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The Use of Fischer Carbene Complexes for the Preparation of Five-Membered Carbocyclic Rings

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Contents

1. Introduction

The aim of this review is to highlight recent discoveries in the use of Fischer carbene complexes in the synthesis of five-membered rings. In recent years, numerous reviews of the use of Fischer carbene complexes in organic synthesis have appeared.[1] By far the most famous and most heavily utilized reaction of Fischer carbene complexes is the synthesis of phenols via the coupling of alkynes with α,β-unsaturated carbene complexes (including arylcarbene complexes), commonly known as the Dötz reaction (depicted in Scheme 1). Many other studies highlight the formation of other ring sizes;[2] the use of Fischer carbene complexes for cyclopropanation of alkenes[3] and for the preparation of four-membered carbocycles via photolytic coupling of carbene complexes and alkenes[1e] have been reviewed. Numerous reaction processes of Fischer carbene

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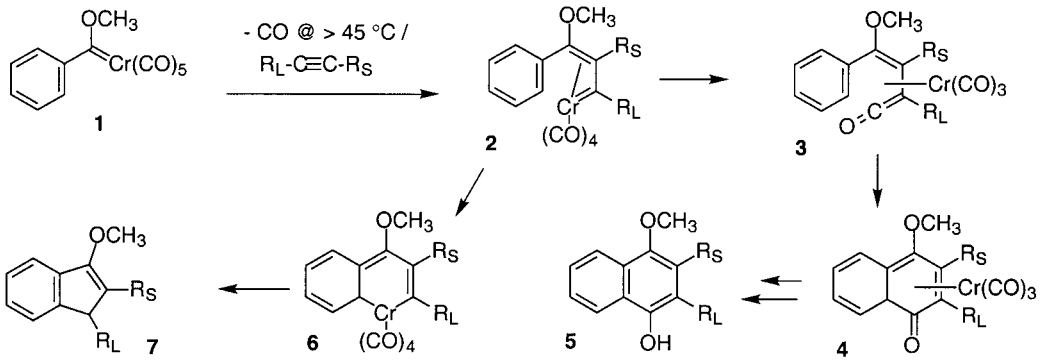


Scheme 1.

complexes result in the formation of five-membered carbocycles,[4] and include both deliberate and accidental discoveries. Many of these processes have been very well studied, and the scope, limitation, and reaction mechanism have been firmly established in many of these cases. In this review, the aim is to present all classes of reactions that result in the transformation of carbene complexes into cyclopentanoid derivatives and to present the scope and limitation for all well-studied processes. In general, this review focuses on processes that consume the carbene complex; processes where the carbene complex is an auxiliary are not presented.

2. Cycloaddition Processes

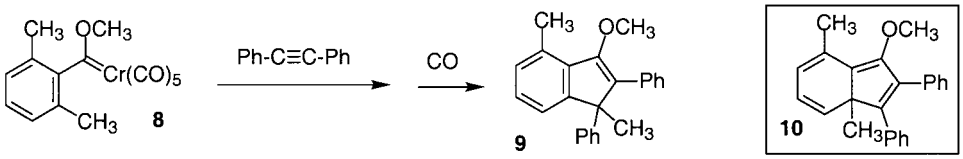
2.1. Omission of CO from the Dötz reaction

The coupling of α,β-unsaturated (including aryl) carbene–chromium complexes (e.g. **1**, Scheme 1) with alkynes (commonly known as the Dötz reaction) is a well-established method for the preparation of phenol derivatives (e.g. **5**); the mechanism for this important reaction is depicted in Scheme 1. Although phenol formation is usually the desired reaction pathway, in many cases other compounds are obtained in addition to phenol products, including five-membered rings (e.g. **7**), furans, cyclobutenones, and products resulting from insertion of more than one alkyne unit. Phenol and five-membered ring formation are related, and differ only in the incorporation of carbon monoxide in a late step of the reaction process, where intermediate vinylcarbene complex **2** can either undergo CO insertion to form vinylketene **3** and eventually the phenol (**5**), or undergo direct cyclization to **6** and eventually form the indene (**7**). Much controversy surrounds the formation of vinylcarbene complex **2**. Although early studies suggested that the conversion of **1** and alkynes to **2** involves CO-dissociation followed by [2+2]-cycloaddition and pericyclic ring opening of the resulting metallacyclobutene,[5] theoretical studies[6] strongly suggest that the η^3-vinylcarbene complexes (e.g. **2**) are the initially formed intermediates from coupling of alkynes and Fischer carbene complexes.

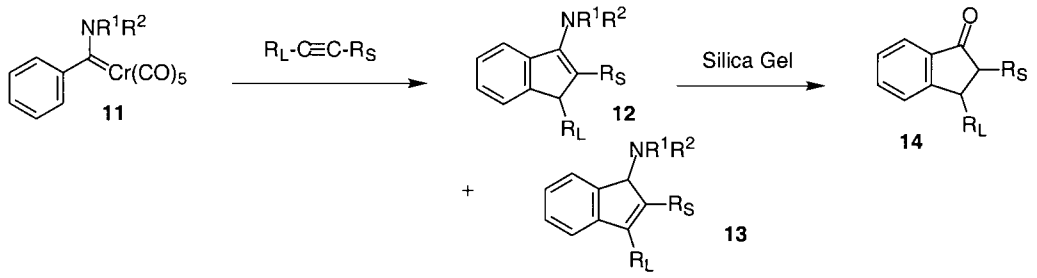
The factors affecting the distribution of five- vs. six-membered ring cycloaddition reactions have been extensively probed.[7] If the naphthol formation pathway is blocked through substitution at both *ortho* positions as in carbene complex **8** of Scheme 2,[8] five-membered ring formation appears to be favored (Scheme 2), however naphthol formation becomes the major reaction pathway if either of the *ortho* positions is unsubstituted. Presumably cyclopentadiene derivative **10** is produced initially, which rearranges to the observed product under the reaction conditions. Indene formation appears to be favored in polar coordinating solvents, and under high dilution conditions.[9] Carbene complexes of molybdenum and tungsten, as well as carbene complexes featuring strongly electron-donating substituents,[10] appear to generally provide less CO-incorporated products than the chromium–alkoxycarbene complexes featured in Schemes 1 and 2. A recent paper notes that the regioselectivity differs for indene and phenol formation, which suggests that the initial alkyne insertion process (e.g. **1**→**2** in Scheme 1) is reversible.[11] In numerous cases, indene formation is the major reaction pathway, and these studies will be discussed in succeeding sections.

2.2. Coupling of phenyl(amino)carbene–chromium complexes with alkynes

Indene formation is the exclusive reaction pathway observed in the coupling of aryl(amino)carbene–chromium complexes (**11**, Scheme 3) and alkynes (Table 1).[12] A mixture of the double position isomers, enamine **12** and allylamine **13**, is produced initially in the reaction, however the enamines are unstable under the isolation conditions; the corresponding indanone derivative **14** is isolated after chromatography. The optimal conditions for this cycloaddition are 120–125°C in DMF solvent. The alkoxy analog



Scheme 2.



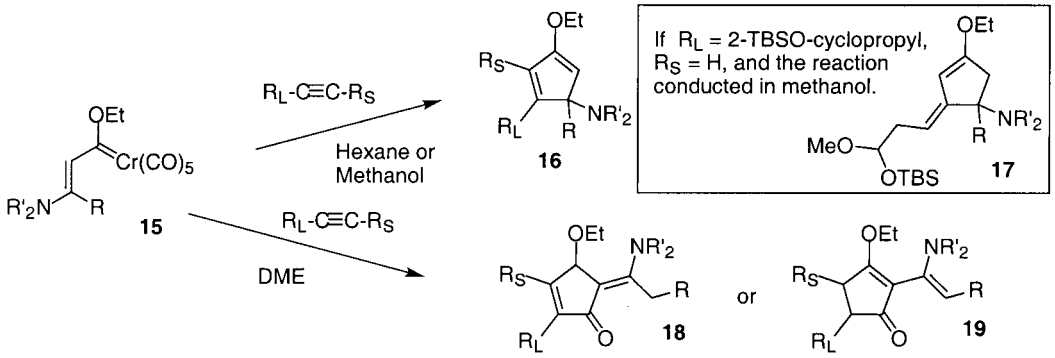
Scheme 3.

Table 1. Synthesis of indane derivatives via the coupling of phenyl(amino)carbene complexes and alkynes

Entry	R^1	R^2	R_L	R_S	Yield **14** (%)	Yield **13** (%)
1	R^1,R^2=–$(CH_2)_2O(CH_2)_2$–		*n*-Bu	H	95	
2	R^1,R^2=–$(CH_2)_4$–		Et	Et	52	
3	R^1,R^2=–$(CH_2)_2O(CH_2)_2$		Et	Et		96
4	R^1,R^2=–$(CH_2)_2O(CH_2)_2$		Ph	CH_3	41	52
5[a]	–CH_2CH=CH_2	H	Et	Et	71[b]	

[a] The pentacarbonyl complex was converted to the alkene–tetracarbonyl complex prior to reaction with the alkyne; the reaction was conducted at 80°C.
[b] The arene–chromium tricarbonyl complex was isolated.

of complex **11** (complex **1**) also affords an indene derivative under these conditions in 83% yield. The reaction proceeds at lower temperatures (refluxing benzene) if the carbene complex is activated by intramolecular alkene coordination (see Entry 5 of Table 1).[13] Formation of indanones has been attributed to the stronger electron-donating ability of the amine group (relative to an alkoxy group), which stabilizes vinylcarbene complex intermediates (e.g. **2** of Scheme 1), and thus suppresses the crucial CO insertion step of the benzannulation process.[10] This reaction process does not



Scheme 4.

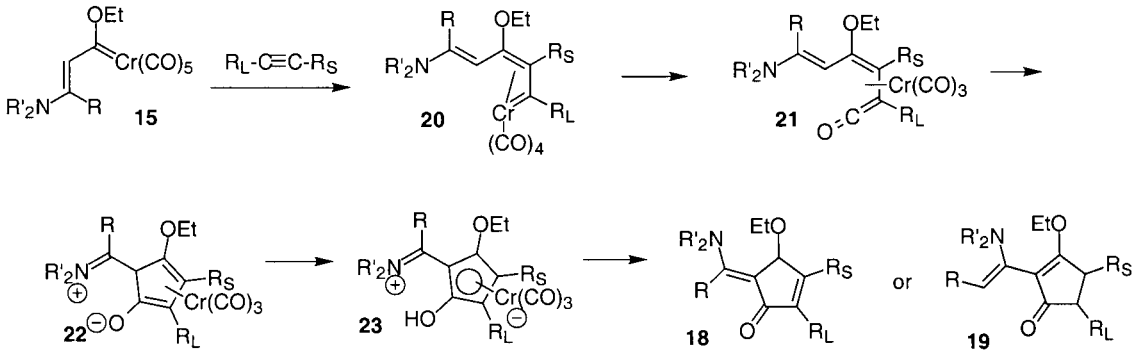
Table 2. Synthesis of aminoyclopentadienes **16** via coupling of **15** and alkynes in pyridine or acetonitrile

Entry	R	R′	R_L	R_S	Yield **16** (%)
1	Cyclopropyl	Me	Cyclopropyl	H	95
2	Me	Me	Me	Me	56
3	Me	Me	CH_2OTBS	H	86
4	Ph	–$(CH_2)_4$–	Cyclopropyl	Cyclopropyl	51
5	–$CH_2CH_2C(Br)$=CH_2	Me	Me	Me	79
6	Cyclopropyl	Me	2-TBSO–cyclopropyl	H	82

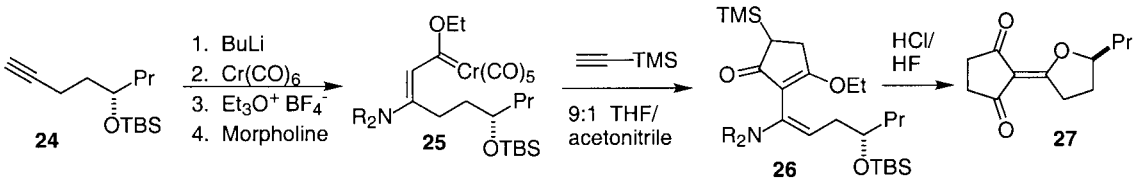
Table 3. Synthesis of **18** or **19** via coupling of **15** with alkynes in DME or THF/acetonitrile

Entry	R	R′	R_L	R_S	Yield **18** (%)	Yield **19** (%)
1	Et	–$(CH_2)_2O(CH_2)_2$–	*n*-Pr	H	66	
2	–$(CH_2)_3OTBS$	–$(CH_2)_2O(CH_2)_2$–	*n*-Pr	H	62	
3[a]	Et	–$(CH_2)_2O(CH_2)_2$–	Ph	H		97
4[a]	–$(CH_2)_3OTBS$	–$(CH_2)_2O(CH_2)_2$–	TBS	H		72

[a] In THF/acetonitrile.



Scheme 5.



Scheme 6.

extend to alkenylcarbene complex analogs, which usually afford benzannulation products.[14,15]

2.3. Coupling of β-amino–α,β-unsaturated carbene complexes with alkynes

A versatile synthesis of various classes of cyclopentanoid derivatives can be achieved through coupling of β-amino–α,β-unsaturated carbene complexes (**15**, Scheme 4) and alkynes.[16] The starting carbene complexes are readily available from the addition of alkynyllithium reagents to chromium hexacarbonyl, followed by alkylation and amine addition. The two different reaction processes depicted in Scheme 4 are commonly observed in the coupling of complex **15** with alkynes, depending primarily upon the structure of the alkyne, the identity of R, and the reaction conditions.

The reaction affords predominantly aminocyclopentadiene derivatives (**16**) under two circumstances: (1) coupling with terminal alkynes; and (2) coupling with internal alkynes using either pyridine or acetonitrile as solvent (Table 2).[17] This reaction is mechanistically analogous to the reaction in the previous section. In reactions using cyclopropylacetylene derivatives performed in methanol, secondary ring opening processes lead to the direct formation of alkylidenecyclopentenes (**17**).[18]

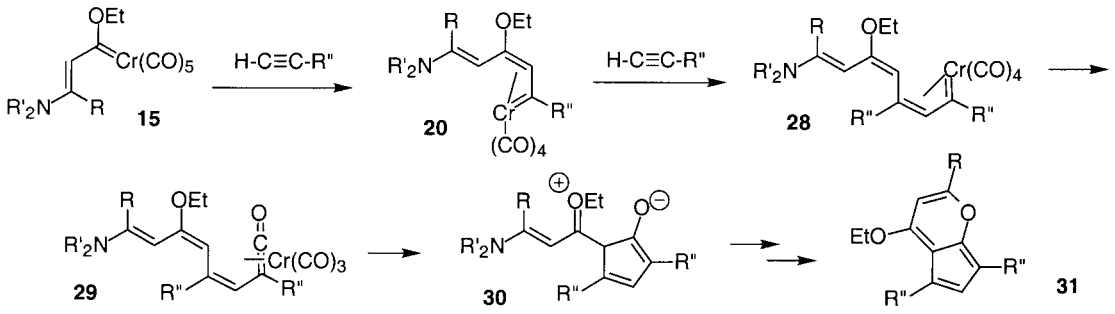
In a mechanistically different process, 5-alkylidene-2-cyclopentenones (**18**) or 2-alkenyl-2-cyclopentenones (**19**) are formed as a result of CO insertion processes (Table 3).[19,20] Cyclopentenone **18** is observed when **15** is coupled with either terminal or internal alkynes in ethereal solvents. If complex **15** features a hydrogen at the 4-position, cyclopentenone **19** can be obtained as the exclusive product if the coupling reaction is performed in 9:1 THF/acetonitrile. In this reaction, a vinylketene complex (**21**, Scheme 5) is formed via alkyne insertion followed by CO-insertion. Nucleophilic addition of the enamine functionality to the vinylketene affords the five-membered ring enolate **22**, which then converts to the aminoalkylidene complex.

The conversion of carbene complex **15** to cyclopentenone **19** has been used as the cornerstone for the total synthesis of the antihypertensive Oudenone (**27**, Scheme 6).[19] Conversion of alkyne **24** to carbene complex **25**, followed coupling with trimethylsilylacetylene affords cyclopentenone **26**, which is transformed to the Oudenone in a single step.

Several processes have been reported in which alkynes of general structure **15** couple with more than one mole of a terminal alkyne to provide cyclopentanoid products.[21,22] For example, the coupling of complexes of general structure **15** and a large excesses of a terminal alkyne led to cyclopentapyran derivatives (Scheme 7 and Table 4). A similar mechanism to Scheme 5 was proposed, however insertion of a second alkyne (**20**→**28**) is preferred over CO insertion (**20**→**21**, Scheme 5) after generation of the initial carbene complex **20**. Subsequent addition/elimination from enolate intermediate **30** leads to the cyclopentapyran system. The unusual formation of spiro[4.4]nonatriene derivatives **33** and **34** was observed in the coupling of carbene complex **32** with large excesses of phenylacetylene derivatives (Scheme 8); the mechanism for this transformation is unclear.[23]

2.4. Coupling of α,β-unsaturated tungsten- and molybdenum carbene complexes with alkynes

Various systematic[24,25] and isolated[26] studies have suggested that the coupling of alkynes and α,β-unsaturated molybdenum- and tungsten carbene complexes is more likely to produce a five-membered ring derivative than chromium analogs, which usually afford phenol derivatives, however in very few cases does the reaction lead to the exclusive formation of five-membered rings. A two-step process, involving the coupling of ynamine **36** with α,β-unsaturated tungsten carbene complex **35** followed by



Scheme 7.

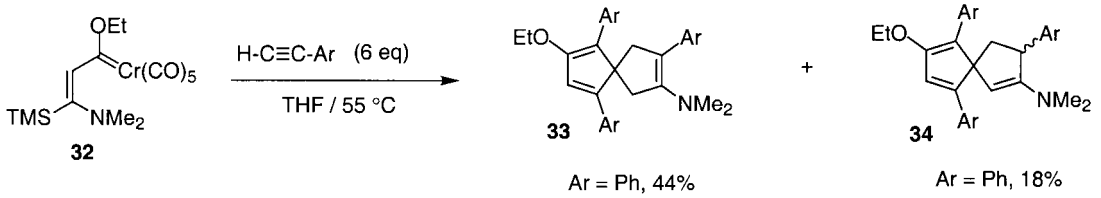
Table 4. Synthesis of fulvenes (**31**) from the coupling of excess terminal alkynes with complex **15**

Entry	R	R′	R″	Yield **31** (%)
A	–C(CH$_3$)Oet	Me	*n*-Pr	59
B	–C(CH$_3$)OEt–	Me	Ph	51
C	Ph	Me	Ph	24
D	*t*-Bu	Me	Ph	52

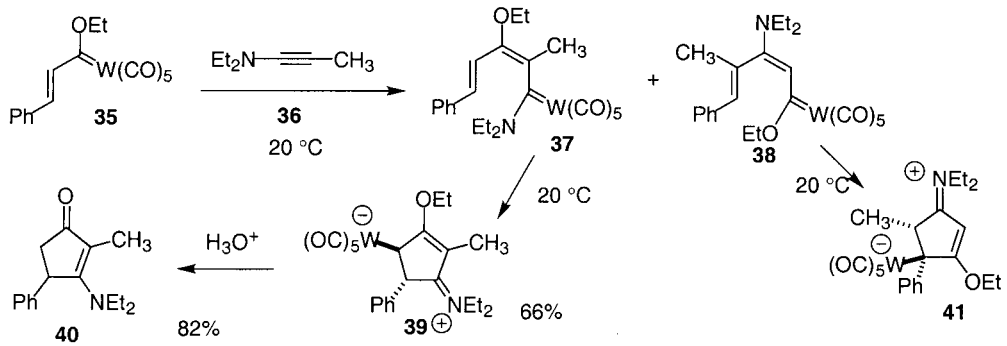
thermal cyclization constitutes a general synthesis of five-membered ring derivatives (Scheme 9).[27] Initial coupling of the carbene complex and ynamine affords a 2:1 mixture of the alkyne insertion product (**37**) and the [2+2]-cycloaddition/ring opening product (**38**). Both of these compounds undergo cyclization to the five-membered ring iminium salts at 20°C. The initially formed cyclopentene–iminium salt **39** is easily transformed to cyclopentenone derivative **40**.

2.5. Coupling of cyclopropylcarbene–chromium complexes with alkynes

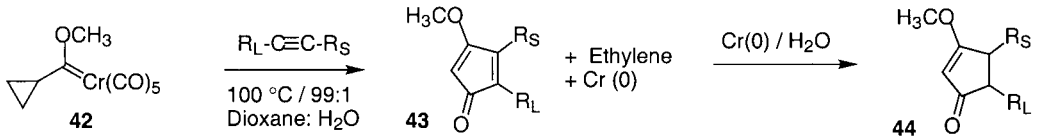
The reaction of cyclopropylcarbene-chromium complex **42** with alkynes leads to 3-methoxy-2-cyclopentenones (**44**) in good to excellent yields using a variety of alkyne derivatives (Scheme 10 and Table 5).[28] The reaction initially produces cyclopentadienone derivatives (**43**), which are then reduced to the corresponding cyclopentenones (**44**) by low-valent chromium byproducts; water (deliberately added) serves as the proton source. In most cases the reaction affords mixtures of *cis* and *trans* stereoisomers, however these mixtures could be isomerized to the *trans* isomer in most cases by treatment with basic methanol. The mechanism depicted in Scheme 11 has been proposed to account for the formation of the five-membered ring derivatives (the mechanism for conversion of cyclopentadienone **43** to cyclopentenone **44** is discussed later). The regioselectivity is similar to that observed in the Dötz reaction, and arises from the same event, alkyne insertion (**42→45**). In cases where both of the alkyne substituents are aromatic rings, the cyclopentadienone derivatives can be isolated in good yield.[29] As noted in Table 5, a wide variety of functional groups are tolerated in the reaction, including alcohols. The reaction was initially a surprise in that the authors expected this reaction to be the homologue of the Dötz reaction, and were actually expecting seven-membered rings (**49**) via reductive elimination in intermediate pentadienoyl complex **47**. Although successful seven-membered ring synthesis



Scheme 8.



Scheme 9.



Scheme 10.

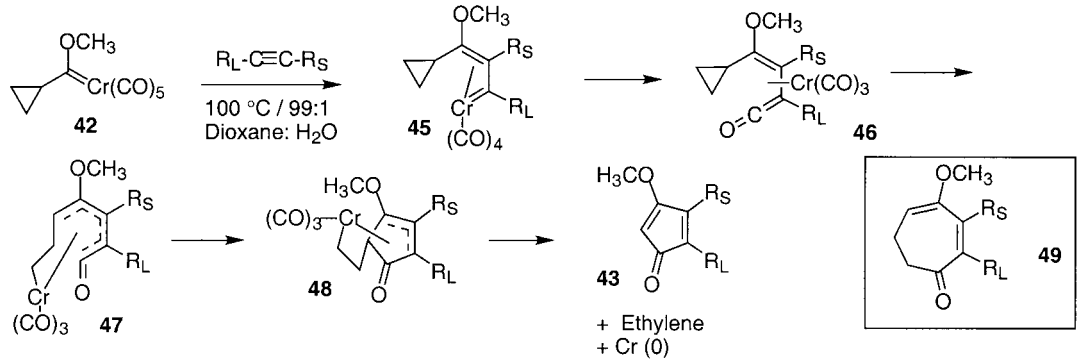
Table 5. Synthesis of cyclopentenone derivatives **44** through coupling of alkynes and complex **42**

Entry	R_L	R_S	**44** (%)	*trans*:*cis*
1	Ph	Ph	78	85:15
2	Ph	CH_3	75	73:27 (7.5:1 regioselectivity)
3	*n*-C_3H_7	H	68	
4	$(CH_2)_4OH$	H	68	
5	$(CH_2)_4OTBS$	H	58	
6	*n*-C_3H_7	*n*-C_3H_7	60	50:50

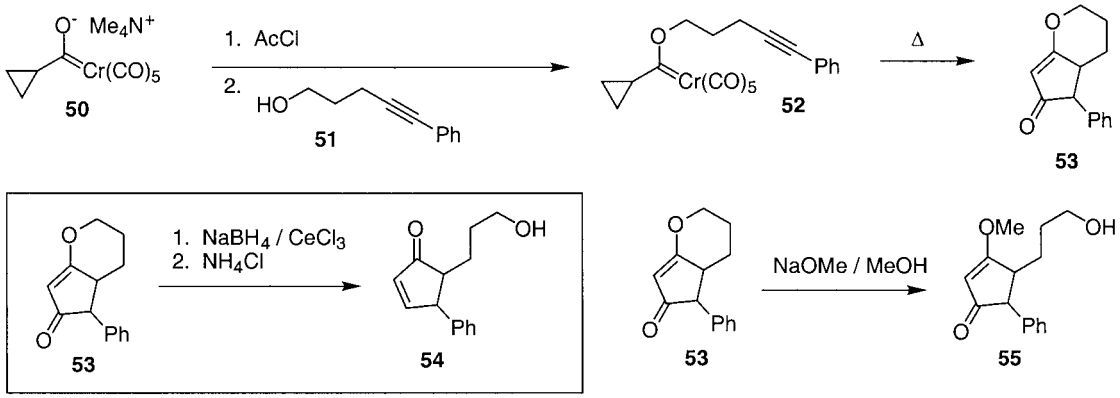
was later achieved using molybdenum and tungsten analogs,[30] the scope and limitation of the five-membered ring synthesis has been studied quite exhaustively. Numerous variants of this reaction process have been developed and will be discussed in succeeding sections.

Intramolecular variants of the above reaction have been studied extensively.[31] Compounds containing both cyclopropylcarbene and alkyne groups (e.g. **52**, Scheme 12) are prepared from the chromium carbene acylate salt and alcohols. In most cases, primary alcohols can be converted to carbene complexes in good yield, however reaction with secondary alcohols is usually less successful. Thermolysis of a variety of alkyne–cyclopropylcarbene complexes in either aqueous dioxane or aqueous toluene leads to cyclopentenone rings fused to oxygen heterocycles (e.g. **53**). The reaction proceeds in good yield when the size of the heterocyclic ring formed is five, six, or seven and an internal alkyne is employed. The reaction using terminal alkynes is effective if the ring size is greater than or equal to six, however silylated alkynes produce products equivalent to those derived from terminal alkynes since the predicted α-silylketone derivatives undergo desilylation under the reaction conditions. The vinylogous ester products undergo facile ring opening reactions (**53**→**54** and **53**→**55**) to afford the monocyclic derivatives with net complete control of regiochemistry.

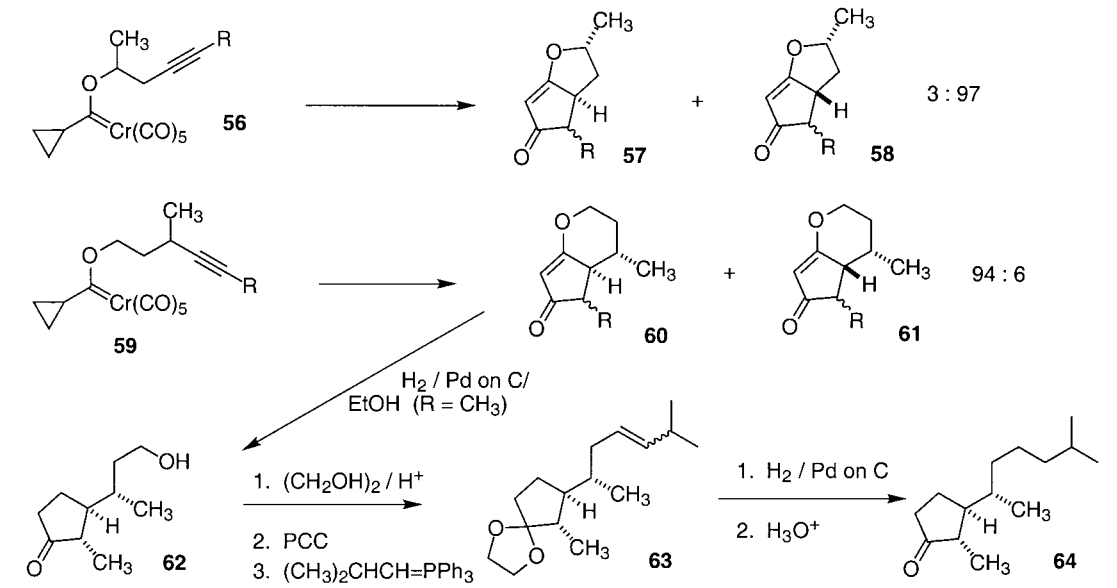
The thermolysis of alkyne–cyclopropylcarbene complexes featuring a stereogenic center in the tethering chain is sometimes highly stereoselective;[32,33] the two substrates (**56** and **59**) depicted in Scheme 13 all proceed with a high degree of



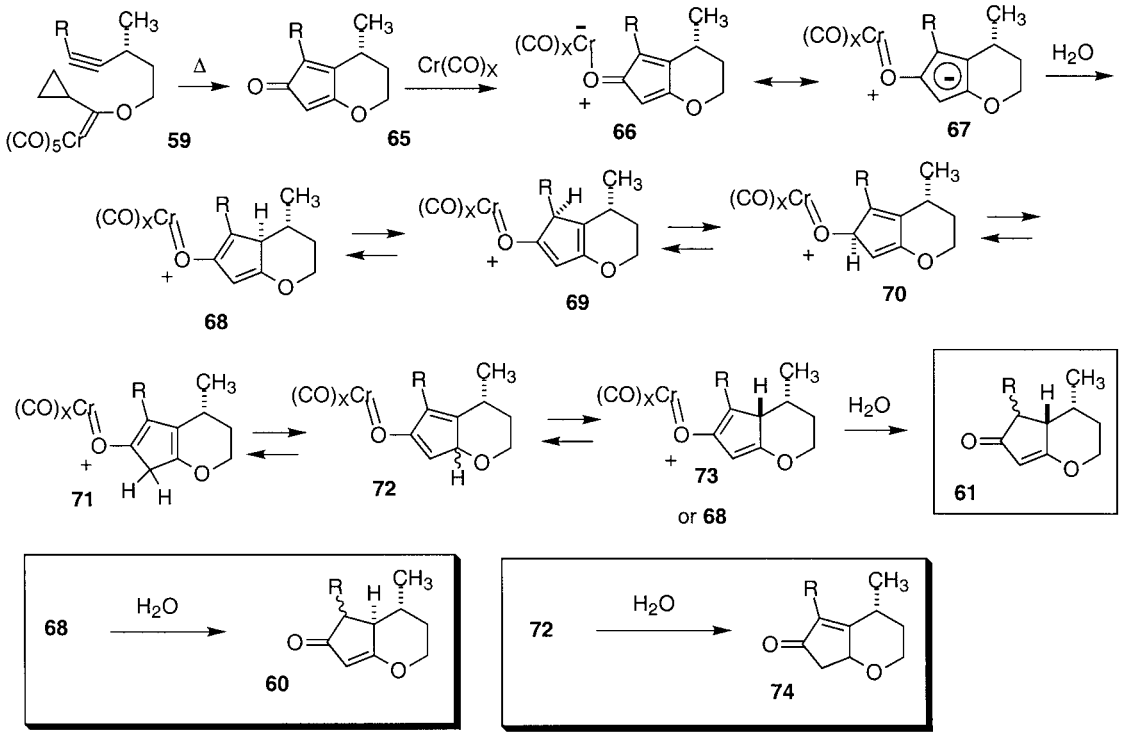
Scheme 11.



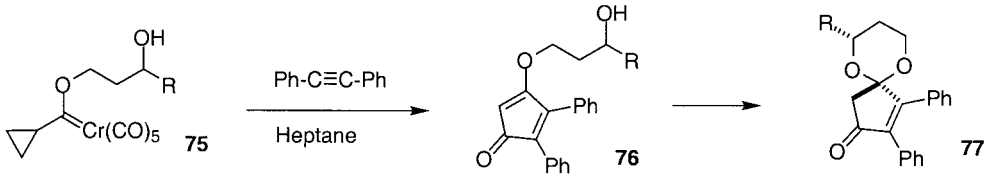
Scheme 12.



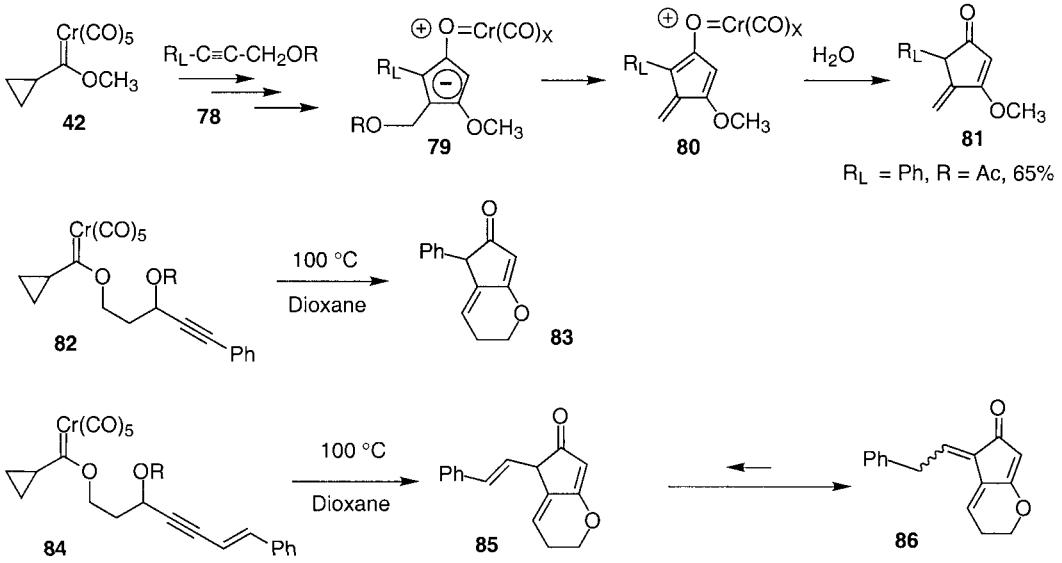
Scheme 13.



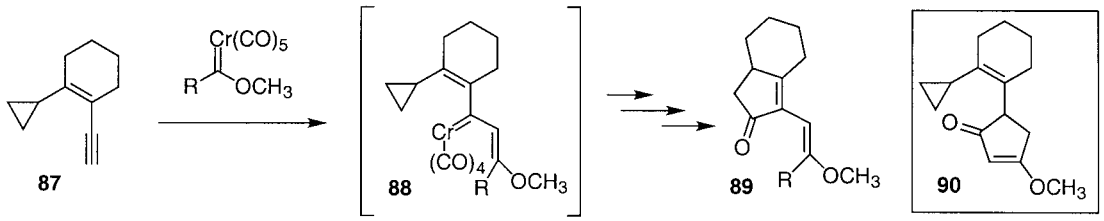
Scheme 14.



Scheme 15.



Scheme 16.



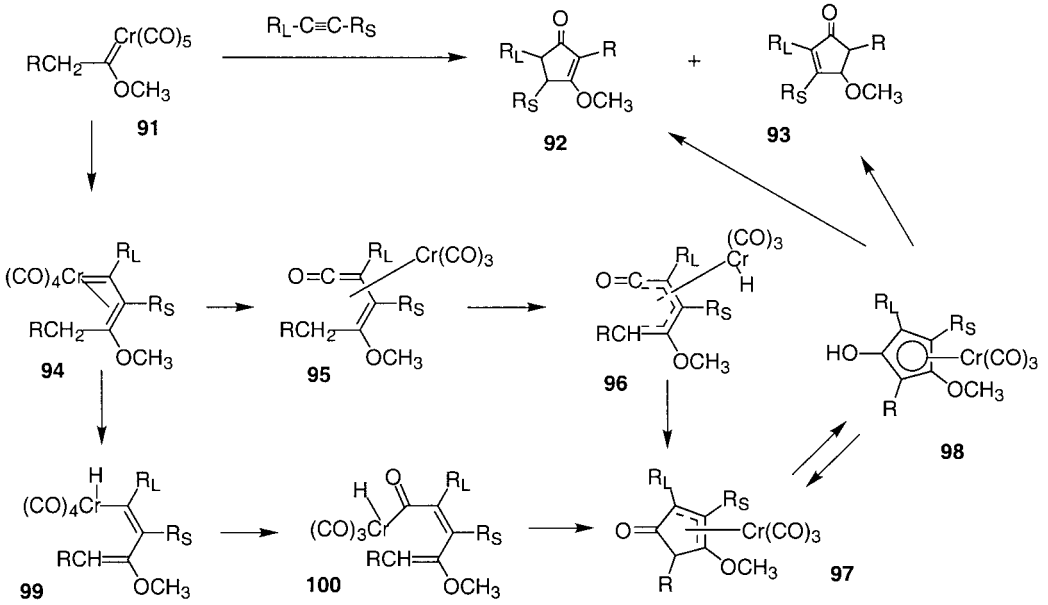
Scheme 17.

stereoselectivity for heterocyclic ring formation; the major stereoisomer corresponds to the thermodynamically more stable isomer. In both of these cases, the high stereoselectivity was observed only in aqueous toluene. Placement of a methyl group at the other positions of five- and six-membered ring forming substrates was also studied, however a much lower level of stereoselection was observed in these cases. This reaction was used as the cornerstone for the synthesis of de-ABC-cholestanone (**64**) a precursor for the D ring of vitamin D.

The stereochemistry is established during the cyclopentadienone reduction step; the mechanism for this process is depicted in Scheme 14 for complex **59** transforming to cyclopentenones **60** and **61**. Reduction of initially formed cyclopentadienone involves a net transfer of two electrons and two protons to the cyclopentadienone nucleus, and this has been supported by deuterium labeling studies. Formation of the oxygen-bound chromium complex (**66**) can lead to electron delocalization into the five-membered ring through resonance form **67**. Protonation leads to cyclopentadienide **68**; cyclopentadienides are well known to scramble above 35°C. Equilibration of all cyclopentadienide isomers (**68**–**73**) prior to addition of the second proton has been suggested as the critical stereochemistry-determining event. The results are consistent with regioisomers **68** and **73** as the major species at equilibrium since protonation provides nearly exclusively the vinylogous ester regioisomers **60** or **61** and not **74**. The net effect is equilibration of **68** and **73**, and protonation of the more stable isomer **68** results in the major product **60**. All other proton sources are inferior to water; the role has been attributed to the crucial hydration of chromium prior to delivery of the second proton. Other reaction processes taking advantage of the anionic nature of the five-membered ring have been designed (described later).

Optimal conditions for the synthesis of cyclopentadienones (e.g. **76**, Scheme 15) involves conducting the reaction in heptane solvent at reflux;[29] the nonpolar solvent system may simply disfavor resonance form **67** of Scheme 14 (i.e. disfavor electron transfer to the cyclopentadienone ligand). Only diphenylacetylene leads to cyclopentadienones in high yield. The reaction of complexes featuring pendant alcohol derivatives (e.g. **75**) leads to cyclopentadienones which are rapidly transformed to cyclopentenedione monoketals (**77**). This reaction process is completely diastereoslective when the pendant alcohol is secondary.

When alkynes featuring a leaving group in the propargyl position (e.g. **78**, Scheme 16) are coupled with cyclopropylcarbene complexes, a β-elimination process can occur from the cyclopentadienide anion (**79**) leading eventually to alkylidenecyclopentenone derivatives (**81**).[34] The reaction featuring propargyl oxygens leads to alkylidenecyclopentenones only if the alkyne is substituted such that the propargyl functionalized side ends up at the 4-position. This

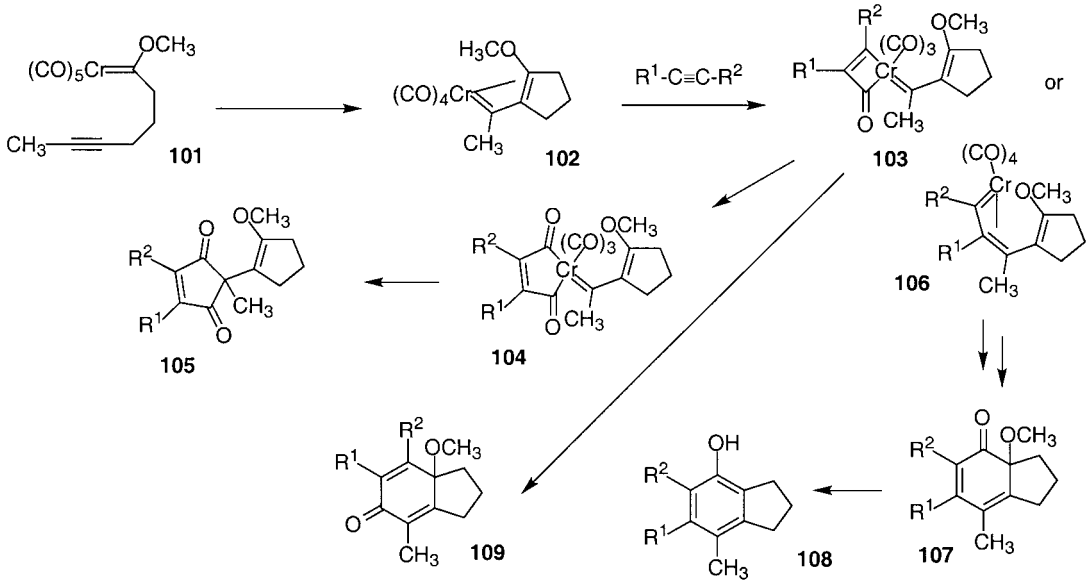


Scheme 18.

Table 6. Synthesis of cyclopentenones **92** and **93** from the coupling of alkylcarbene complexes and alkynes

Entry	R	R_S	R_L	Yield (*cis*:*trans*)	Yield **93** (%)
1	H	H	Ph	28	
2	H	*n*-Pentyl	*n*-Pentyl	34 (2:1)	24
3	H	H	[a]	52	
4	H	Ph	Ph	23 (2:1)	13
5	Pr	Ph	Ph	26 (89:11)	12
6	$TMSCH_2CH_2$–	Ph	Ph	48	12
7	$PhCH_2$–	Ph	Ph	28	
8[b]	Pr	H	$-CH_2CH_2O$-allyl	26[c]	

[a] R_L=–$CH(CH_3)CH_2CH_2C(CH_3)$=CH_2.
[b] The molybdenum complex was used.
[c] Also a cyclopropyltetrahydropyran derivative (8%) and a furanone (29%) were obtained.



Scheme 19.

Table 7. Synthesis of cyclopentenediones (**105**) via coupling of carbene complex **101** and two alkynes

Entry	R_1	R_2	Yield **105** (%)	Yield **108** (%)	Yield **109** (%)
1	H	Ph	54	16	20
2	Et	Et	27	0	11
3	H	*n*-Pr	55	18	15
4	H	$-(CH_2)_3COOEt$	41		

can be achieved either by placing the propargyl alcohol derivative at the smaller side of the alkyne (as in general structure **78**) or placement within the tethering chain in an intramolecular reaction (as in substrates **82** and **84**). In virtually every case tested, some of the alkylidenecyclopentenone is observed as a product of the carbene–alkyne coupling reaction, however the acetate group is completely eliminated in every system examined. In the 5,6-fused cases represented by **82** and **84** in Scheme 16, all oxygen groups are eliminated (R=H, TBS, or THP were tested), however in the 5,5 cases and in acyclic systems, alcohol and ether groups are not completely eliminated. In cases where alkenylacetylene derivatives are employed (e.g. **84**), the reaction affords predominantly the 4,5-dialkylidenecyclopentenone derivatives (**86**), which result from isomerization of the initially anticipated 5-alkenyl-4-alkylidene-2-cyclopentenones (**85**). The 4,5-dialkylidenecyclopentenone ring system is relatively rare.[35]

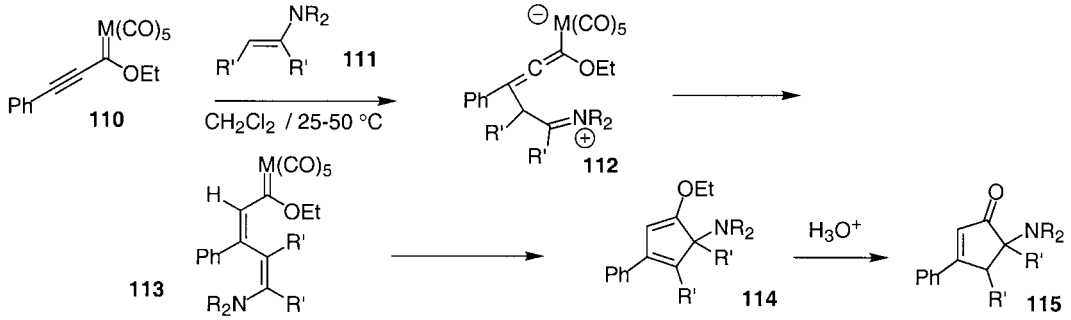
Independent generation of cyclopropylvinylcarbene complex intermediates analogous to **45** of Scheme 11 via an alternate pathway, coupling of cyclopropylvinylacetylene **87** (Scheme 17) and simple carbene complexes (note the structural similarity of **45** of Scheme 11 and **88** of Scheme 17), can also lead to the formation of cyclopentenone derivatives (**89**).[36] Remarkable annulation selectivity is observed in the coupling of cyclopropylvinylacetylene **87** with the cyclopropylcarbene complex **42** (R=cyclopropyl in Scheme 17). Complete selectivity for opening of the cyclopropane ring at the enyne has been reported, and none of the product from coupling of the cyclopropylcarbene at the alkyne, **90**, is detected in the reaction.

2.6. Coupling of alkylcarbene complexes with alkynes

Cyclopentenone products similar to those from the previous section can also be produced from the coupling of alkylcarbene complexes with alkynes (Scheme 18 and Table 6),[37] however the reaction is mechanistically quite different. This method is most effective for dialkylacetylenes; cyclobutenones and two-alkyne insertion products are formed as minor byproducts in most of these studies. Compounds of this type have also been observed in the coupling of molybdenum carbene complexes with alkynes,[38,39] and in intramolecular couplings involving aminocarbene complexes.[40] A variety of mechanistic proposals have been offered for this transformation, which can be divided into two major themes differing in the timing of the C–H activation (**94→99** and **95→96**) and CO insertion (**94→95** and **99→100**) events. The involvement of a free ketene (**95**, uncomplexed) in these reactions was ruled out through independent generation by cyclobutenone thermolysis. Mixtures of the vinylogous ester isomer **93** and the 4-alkoxy-2-cyclopentenone isomer **94** were obtained in most cases.

2.7. Coupling of carbene complexes with multiple alkynes

The coupling of carbene complexes with two alkyne molecules can result in the formation of 2-alkenyl-4-cyclopentene-1,3-diones (**105**, Scheme 19 and Table 7).[41] In general, this class of products is produced efficiently only if a five- or six-membered ring-forming intramolecular carbene alkyne coupling (e.g. **101→102**) is followed by an intermolecular carbene–alkyne coupling, as is depicted in the general reaction equation in Scheme 19. In most cases,

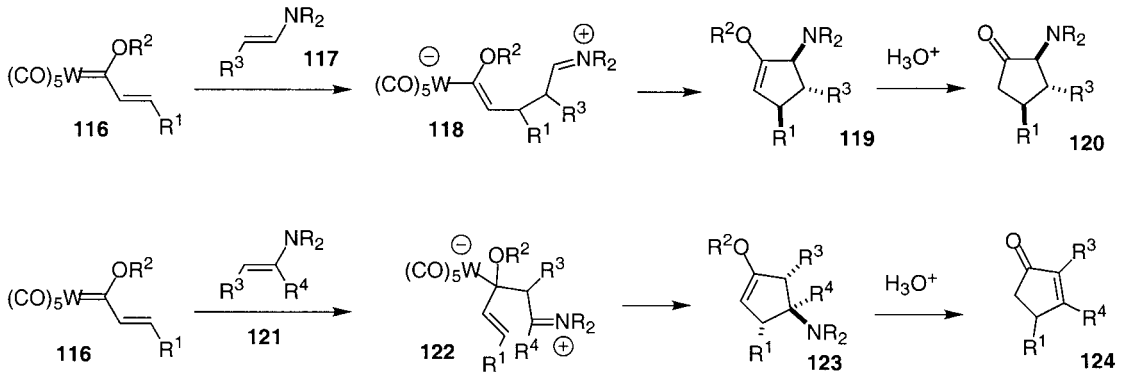


Scheme 20.

Table 8. Synthesis of cyclopentadiene **114** from the coupling of alkynylcarbene complexes and enamines

Entry	R	R′	M	Yield **114** (%)
1	Me	$-(CH_2)_3-$	W	73
2	$-(CH_2)_4-$	$-(CH_2)_3-$	W	72
3	$-(CH_2)_4-$	$-(CH_2)_3-$	Cr	87
4	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_4-$	W	87
5	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_5-$	W	76

phenols that result from a two-alkyne-benzannulation process (e.g. **108**, described in the cyclization section) are obtained as minor but significant byproducts, accompanied by the cyclohexadienone derivative **109**. The mechanism in Scheme 19 has been proposed to account for the formation of these products. Conversion of intermediate vinylcarbene complex to the metallacyclobutenone (**103**) and maleoyl–metal complexes (**104**) have been suggested as key intermediates for cyclopentenedione formation.



Scheme 21.

Table 9. Stereoselective synthesis of cyclopentanones from the coupling of enamines and alkenylcarbenes

Entry	R	R^1	R^2	R^3	R^4	**119** (ee) (%)	**123**[a] (%)
1	$-(CH_2)_4-$	2-Furyl	CH_3	CH_3	CH_2CH_3		95
2	$-(CH_2)_3CH(CH_2OCH_3)-$[b]	2-Furyl	CH_3	CH_3	CH_2CH_3		88 (>80)
3	$-(CH_2)_4-$	2-Furyl	CH_3	*i*-Pr	H	72–95	
4	$-(CH_2)_3CH(CH_2OCH_3)-$[b]	2-Furyl	CH_3	*i*-Pr	H	74–91 (>99)	
5	$-(CH_2)_4-$	2-Furyl	*t*-Bu	*i*-Pr	H	94	

[a] The number in parentheses refers to the de relative to the chiral auxiliary.
[b] The stereogenic center is *S*.

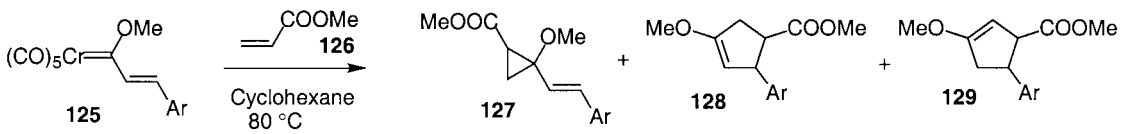
2.8. Coupling of α,β-unsaturated carbene complexes with enamines

The synthesis of cyclopentadiene derivatives (**114**, Scheme 20) is readily achieved through the reaction of alkynylcarbene–chromium and –tungsten complexes (**110**) and enamines (**111**).[42–44] A variety of five-, six-, and seven-membered ring and acyclic enamines have been tested in their reaction with phenylethynylcarbene complexes (Table 8). In some cases, the enol ether derivatives **114** cannot be isolated due to hydrolysis on silica gel, and the enone derivatives (**115**) are obtained after chromatography. A mechanism involving Michael addition of the enamine (**110**+**111**→**112**) followed by 1,3-proton transfer affords the α,β,γ,δ-unsaturated carbene complex **113**, which cyclizes (see similar intermediates in Scheme 1) to afford cyclopentadiene **114**.

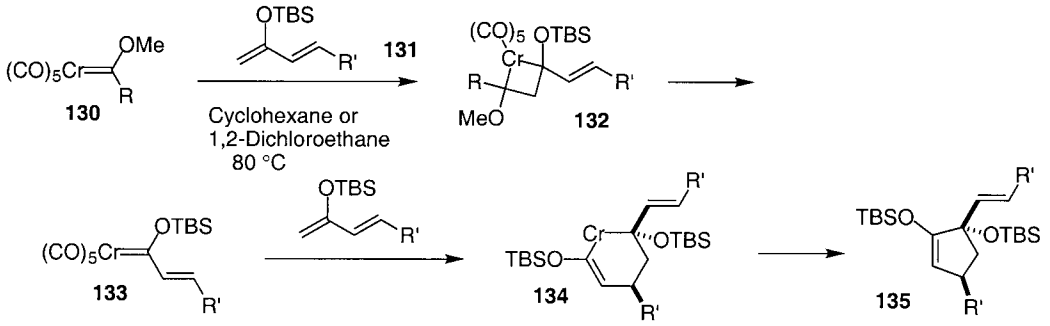
A stereoselective [3+2]-cycloaddition process also occurs when alkenylcarbene–tungsten complexes (**116**, Scheme 21) couple with enamines at 25–60°C in THF, leading to either cyclopentenes **119** or **123** (Table 9).[45] The regiochemistry of addition is different for enamines derived from aldehydes (**117**) and enamines derived from ketones (**121**), and this regiochemistry different has been attributed to competing Michael and 1,2-addition processes of the enamines. For ketone-derived enamines, a mechanism involving 1,2-addition (**116**+**121**→**122**) followed by intramolecular coupling of the allyltungsten nucleophile with the iminium salt has been proposed. For aldehyde-derived enamines, a mechanism involving Michael addition (**116**+**117**→**118**) followed by intramolecular C–C bond formation has proposed; reactions employing the *t*-butoxycarbene complex are completely regioselective while a minor regioisomer is observed in reactions employing methoxycarbene complexes. The relative stereochemistry of the five-membered ring substituents is established with a very high degree of selectivity. A high degree of relative asymmetric induction is observed for enamines featuring chiral auxiliaries in the R groups at nitrogen (entries 2 and 4 of Table 9). Hydrolysis of the initially obtained enol ethers **119** and **123** affords ketones **120** and **124**, respectively.

2.9. Coupling of carbene complexes with dienol ethers

The coupling of alkenylcarbene complexes (**125**, Scheme 22) and methyl acrylate (**126**) affords mixtures of the expected vinylcyclopropane derivative **127** and cyclopentene derivatives **128** and **129**.[46,47] Cyclopentene **128** does not arise through rearrangment of vinylcyclopropane derivative **127**. The product distribution can be controlled by solvent effects, and cyclopentenes are the exclusive products from the coupling of pyrrolyl derivatives of **125** (Ar=2-pyrrolyl). Examples where the cyclopropanation and vinylcyclopropane rearrangement are performed in separate steps have also been documented.[48]



Scheme 22.



Scheme 23.

Table 10. Coupling of carbene complexes with diene–enol ethers

Entry	R	R′	Solvent	Yield **135** (%)
1	Ph	COOMe	$ClCH_2CH_2Cl$	99
2	Ph	COOMe	Cyclohexane	39
3	CH_3	COOMe	Cyclohexane	17
4	Ph	Ph	Cyclohexane	99
5	CH_3	Ph	Cyclohexane	59

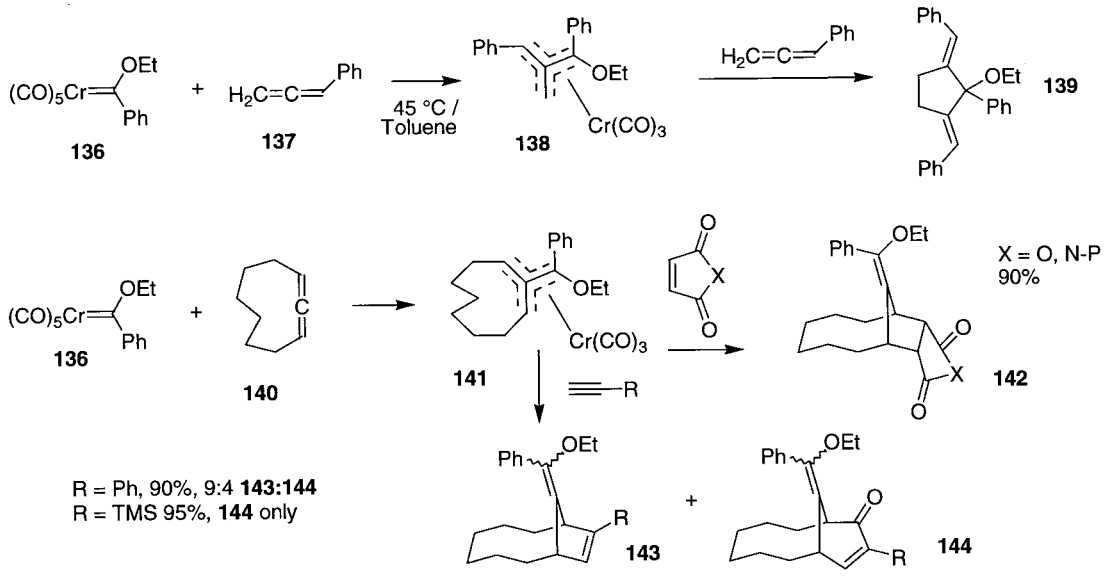
In a related study, the reaction of carbene complexes with diene–enol ethers (**131**, Scheme 23) affords vinylcyclopentene derivatives **135** (Table 10).[49] This unusual reaction involves the coupling of two moles of the diene with one mole of carbene complex. The proposed mechanism involves an initial alkene metathesis, giving silyloxy–vinylcarbene complex **133**, followed by [4+2]-cycloaddition of the diene to the chromium–carbon double bond (**133→134**), followed by reductive elimination. The unusual [4+2]-cycloaddition mechanism accounts for the observed regiochemistry, which is opposite to that expected from a cyclopropanation-rearrangement sequence as was reported in Scheme 22. A similar product is obtained in 72% yield from the direct coupling of an α,β-unsaturated carbene complex (the methoxy analog of **133**) and diene **131** (R′=COOMe).

2.10. Generation of trimethylenemethane complexes followed by cycloaddition

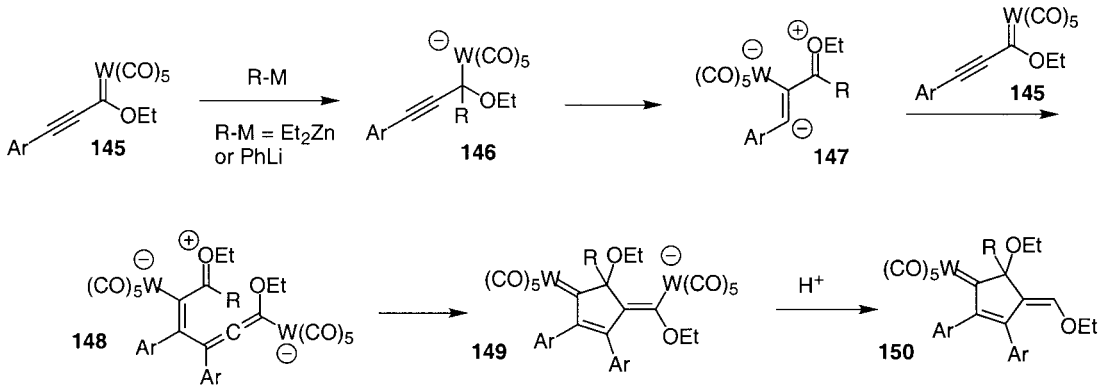
Coupling of allenes (**137** and **140**, Scheme 24) and Fischer carbene complexes affords trimethylenemethane derivatives (**138** and **141**), which afford cyclopentane derivatives after subsequent cycloaddition with suitable alkenes.[50] Dialkylidenecyclopentane derivative **139** can be obtained by either isolation of complex **138** and treatment with allene **137**, or by prolonged coupling of complex **136** and allene **137**. The isolated trimethylenemethane derivative **141** can also couple with alkynes in a separate step to provide mixtures of alkylidenecyclopentene (**143**) and alkylidenecyclohexenone derivatives (**144**),[51] which result from CO insertion processes. An efficient cycloaddition reaction occurs when trimethylenemethane complex **141** is treated with maleoyl derivatives, resulting in the exclusive formation of alkylidenecyclopentenes (**142**).

2.11. Reductive dimerization of alkynylcarbene complexes

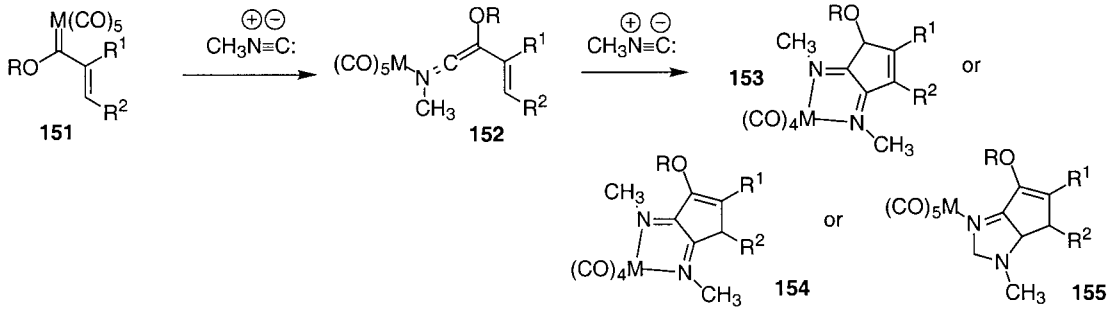
Treatment of alkynylcarbene-tungsten complexes (**145**, Scheme 25) with diethylzinc[52] or phenyllithium[53] results



Scheme 24.



Scheme 25.



Scheme 26.

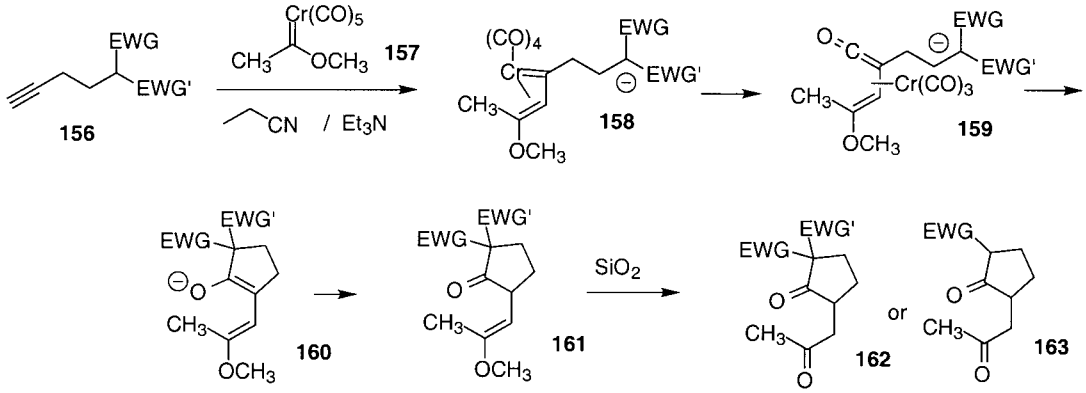
Table 11. Synthesis of cyclopentanediimines from coupling of isocyanides and carbene complexes

Entry	M	R_1	R_2	**153** (%)	**154** (%)	**155** (%)
1	Cr	R_1,R_2=–CH=CH–CH=CH–		41		
2	Mo	R_1,R_2=–S–CH=CH–		42		
3	Mo	R_1,R_2=–CH=CH–S–		30		
4	Cr	H	Ph		25	17

in cyclopentane derivatives (**150**) which incorporate two moles of the carbene complex. The key step in this transformation is a 1,2-shift of tungsten in the intermediate propargylmetal complex **146** which then undergoes Michael addition with another mole of **145**, forming **148**. Cyclization and protonation afford **150**.

2.12. Double isocyanide insertion–cyclization of arylcarbene complexes

The 2:1 coupling of isocyanides and arylcarbene[54] or alkenylcarbene[55] complexes affords indane-diimine derivatives (**153**–**155**, Scheme 26 and Table 11). The proposed



Scheme 27.

Table 12. Coupling of carbene complex **157** with alkynyl carbonyl compounds (**156**)

Entry	EWG	EWG′	Yield **162** (%)
1	COOMe	COOMe	46
2	COMe	COMe	48
3	COOMe	$P(O)(OEt)_2$	16
4	COOMe	COMe	77[a]

[a] Deacylation of the acetyl group occurred and only **163** was isolated.

mechanism proceeds by formation of the ketimine complex **152**, followed by addition of another equivalent of isocyanide. Mixtures of enol ethers **154** and **155** are the products from alkenylcarbene complexes, while compounds of general structure **153** are obtained from arylcarbene complexes. A clean demetallation procedure was not reported; treatment of the bis imine complex with HIO_4 affords mixtures of the imine hydrolysis product and carbon–carbon bond cleavage products.

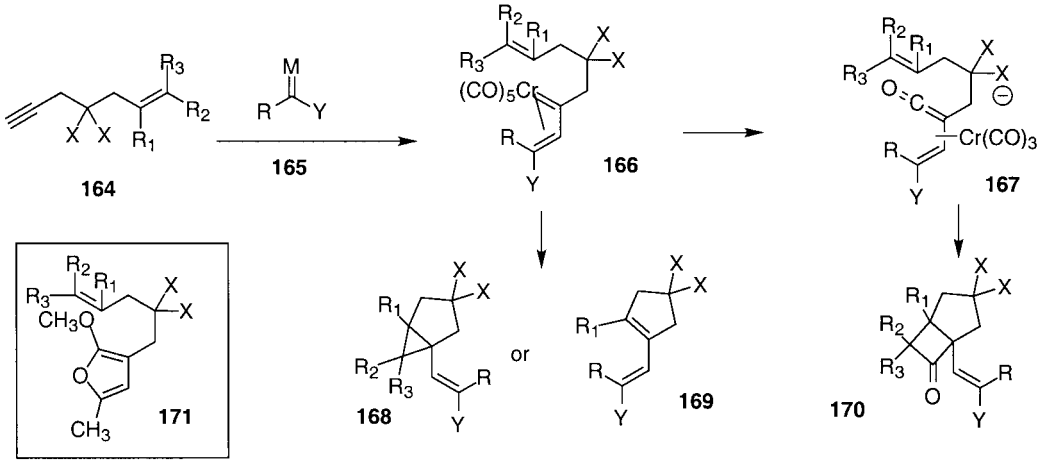
3. Cyclization Processes

3.1. Reaction of active methylene-containing compounds with carbene complexes

Cyclopentanones (**161**–**163**, Scheme 27 and Table 12) are readily produced from the coupling of methylcarbene–chromium complex **157** with alkynes of general structure **156**, which feature an acidic hydrogen at the 5-position (relative to the alkyne).[56] A mechanism involving formation of a vinylketene (**159**), followed by coupling of the ketene with an in-situ generated enolate has been proposed. This reaction is restricted to the highly acidic compounds featuring two electron-withdrawing groups at a single carbon atom. In most cases, the enol ether (**161**) transforms to the corresponding diketone **162** upon purification. In the β-ketoester case (Entry 4 of Table 12), the ketone group is deacylated during attempted purification, resulting in **163**.

3.2. Coupling of 1,6-enynes with carbene complexes

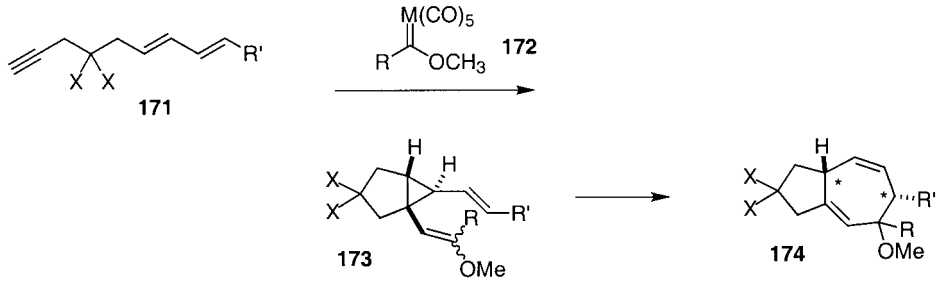
Five-membered rings fused to either three- or four-membered rings are readily prepared from the coupling of simple carbene complexes with derivatives of 1-hepten-6-yne (**164**+**165**→**168**–**170**, Scheme 28 and Table 13); numerous variants of this reaction have been reported using a variety of different types of carbene complexes. Coupling of alkoxycarbene complexes with this class of compounds leads to either bicyclo[3.2.0]heptan-4-one derivatives (**170**) or bicyclo[3.1.0]hexane (**168**) derivatives accompanied by minor amounts of furan (**171**) byproducts. The unsubstituted enyne (**164**, X=H) affords only the cyclobutanone derivatives (Table 12, Entry 1),[57] while the gem diester derivative (**164**, X=COOR, Entries 2–5) affords mostly cyclopropanes (except for Entry 4), accompanied by minor amounts of metathesis product **169**.[58] The two classes of products differ in the timing of the CO insertion and cyclization events for vinylcarbene intermediate **166**; formation of the cyclopropane in the latter case has been



Scheme 28.

Table 13. Cyclization of 1,6-enynes using carbene complexes

Entry	M	Y	R	R_1	R_2	R_3	X	**168** (%)	**169** (%)	**170** (%)	**171** (%)
1	$Cr(CO)_5$	OCH_3	CH_3	H	H	H	H			45	
2	$Cr(CO)_5$	OCH_3	CH_3	H	H	H	COOMe	69			
3	$Cr(CO)_5$	OCH_3	CH_3	CH_3	H	H	COOMe	22	30		
4	$Cr(CO)_5$	OCH_3	CH_3	H	CH_3	H	COOMe	2	6	30	7
5	$Cr(CO)_5$	OCH_3	CH_3	COOMe	H	H	COOMe	64			
6	$Mo(CO)_5$	OCH_3	Bu	COOMe	H	H	H	76			
7	$Cr(CO)_5$	NC_4H_8	CH_3	H	H	H	COOMe	88			
8	$Cr(CO)_5$	NC_4H_8	CH_3	CH_3	H	H	COOMe	58			
9	$Mn(CO)_5Cp$	OCH_3	CH_3	H	H	H	COOMe	71			
10	$Mn(CO)_5Cp$	OCH_3	CH_3	H	CH_3	H	COOMe	65			



Scheme 29.

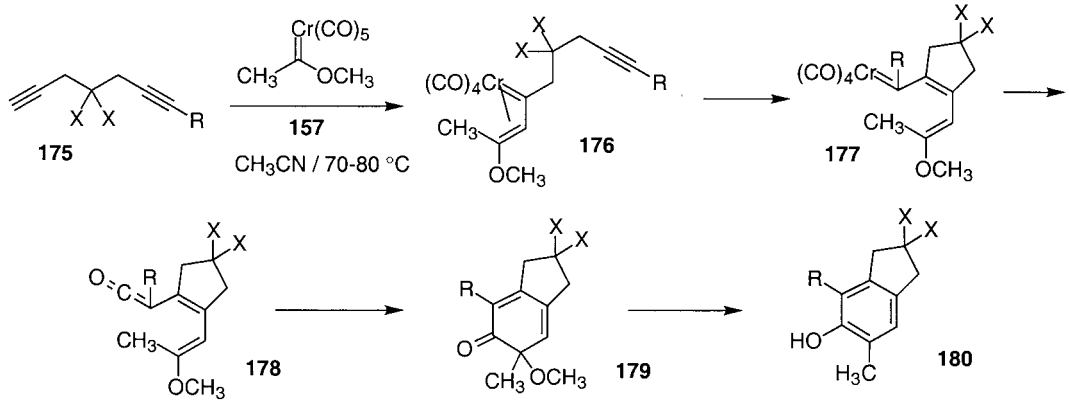
Table 14. Synthesis of hydroazulenes from the coupling of carbene complexes and dienynes (**171**)

Entry	M	X	R	R′	**174** (%)	Stereochemistry
1	Mo	H	Bu	COOMe	87	4.8:1
2	Cr	H	CH_3	COOMe	24	1.2:1
3	Mo	COOMe	Bu	COOMe	81	1.3:1
4	Mo	COOMe	H	H	42[a]	1:1
5	Mo	H	Ph	–CH=CHCOOMe	50	2:1
6	Mo	COOMe	2-Furyl	–CH=CHCOOMe	42	One diastereomer

[a] A metathesis product analogous to **169** of Scheme 28 was also observed in 11% yield.

attributed to faster cyclization due to the Thorpe–Ingold effect provided by the gem diester groups. Efforts to suppress the CO-insertion process through use of electron rich aminocarbene complex analogs (Entries 7 and 8)[59] and manganese (Entries 9 and 10)[60] and molybdenum (Entry 6)[61] carbene complex analogs have been successful. Formation of six-membered rings from 1,7-enynes has also been demonstrated for many of the examples.

If a diene (as in **171**, Scheme 29 and Table 14) is used to trap the initial carbene complex, the resulting divinylcyclopropane (**173**) can undergo rearrangement to the seven-membered ring derivative (**174**); this process leads to the synthetically important hydroazulene ring system in a single step.[62] The reaction is most efficient when molybdenum carbene complexes are employed. The divinylcyclopropane derivatives (**173**) can be isolated in some cases if the carbene–alkyne coupling is performed at 40°C, however only the hydroazulene derivatives (**174**) are observed from the reaction conducted at 60°C. The relative stereochemistry at the asterisked carbons is effectively controlled through stereospecific cyclopropanation followed by Cope

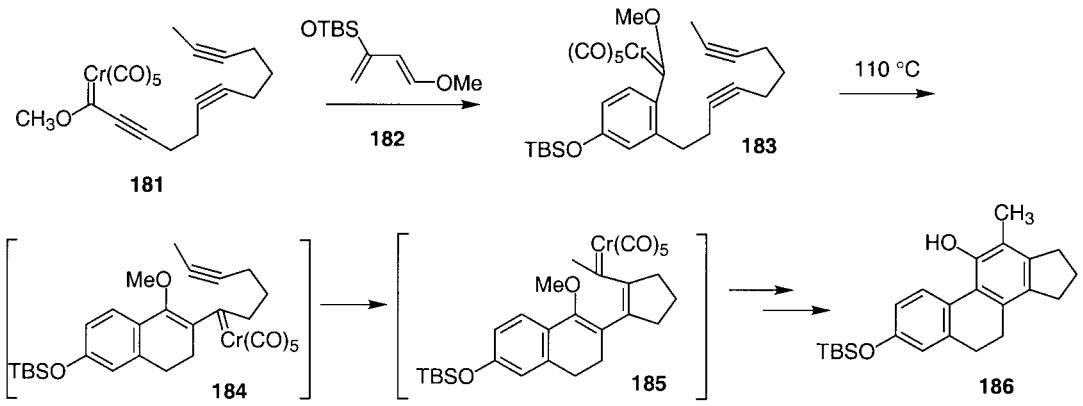


Scheme 30.

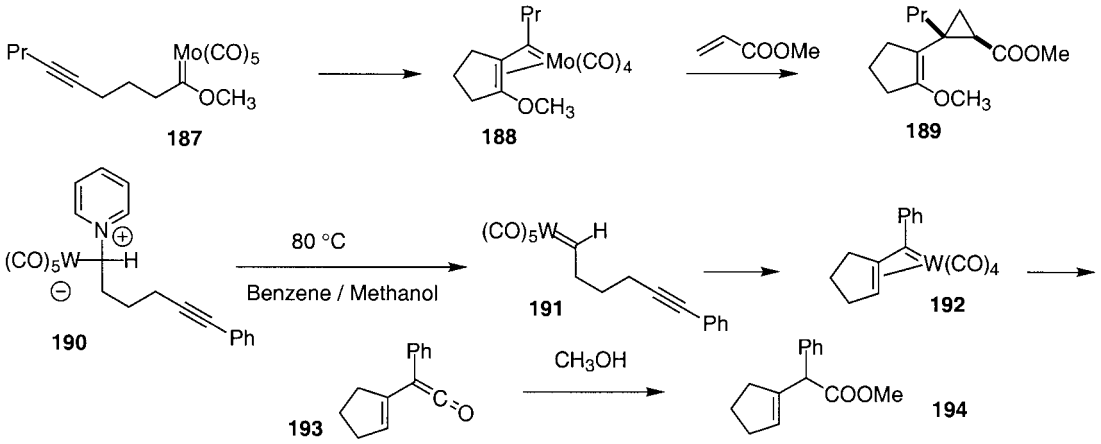
Table 15. Two alkyne annulation processes leading to indene derivatives

Entry	M	X	R	**179** (%)	**180** (%)
1	Cr	H	H		57
2	Cr	COOEt	H		57
3	Mo	H	H	5	62
4	W	COOEt	H		72
5	Cr	H	TMS		73

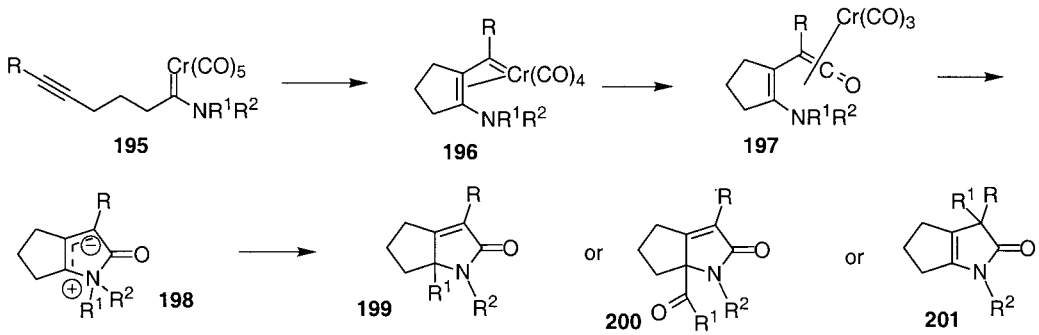
rearrangement through a boat transition state; the stereochemistry at the remaining stereocenter is controlled by the alkene geometry of the enol ether, which is established as in the initial alkyne insertion (i.e. **164**+**165**→**166** in Scheme 28). An intramolecular version of this reaction has also been reported.[63] The coupling proceeds similarly for arylcarbene–molybdenum complexes, however Dötz-type products are the major products from reactions of alkenylcarbene complexes.[39]



Scheme 31.



Scheme 32.

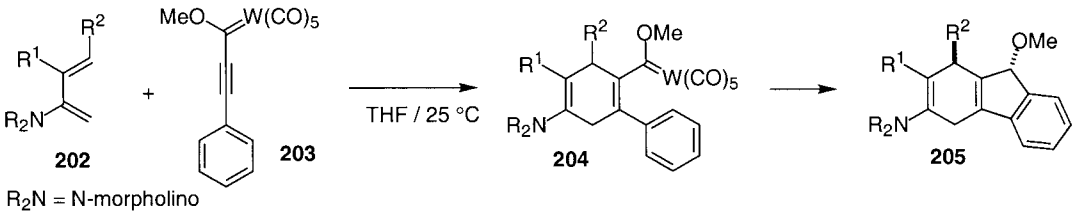


Scheme 33.

Table 16. Synthesis of lactams via the intramolecular alkyne–aminocarbene coupling

Entry	R	R^1	R^2	**199** (%)	**200** (%)	**201**	**198** (%)
1	Ph	$PhCH_3$	Me	9	47[a]		
2	Ph	R_1,R_2=–$(CH_2)_3$–		31	12		
3	Ph	R_1,R_2=–CH_2CH=$CHCH_2$–		15			
4	Ph	R_1,R_2=–$(CH_2)_4$–		13[b]			45

[a] Total yield complexed+uncomplexed phenyl ring.
[b] Obtained through treatment of the stable ylide with oxygen and light.



Scheme 34.

Table 17. Synthesis of indenes (**205**) via tandem Diels–Alder and cyclopentannulation reactions

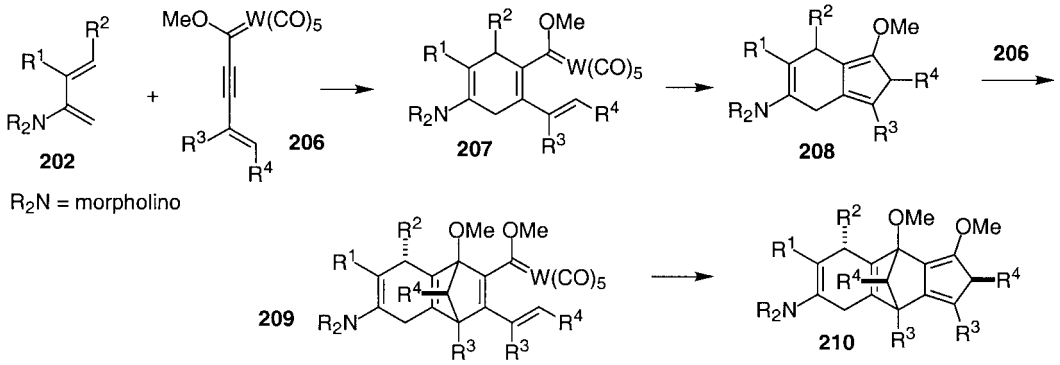
Entry	R^1	R^2	**205** (%)
1	Me	H	95
2	Me	CH_2OMe	95
3	R^1,R^2=–$(CH_2)_4$–		92

3.3. Two-alkyne annulations

Coupling of carbene complex **157** and 1,6-diynes (**175**) (Scheme 30 and Table 15) also leads to five-membered ring derivatives (**179** and **180**) according to the mechanism in Scheme 30.[64] Generation of a vinylcarbene complex (**176**) in situ via coupling of the carbene complex with the less substituted alkyne, followed by intramolecular coupling with the remaining alkyne affords the divinylcarbene complex (**177**), which cyclizes to a six-membered **179** as was proposed for the Dötz reaction in Scheme 1. Reduction of cyclohexadienone **179** by the low oxidation state chromium byproducts then affords the phenol products (**180**). The cyclohexadienone derivatives can be isolated from the reaction, however the phenol derivatives are the exclusive products upon extended reaction time. The six-membered ring forming analog of this reaction is considerably less efficient. The reaction has been used as the cornerstone of a novel approach to the steroid ring system (Scheme 31).[65] Trialkynylcarbene complex **181** is transformed to a steroid derivative in two-steps: (1) Diels–Alder reaction with diene **182** followed by (2) intramolecular two-alkyne annulation.

3.4. Intramolecular alkyne–carbene coupling

Thermolysis of a 5-alkynylcarbene complex (e.g. **187** or **191**, Scheme 32) typically leads to cyclopentenylcarbene derivatives (**188** or **192**), which can then undergo various trapping reactions. Thermolysis of alkyne–carbene complex **187** in the presence of methyl acrylate afforded the cyclopropylcyclopentene derivative **189** in 71% yield as a 2.5:1 mixture (major isomer depicted).[66] Thermolysis of the ylide **190** leads to the unstable hydridocarbene complex **191**, which undergoes the intramolecular insertion and CO insertion to provide the vinylketene derivative **193**, which can be trapped by alcohols (to afford ester **194**) and alkenes.[67] The most thoroughly studied version of this reaction is the intramolecular coupling of aminocarbene–chromium complexes and alkynes (Scheme 33 and Table 16 **195→199–201**). Thermolysis of **195** initially affords nitrogen ylide derivatives (**198**), which subsequently undergo Stevens-type rearrangements to afford lactam derivatives **199–201**.[68] This reaction is also efficient for the formation of six-membered ring analogs.



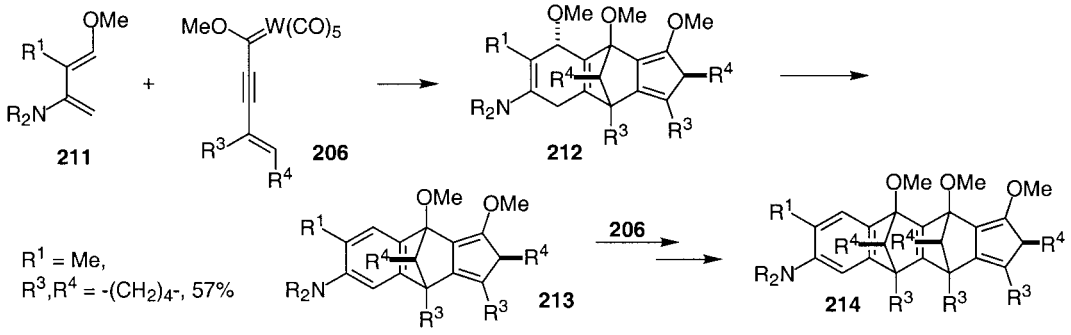
Scheme 35.

Table 18. Tandem Diels–Alder-cyclopentannulation reactions of alkynylcarbene complexes

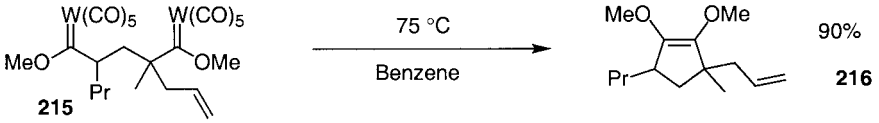
Entry	R^1	R^2	R^3	R^4	**210** (%)
1	Me	H	H	Ph	95
2	Me	H	Me	Ph	67
3	Me	CH_2OMe	R^3,R^4=–$(CH_2)_4$–		85
4	R^1,R^2=–$O(CH_2)_3$–		R^3,R^4=–$(CH_2)_4$–		87

3.5. Cyclization of dienylcarbene complexes

Phenylethenylcarbene complexes (**204**, Scheme 34 and Table 17) and dienylcarbene complexes (**207**, Scheme 35 and Table 18) featuring a *Z* central alkene geometry undergo conversion to the corresponding cyclopentadienes (**205** or **208**) upon mild heating.[69–71] These complexes are easily



Scheme 36.

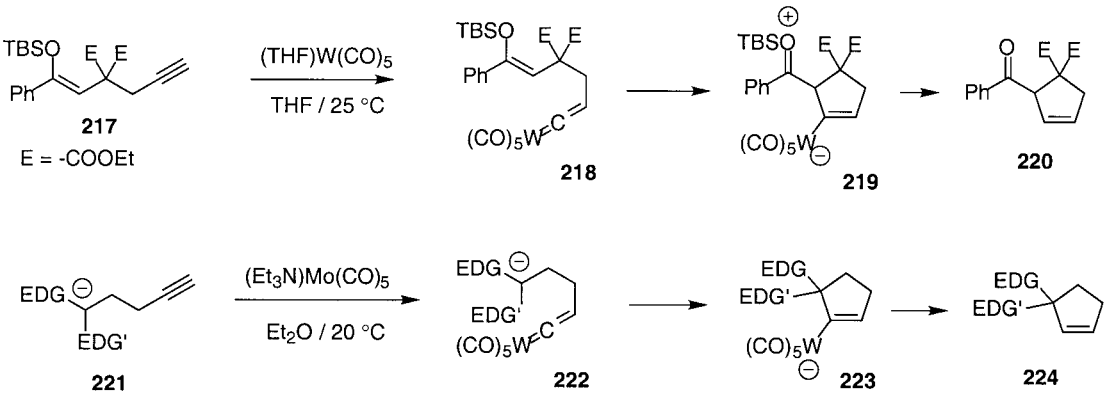


Scheme 37.

generated through coupling of aminobutadienes (**202**) with phenylethynylcarbene (**203**) or vinylethynylcarbene (**206**) complexes, and undergo cyclization to a five-membered ring in situ when the coupling reactions were conducted at room temperature in THF. Alternatively phenylethenylcarbene complexes (which also cyclize) can be generated by addition of secondary phosphines to alkynylcarbene complexes,[72] or by methylation of propargyltungsten anions.[73] In cyclization reactions of vinylcarbene complexes (Scheme 35), the same reaction conditions lead to the norbornene derivatives (**210**), which result from Diels–Alder reaction of the initially generated cyclopentadiene **208** and the starting alkynylcarbene complex, followed by cyclization. If the six-membered ring of **209** is aromatic (as in **213**, Scheme 36) Diels–Alder reaction-cyclization can occur with a third equivalent of the alkenylcarbene complex.

3.6. Intramolecular carbene dimerization

A single but high-yielding example of the intramolecular decomposition of bis carbene complexes (e.g. **215**, Scheme 37) has been reported. Complex **215**, which is very readily obtained through Michael addition of a carbene complex-stabilized anion to an α,β-unsaturated carbene complex, forms exclusively the dimer (**216**) upon thermolysis at 75°C.[74]



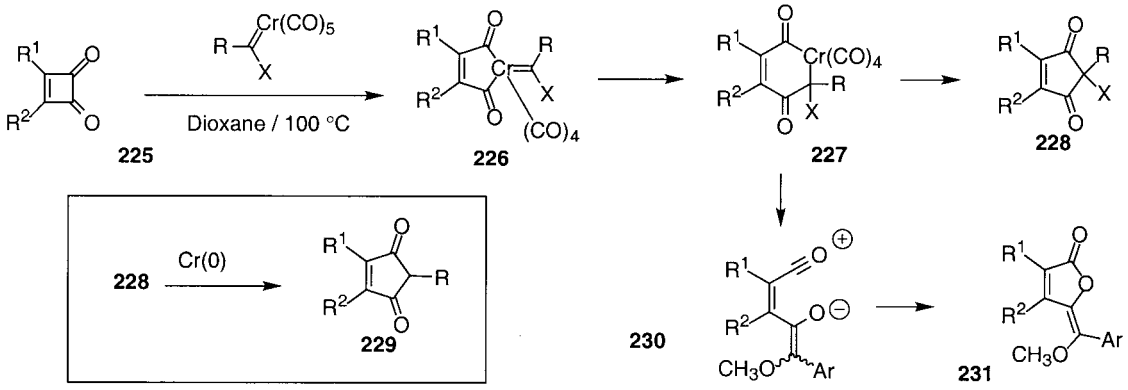
Scheme 38.

Table 19. Cyclization of 1,3-dicarbonyl-alkyne derivatives (**221**) to cyclopentenes (**224**)

Entry	EDG	EDG′	**224** (%)
1	COOMe	COOMe	60
2	COOMe	COMe	42
3	COMe	COMe	57

3.7. Generation/capture of metal vinylidene complexes

The reaction of enol ether-terminal alkyne **217** with $(THF)W(CO)_5$ affords cyclopentene **220**.[75] Cyclopentene derivative **220** is formed via conversion of the terminal alkyne to vinylidene **218** followed by intramolecular nucleophilic attack by the enol ether (Scheme 38). In a mechanistically similar process, treatment of alkynes of

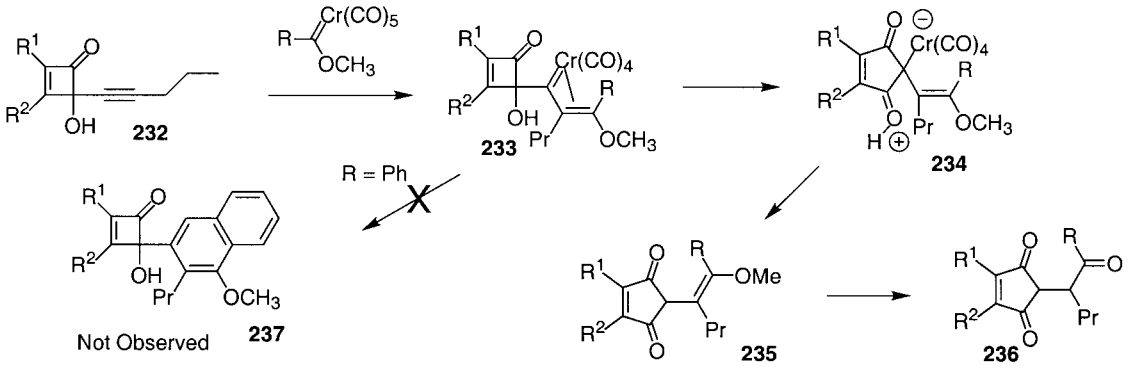


Scheme 39.

Table 20. Coupling of cyclobutenediones with carbene complexes

Entry	R	R^1	R^2	X	**228** (%)	**229** (%)	**231** (%)
1	CH_3	*i*-PrO	*i*-PrO	OCH_3	31	14	
2	CH_3	*i*-PrO	*i*-PrO	$N(CH_3)_2$	12		
3	Cyclopropyl	*i*-PrO	*i*-PrO	OCH_3	34	17	
4	CH_3	*i*-PrO	CH_3	OCH_3	25	16	
5	CH_3	Ph	CH_3	OCH_3	20	15	
6	Ph	*i*-PrO	CH_3	OCH_3	20	21	14
7	Ph	*i*-PrO	*i*-PrO	OCH_3			55

general structure **221** with $(Et_3N)Mo(CO)_5$ affords cyclopentenes of general structure **224** (Table 19).[76] In this reaction process, 0.5 equiv. of anion **221** is generated from the corresponding 1,3-dicarbonyl compound and sodium hydride; the proton required in the final step (**223→224**) comes from the 1,3-dicarbonyl compound. The reaction is somewhat catalytic in that 0.5 equiv. of base and molybdenum complex are used in the conversion of **221** to **224**. The reaction is similarly efficient for the preparation of six-membered ring homologues.



Scheme 40.

Table 21. Synthesis of cyclobutenediones via coupling alkynylcyclobutenones and carbene complexes

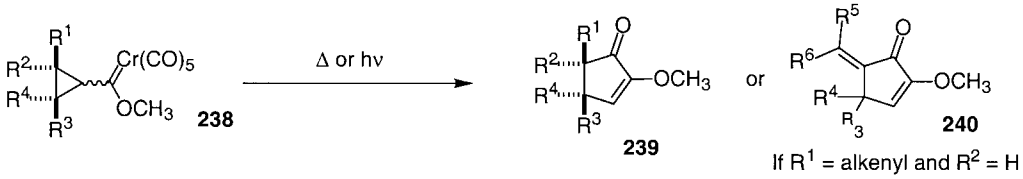
Entry	R	R_1	R_2	**235** (%)	**236** (%)
1	CH_3	*i*-PrO	*i*-PrO	72	
2	Ph	*i*-PrO	*i*-PrO		72
3	Cyclopropyl	*i*-PrO	*i*-PrO		66
4	$CH_3CH{=}CH{-}$	*i*-PrO	*i*-PrO	60[a]	
5	CH_3	*i*-PrO	CH_3		58[b]

[a] A 2:1 mixture of **235** and a 1,5-hydrogen shift product (2-alkylidene-4-cyclopentene-1,3-dione) is obtained.
[b] A 2.2:1 mixture of diastereomers is obtained.

4. Ring Expansion Processes

4.1. Reaction of cyclobutenediones with carbene complexes

The reaction of cyclobutenediones (**225**, Scheme 39 and Table 20) with Fischer carbene–chromium complexes leads to cyclopentenedione derivatives (**228** and **229**).[77,78] The reaction is general for alkylcarbene complexes, however the reaction involving arylcarbene complexes (Entries 6 and 7) affords mixtures of cyclopentenediones and 5-alkylidenefuranones (**231**). The reaction mechanism



Scheme 41.

Table 22. Synthesis of 2-alkoxycyclopentenones from ring expansion of cyclopropylcarbene complexes (unless otherwise noted, all thermolyses were conducted in refluxing dioxane)

Entry	R^1	R^2	R^3	R^4	R^5	R^6	**239** (%)	**240** (%)
1	$-CH=CH_2$	CH_3	H	H			43 (68)[a]	
2	Ph	CH_3	H	H			27	
3	1-Cyclopentenyl	H	H	H	$R^5,R^6=-(CH^2)^4-$			69
4	$-CH=CHCH_3$	H	H	CH_3	H	CH_2CH_3		53
5	$-CH=CHPh$	CH_3	H	D			35	
6	$-CH=CH_2$	CH_3	H	CH_3			53	
7	$-CH=CH_2$	CH_3	CH_3	H			25[b]	
8[c]	$-CH=CH_2$	H	CH_3	CH_3			83	
9[c]	H	H	H	H			68	

[a] Yield in DMF at 100°C.
[b] The reaction is not stereospecific, a 60:40 mixture of *trans* methyl/*cis* methyl is obtained.
[c] Photochemical reaction.

involves oxidative addition into the acyl–acyl bond of the cyclobutenedione, followed by an acyl shift process (**226→227**) and reductive elimination. A secondary reduction process induced by low-valent chromium accounts for the formation of deoxygenated cyclopentenedione **229**. Alkylidenefuranone formation has been attributed to ionization of the C–Cr bonds (**227→230**) followed by *O*-acylation of the enolate intermediate. The coupling is facile only for alkoxycarbene complexes; only a low yield of product is observed for the aminocarbene complex (Entry 2). The best product yields are obtained for the dioxygenated cyclobutenedione derivative; this observation has been attributed to instability of the non-oxygenated cyclobutenedione derivatives. No other four-membered ring systems undergo this type of reactivity. Only one other ring system, cyclopropenones, undergoes a similar two-component ring expansion process.[79]

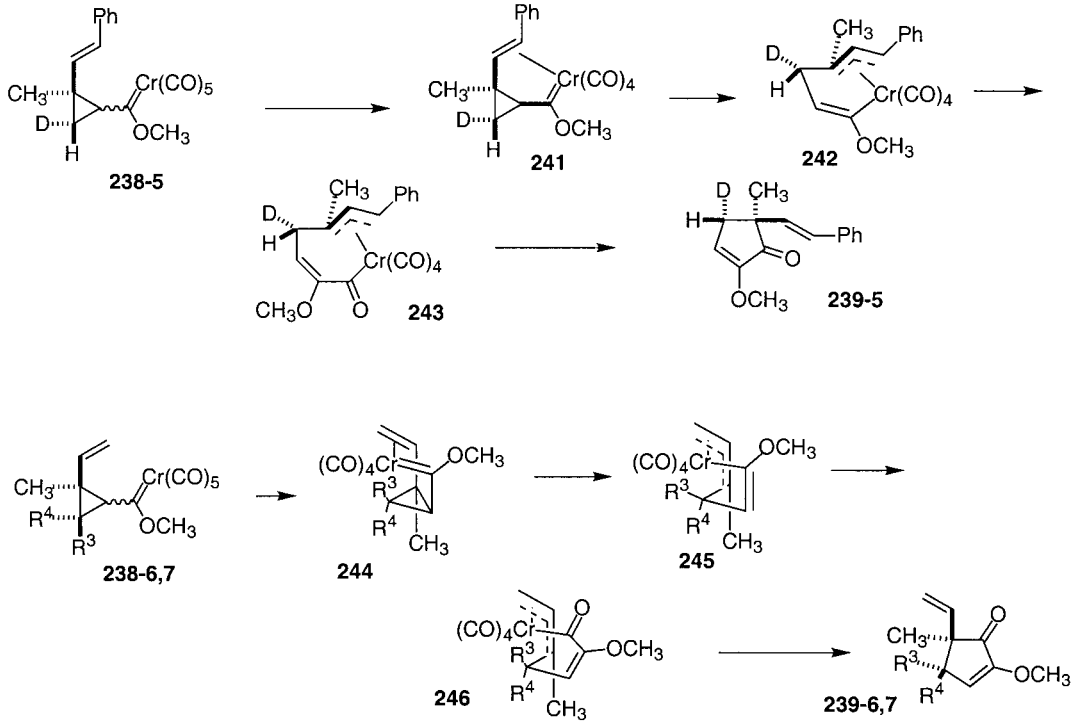
4.2. Reaction of alkynylcyclobutenols with carbene complexes

The coupling of alkynylcyclobutenols (**232**, Scheme 40 and Table 21), readily derived from cyclobutenedione **225**, with Fischer carbene–chromium complexes leads to five-membered ring derivatives (**235**).[80] A mechanism involving alkyne insertion, leading to the unstable but electrophilic vinylcarbene complex intermediate **233**, followed by acyl migration to the electrophilic carbene carbon and demetallation has been proposed. The reaction process is general for a variety of carbene complexes, including alkylcarbene, arylcarbene, vinylcarbene, and cyclopropylcarbene complexes. This reaction is unique to the cyclobutenedione-derived systems; other related systems, including the saturated cyclobutane ring system do not undergo the analogous reaction process. In most cases, the crude enol ether has been subjected to a hydrolysis procedure prior to final purification, and the yield for triketone **236** is reported. In cases where there is competition from Dötz-type reaction pathways (Entries 2 and 4), the ring expansion pathway is the exclusive reaction pathway.

4.3. Thermolysis and photolysis of cyclopropylcarbene–chromium complexes

Thermolysis of certain cyclopropylcarbene complexes (**238**, Scheme 41 and Table 22) leads to 2-alkoxy-2-cyclopentenone derivatives (**239**).[81] The thermal ring expansion reaction appears to be unique to 2-alkenylcyclopropylcarbene complexes (R^1 or R^2=alkenyl). Several trends have been noted. The reaction of the complexes featuring *cis* alkene and carbene groups are considerably more reactive than the *trans* isomers. Second, the reaction appears to be stereospecific in most cases (Entries 5 and 6, but not Entry 7),[82] and in a sterically unbiased system (Entry 5) the reaction appears to proceed with complete retention of stereochemistry. In cases where there is a proton at the 2-position of the cyclopropane ring (Entries 3 and 4), predominantly the conjugated isomer (**240**) is obtained after purification. The conversion of cyclopropylcarbenes to 2-alkoxy-2-cyclopentenones can also be induced by photolysis (entries 8 and 9).[83] In this case, even the simple unsubstituted cyclopropylcarbene complex (**238**, all R groups=H) is efficiently transformed to the corresponding cyclopentenone.

The mechanism depicted in Scheme 42 has been proposed for the thermal ring expansion process. The photochemical process is though to occur via conversion of the corresponding carbene complex to the ketene complex, followed by rearrangement of the cyclopropylketene. Initially, CO dissociation followed by alkene complexation affords internally-coordinated complex **241**, which undergoes a Cope-like process to generate internally coordinated π-allyl complex **242**. CO insertion and reductive elimination



Scheme 42.

then affords vinylcyclopentenone **239**. These events are consistent with key observations, including: (1) the reaction is inhibited by external CO or triphenylphosphine (CO dissociation is the first step); (2) the reaction is considerably more facile for alkenylcyclopropylcarbene complexes than for arylcyclopropylcarbene complexes (coordination of the alkene is required); (3) the isomer where the carbene complex and alkene are *cis* is kinetically more reactive (the *trans* alkene is too far away); and (4) the reaction proceeds with retention of stereochemistry (π-allyl complex formation and reductive elimination each occur with retention of configuration). One case (Entry 7 of Table 22) did not proceed with retention of stereochemistry, and the mechanistic/conformational picture in Scheme 42 may account for this observation. If R^3 in **238-6,7** is not equal to H, it is difficult for the π-bonds to attain the *endo* conformation (depicted by structure **244** of Scheme 42), thus ring expansion by the mechanism in Scheme 42 is inhibited. The reaction in Entry 7, where R^3=CH_3, is considerably slower and lower yielding than the reaction in Entry 6, where R^3=H. This conformational dependence has been supported through studies of conformationally locked derivatives.[84]

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References

1. Since 1996: (a) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187–198. (b) Wulff, W. D. *Organometallics* **1998**, *17*, 3116–3134. (c) Harvey, D. F.; Sigano, D. M. *Chem. Rev. 1996*, *96*, 271–288. (d) Aumann, R.; Nienaber, H. *Adv. Organometal. Chem.* **1997**, *41*, 163–242. (e) Hegedus, L. S. *Tetrahedron* **1997**, *53*, 4105–4128.

2. Wulff, W. D. In *Comprehensive Organic Synthesis*, Trost, B. M., Fleming, I., Paquette, L. A. Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1065–1113.

3. Brookhart, M. S.; Studebaker, W. B. *Chem. Rev.* **1987**, *87*, 411–432.

4. For general discussions of synthetic approaches to five-membered rings, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41–165. (b) Ramaiah, M. *Synthesis* **1984**, 529–570. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141–170.

5. Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organometal. Chem.* **1987**, *334*, 9–56.

6. Hofmann, P.; Haemmerle, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 908–910.

7. Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang,

D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41* 5813–5832. See also Ref. 5.
8. Dötz, K. H.; Dietz, R.; Kappenstein, D.; Neugebauer, D.; Schubert, V. *Chem. Ber.* **1979**, *112*, 3682–3690.
9. Bos, M. E.; Wulff, W. D.; Miller, R. A.; Chamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293–9319.
10. Grotjahn, D. B.; Kroll, F. E. K.; Schaefer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, *11*, 298–310.
11. Waters, M. L.; Bos, M. E.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 6403–6413.
12. Yamashita, A. *Tetrahedron Lett.* **1986**, *27*, 5915–5918.
13. Alvarez, C.; Parlier, A.; Rudler, H.; Yefsah, R.; Daran, J. C.; Knobler, C. *Organometallics* **1989**, *8*, 2253–2259.
14. Rahm, A.; Wulff, W. D. *Tetrahedron Lett.* **1995**, *36*, 8753–8756.
15. Wulff, W. D.; Gilbert, A. M.; Rahm, A. *J. Org. Chem.* **1995**, *60*, 4566–4575.
16. de Meijere, A. *Pure Appl. Chem.* **1996**, *68*, 61–72.
17. Flynn, B. L.; Funke, F. J.; Silveira, C. C.; de Meijere, A. *Synlett* **1992**, 1007–1010.
18. Flynn, B. L.; de Meijere, A. *J. Org. Chem.* **1999**, *64*, 400–404.
19. Flynn, B. L.; Silveira, C. C.; de Meijere, A. *Synlett* **1995**, 812–814.
20. Duetsch, M.; Vidini, S.; Stein, F.; Funke, F.; Noltemeyer, M.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1994**, 1679–1680.
21. Stein, F.; Duetsch, M.; Noltemeyer, M.; de Meijere, A. *Synlett* **1993**, 486–488.
22. Stein, F.; Duetsch, M.; Lackmann, R.; Noltemeyer, N.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1658–1660.
23. Schirmer, H.; Duetsch, M.; Stein, F.; Labahn, T.; Knieriem, B.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1285–1287.
24. Wulff, W. D.; Bax, B. M.; Brandvold, T. A.; Chan, K. S.; Gilbert, A. M.; Hsung, R. P.; Mitchell, J.; Clardy, J. *Organometallics* **1994**, *13*, 102–126.
25. Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994**, *116*, 6719–6732.
26. Foley, H. C.; Strubinger, L. M.; Targos, T. S.; Geoffrey, G. L. *J. Am. Chem. Soc.* **1983**, *105*, 3064–3073.
27. Aumann, R.; Heinen, H.; Mechthild, D.; Krebs, B. *Chem. Ber.* **1991**, *124*, 2343–2347.
28. Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394–8404.
29. Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, *38*, 59–62.
30. Herndon, J. W.; Zora, M.; Patel, P. P.; Chatterjee, G.; Matasi, J. J.; Tumer, S. U. *Tetrahedron* **1993**, *53*, 5507–5530.
31. Herndon, J. W.; Matasi, J. J. *J. Org. Chem.* **1990**, *55*, 786–788.
32. Herndon, J. W.; Yan, J. *J. Org. Chem.* **1998**, *63*, 2325–2331.
33. Yan, J.; Zhu, J.; Matasi, J. J.; Herndon, J. W. *J. Org. Chem.* **1999**, *64*, 1291–1301.
34. Herndon, J. W.; Zhu, J. *Org. Lett.* **1999**, *1*, 15–18.
35. For the only other example, see Kascheres, A.; Kascheres, C.; Braga, A. C. H. *J. Org. Chem.* **1993**, *7* 1702–1703.
36. Herndon, J. W.; Hayford, A. *Organometallics* **1995**, *14*, 1556–1558.
37. Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S. A.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359–1376.
38. Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424–8434.
39. Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994**, *116*, 6719–6732.
40. Chelain, E.; Parlier, A.; Audoin, M.; Rudler, H.; Daran, J. C.; Vaissermann, J. *J. Am. Chem. Soc.* **1993**, *115*, 10 568–10 580.
41. Xu, Y.-C.; Challener, C. A.; Dragisch, V.; Brandvold, T. A.; Peterson, G. A.; Wulff, W. D. *J. Am. Chem. Soc.* **1989**, *111*, 7269–7271.
42. Aumann, R.; Meyer, A. G.; Fröhlich, R. *Organometallics* **1996**, *15*, 5018–5027.
43. Meyer, A. G.; Aumann, R. *Synlett* **1995**, 1011–1013.
44. Aumann, R.; Kössmeier, M.; Jäntti, A. *Synlett* **1998**, 1120–1122.
45. Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Brillet, C.; García-Granda, S.; Piñera-Nicolas, A.; Vázquuez, J. T. *J. Am. Chem. Soc.* **1999**, *121*, 4516–4517.
46. Wienand, A.; Reissig, H.-U. *Chem. Ber.* **1991**, *124*, 957–965.
47. Hoffman, M.; Reissig, H.-U. *Synlett* **1995**, 625–627.
48. Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660–5662.
49. Hoffman, M.; Buchert, M.; Reissig, H. -U. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 283–285.
50. Aumann, R.; Uphoff, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 357–359.
51. Aumann, R.; Trentmann, B. *Chem. Ber.* **1991**, *124*, 2335–2342.
52. Dötz, K. H.; Christoffers, C.; Knochel, P. *J. Organometal. Chem.* **1995**, *489*, C84–C86.
53. Fischer, H.; Meisner, T.; Hofmann, J. *Chem. Ber.* **1990**, *123*, 1799–1804.
54. Aumann, R.; Heinen, H. *Chem. Ber.* **1985**, *118*, 4186–4195.
55. Aumann, R.; Heinen, H. *Chem. Ber.* **1986**, *119*, 3801–3811.
56. Ishibashi, T.; Mori, M. *J. Org. Chem.* **1997**, *62*, 7058–7060.
57. Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461–1463.
58. Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, 2676–2678.
59. Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 3014–3015.
60. Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 2070–2071.
61. Harvey, D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311–6314.
62. Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066–5068.
63. Harvey, D. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559–5561.
64. Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P.-C. *J. Am. Chem. Soc.* **1985**, *107*, 1060–1062.
65. Bao, J. M.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616–7630.
66. Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990**, *112*, 7807–7809.
67. Martín-Vaca, B.; Rudler, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3119–3121.
68. Chelain, E.; Goumont, R.; Hamon, L.; Parlier, A.; Rudler, M.; Daran, J. C.; Vaissermann, J. *J. Am. Chem. Soc.* **1992**, *114*, 8088–8098.
69. Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S.; Piñera-Nicolás, A. *Chem. Eur. J.* **1998**, *4*, 2280–2298.
70. Barluenga, J.; Aznar, F.; Barluenga, S. *J. Chem. Soc., Chem. Commun.* **1995**, 1973.
71. Barluenga, J.; Aznar, F.; Barluenga, S.; Martín, A.; García-Granda, S.; Martín, E. *Synlett* **1998**, 473.

72. Aumann, R.; Jasper, B.; Fröhlich, R. *Organometallics* **1995**, *14*, 231–238.
73. Barluenga, J.; Trabanco, A. A.; Flörez, J.; García-Granda, S.; Llorca, M.-A. *J. Am. Chem. Soc.* **1998**, *120*, 12 129–12 130.
74. Macomber, D. W.; Hung, M. -H.; Verma, A. G.; Rogers, R. D. *Organometallics* **1988**, *9*, 2072–2074.
75. Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929.
76. McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691–7692.
77. Zora, M.; Herndon, J. W. *Organometallics* **1993**, *11*, 249–250.
78. Zora, M.; Li, Y.; Herndon, J. W. *Organometallics* **1999**, *18*, 4429–4436.
79. Zora, M.; Herndon, J. W. *Organometallics* **1994**, *12*, 3370–3374.
80. Zora, M.; Herndon, J. W. *J. Org. Chem.* **1994**, *59*, 699–701.
81. Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 6854–6856.
82. Herndon, J. W.; Hill, D. K.; McMullen, L. A. *Tetrahedron Lett.* **1995**, *36*, 5687–5690.
83. Moser, W. H.; Hegedus, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 7873–7880.
84. Hill, D. K.; Herndon, J. W. *Tetrahedron Lett.* **1996**, *37*, 1359–1362.

Biographical Sketch

James Herndon was born in 1957 in North Carolina, and obtained his BS in Chemistry from the University of North Carolina at Greensboro in 1979, where he conducted research in the laboratory of Professor J. C. Barborak. He immediately entered graduate school at Princeton University, working under the direction of Professor M. F. Semmelhack in the areas of organic synthesis and organometallic chemistry, and obtained his PhD in 1983. He then worked as an NIH postdoctoral fellow in the laboratory of Professor B. M. Trost at the University of Wisconsin-Madison. Professor Herndon began his academic career at the University of Maryland-College Park in 1985 as an Assistant Professor and was promoted to Associate Professor in 1991. In 1997, he moved to New Mexico State University, where he is now Associate Professor of Chemistry.