obtained from the hydroquinone complexes (scheme 9).

The carbene complex route to vitamin K requires non-conjugated enynes introducing a bifunctionality into the alkyne component. It turned out, however, that the carbene transfer occurs much more readily to the C=C bond than to the C≡C bond (27). For instance, cyclopropanation by alkoxycarbene ligands is limited to activated alkenes such as unsaturated alkyl carboxylates or enol ethers (7,8).

Scheme 9

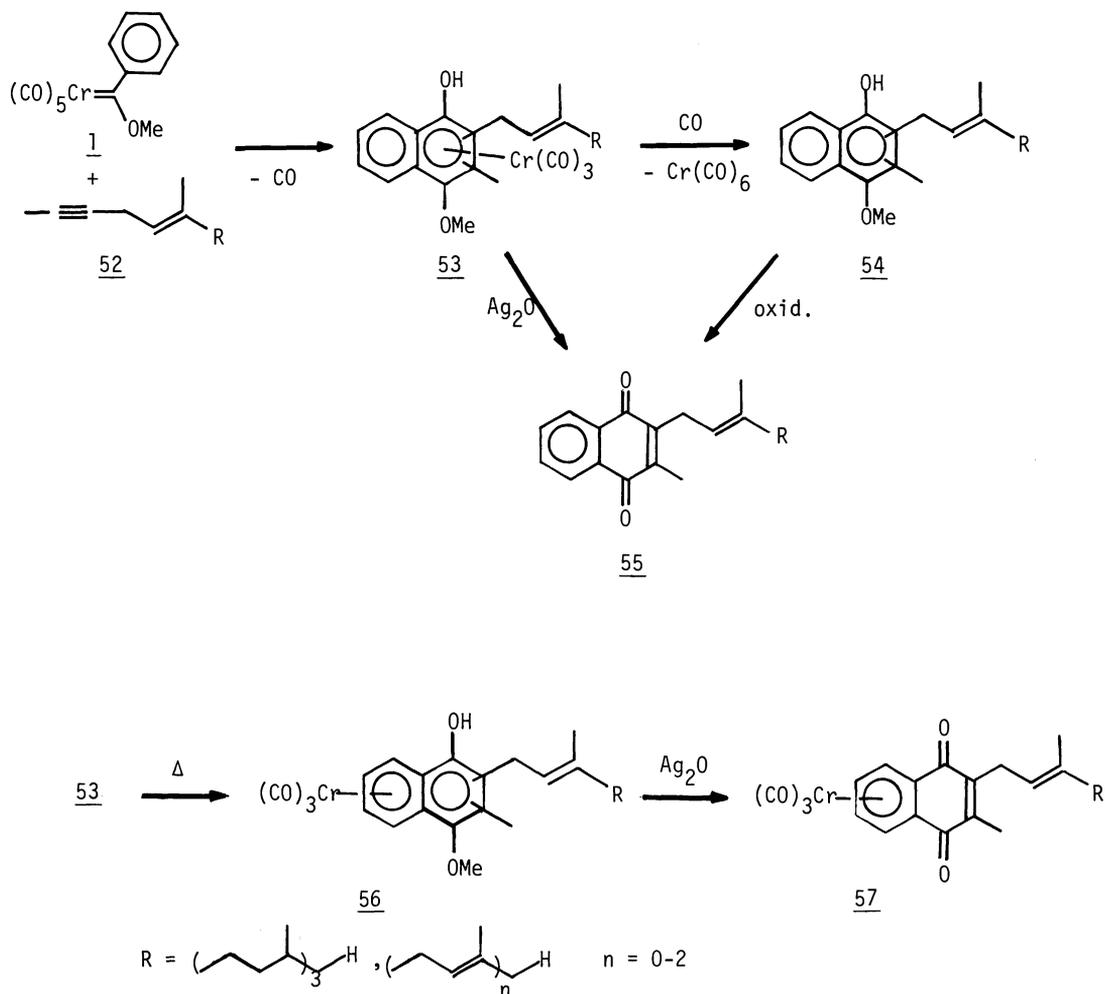


Starting from the methoxy(phenyl)carbene complex 1 and non-conjugated oligo-en-yne 52, naphthohydroquinone(monoether) complexes 53 are obtained as single products (52,53). Again, 2-alkynes lead to the formation of both regioisomers with respect to the 2,3 positions. We have optimized the reaction conditions using 6,10,14,18-tetramethyl-5-nonadecen-2-yne (methylphytylacetylene) 52 [$\text{R} = (-\text{CH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3)_3\text{CH}_3$] which is required as alkyne component in the synthesis of the most important representative of the vitamin K series, $\text{K}_{1(20)}$. After warming in tert.butyl methyl ether for 2 hours at 45°C the dihydrovitamin $\text{K}_{1(20)}$ complex 53 can be isolated in 92% yield. In this particular case the regioisomers have been separated by column chromatography techniques yielding a 63/37 ratio of 2-phytyl/3-phytyl compounds. The regiochemistry has been established by ring-closure of the major isomer to give the naphthochromanol derivative.

The cleavage of the arene-metal bond effected by carbon monoxide in practically quantitative yield leads to the dihydrovitamin K derivatives 54 which can be oxidized by standard procedures. Alternatively, the K-vitamins 55 have been obtained in lower overall yields by the direct oxidation of the hydroquinone complexes 53. By this route silver(I) oxide has proved to be a selective oxidative agent; metal-ring cleavage occurs only for the 1-4:9,10- η -complexes 53 containing chromium bonded to the hydroquinone ring. In the 5-10- η -compounds 56 in which the metal is co-ordinated to the unsubstituted ring and which are obtained by metal migration on prolonged warming the oxidation to the quinone system leaves the chromium arene bond unchanged. Thus violet vitamin K complexes 57 are obtained representing the first examples of η^6 -co-ordinated naphthoquinones which are inaccessible by customary substitution reactions (scheme 10).

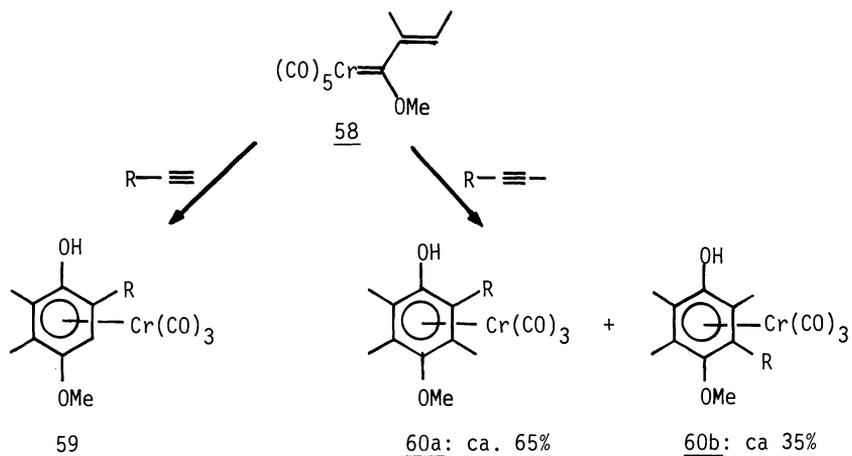
An important criterion of a vitamin K synthesis is the stereoselectivity with respect to the allylic C=C bond. Studying the incorporation of C_{23} -enyne, C_{13} -dienyne and C_{18} -trienyne compounds 52 into vitamins $\text{K}_{1(20)}$, $\text{K}_{2(10)}$ and $\text{K}_{2(15)}$ 55 the stereospecificity has been established within the accuracy of ^1H NMR spectroscopy. These results have been confirmed by HPLC analysis using a 97/3 *E/Z* mixture of the C_{23} -enyne.

Scheme 10



Since the syntheses of vitamins K and E have many common features we extended our studies to the annulation of α,β -unsaturated alkoxy-carbene ligands. The regioselectivity of the alkyne incorporation is similar to that observed in the phenylcarbene series: Aliphatic 1-alkynes yield regioselectively 2-alkyl-1,4-benzohydroquinones 59; 2-alkynes lead to an approximately 2/1 mixture of 60a and b the longer alkyl chain ending up nearer the phenolic group in the major isomer (54) (scheme 11).

Scheme 11



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