Carbene–Alkyne–Alkene Cyclization Reactions

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Contents

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I. Introduction

Over the last several decades, our understanding of the reactivity of organotransition metal complexes has improved tremendously. Many organotransition-metal-based processes are now widely utilized in connection with the total synthesis of structurally complex natural products. Today it is rare to find a completed total synthesis that does not use a transition-metal-based reaction to accomplish at least one critical transformation. Transition-metal-based reactions are often employed because they frequently exhibit higher levels of chemo-, regio-, and stereoselectivity than more conventional methodologies. In other situations they are advantageous because of their capability to create several new bonds in one reaction process.

The reactivity of alkylidene (carbene) complexes has been extensively investigated and a number of general and useful transformations have been reported.[1] Many transition metal carbene complexes readily react with alkynes, generally resulting in the formation of vinylcarbene complex intermediates (eq 1).

Carbene complexes also react with alkenes, often via [2 + 2] cyclization to generate a metallacyclobutane intermediate. Such an intermediate can un-

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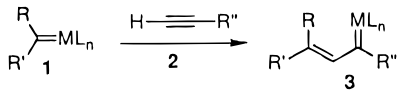
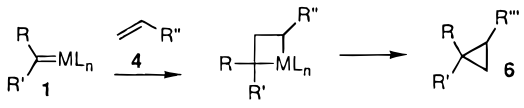


(eq. 1)

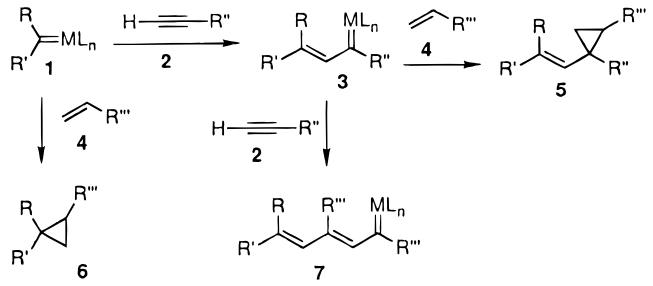
dergo a variety of subsequent transformations, one of which is reductive elimination to form a cyclopropane ring (eq 2).



(eq. 2)

The feasibility of combining the reactivity of transition metal carbene complexes with alkynes with their reactivity toward alkenes (Scheme 1) has at-

Scheme 1



tracted the attention of a variety of investigators and is the primary subject of this review. Initial reaction of carbene complex **1** with an alkyne (**2**) leads to vinylcarbene complex **3**. Subsequent reaction of **3** with alkene **4** leads to vinylcyclopropane **5**. This three-component coupling reaction represents a rapid approach to highly functionalized vinylcyclopropane systems.

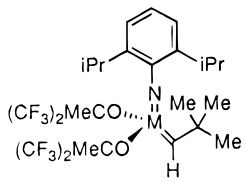
There are some obvious difficulties inherent in the development of a three-component coupling reaction of this type. Initially, reaction of complex **1** with alkyne **2**, leading to vinylcarbene complex **3**, must be favored over direct cyclopropanation of the alkene (**4**) to give **6**. Similarly, once vinylcarbene **3** has been formed, reaction of **3** with **4** must be favored over reaction of **3** with additional equivalents of the alkyne (**2**), leading to oligomer **7**. In this review, the reactivity of carbene complexes with alkynes (eq 1) and carbene complexes with alkenes (eq 2) will be discussed and examples of carbene−alkyne−alkene three-component coupling reactions (Scheme 1) will be presented. Additionally, some of the factors which influence the viability of this termolecular pathway will be analyzed.

II. Reactions of Carbene Complexes with Alkynes

Carbene complexes are capable of reacting with alkynes to form a diverse array of structurally interesting compounds. The products produced have been found to vary considerably depending on the metal employed and the ancillary ligands that are present. In some cases, alkyne polymerization occurs, leading to the formation of polyacetylene systems. While in other cases, isolable alkyne addition products are obtained. Frequently, when ancillary carbon monoxide ligands are present, CO insertion occurs, resulting in the formation of a vinylketene intermediate, which leads to a variety of novel structural classes.

Polymerization

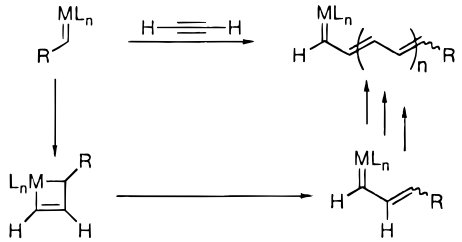
Alkynes can be polymerized by a number of different transition metal catalysts. Systems analogous to olefin metathesis catalysts catalyze alkyne polymerization via a mechanism believed to involve direct insertion of an alkyne into a vinylmetal intermediate.[2] Schrock and co-workers have shown that alkynes can also be polymerized by isolable alkylidene complexes such as **8a**,**b**.[3] Indirect evidence



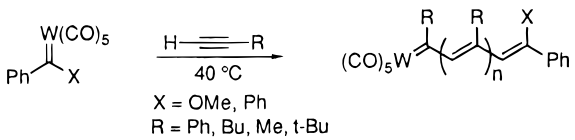
8a M = Mo
8b M = W

suggests that these complexes catalyze alkyne polymerization via an "alkylidene mechanism" wherein the alkyne reacts with the M=C bond to form a metallacyclobutene intermediate. Subsequent rearrangement results in the formation of a vinylalkylidene complex (Scheme 2).

Scheme 2

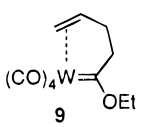


Tungsten Fischer carbene complexes are also capable of catalyzing the polymerization of alkynes.[4,5] In catalytic amounts, olefin-chelated Fischer carbene complexes, such as **9**, react with alkynes at room temperature to give linear polyenes.[6]



X = OMe, Ph
R = Ph, Bu, Me, t-Bu

(eq. 3)



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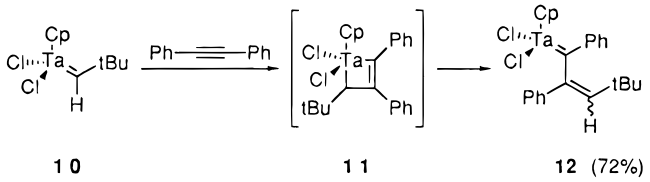
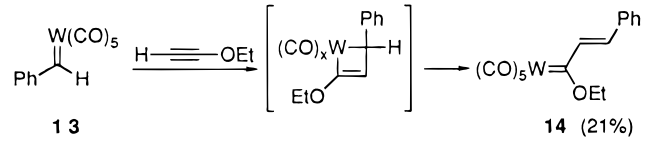
Alkyne Insertion

In some cases, transition metal carbene complexes react with alkynes to give discreet insertion products without subsequent polymerization. For example, diphenylacetylene reacts with tantalum carbene complex **10** to give insertion product **12**[7] (Scheme 3). This reaction is thought to proceed through nonisolable metallacyclobutene intermediate **11**. The interme-

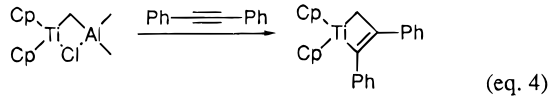
Scheme 3



Scheme 4

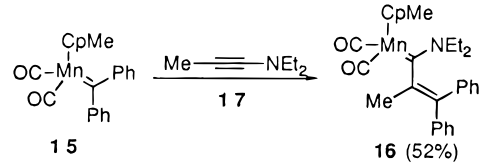


diacy of metallacyclobutenes in this reaction is supported by the observation that isolable metallacyclobutenes are obtained upon treatment of diphenylacetylene with Tebbe's reagent (eq 4).[8,9,10]



(eq. 4)

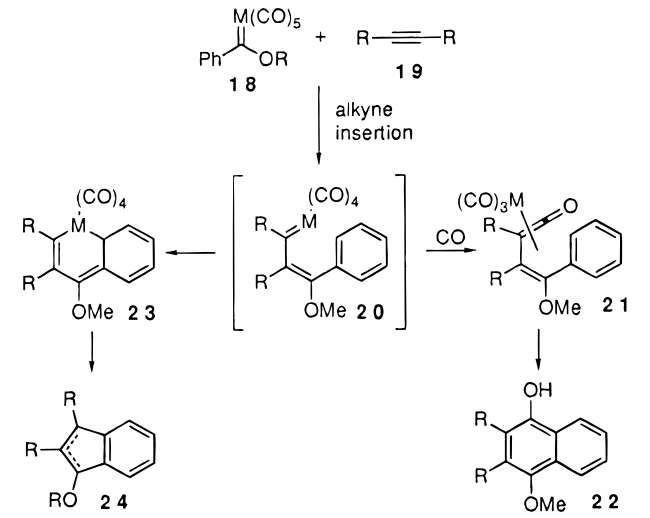
Tungsten carbene complex **13** reacts with ethoxyacetylene to produce styrylethoxycarbene complex **14**[11] (Scheme 4). This reaction is also envisioned to proceed through a metallacyclobutene intermediate. Similarly, Dötz has shown that *N*,*N*-diethylaminopropyne (**17**) will insert into the manganese-carbon double bond of **15** to give vinylcarbene complex **16**.[12]



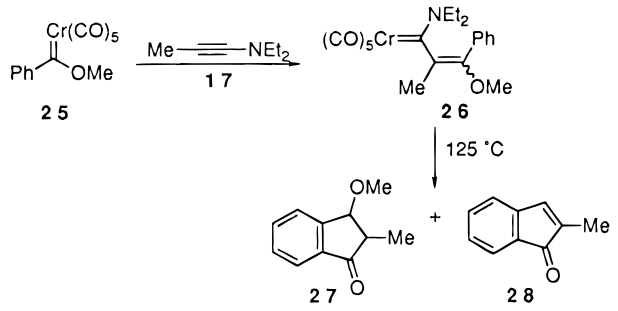
Insertion of Alkynes and CO

Dötz described the reaction of arylmethoxycarbene complexes with diphenylacetylene to give naphthols and indenes in 1975[13,14] (Scheme 5). The key step of this cyclization reaction is the formation of vinylcarbene intermediate **20**. From **20** there is competition between CO insertion, to form vinylketene complex

Scheme 5



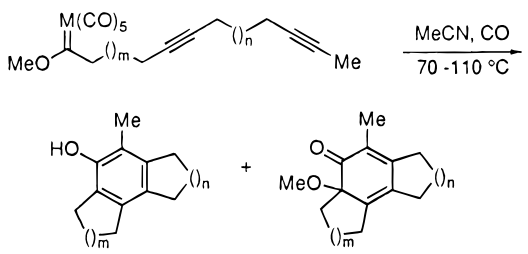
Scheme 6



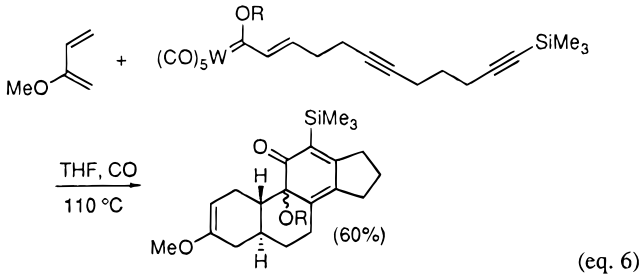
21, which subsequently cyclizes to hydroquinone derivative **22**, and direct cyclization to form indene **24**, presumably via metallacyclohexadiene **23** with subsequent reductive elimination and hydrogen migration.[15] The synthetic utility of this reaction has been amply demonstrated in connection with natural products synthesis.[16]

The intermediacy of vinylcarbene complexes in this reaction is supported by the isolation of vinylcarbene complex **26** upon treatment of **25** with *N*,*N*-diethylaminopropyne **17** (Scheme 6). Subsequent thermolysis leads to the formation of indene-derived products **27** and **28**.[17]

Wulff has investigated an all-intramolecular diyne annulation in which the diyne is tethered to the carbene complex (eq 5).[18] An all intramolecular annulation of an enediyne tethered tungsten carbene complex has been adapted to give a steroid skeleton (eq 6).[18]

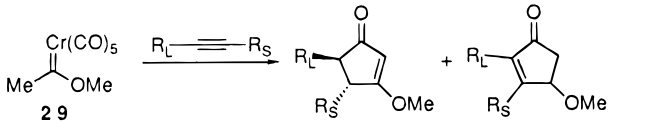


(eq. 5)

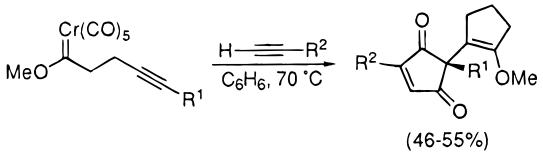


(eq. 6)

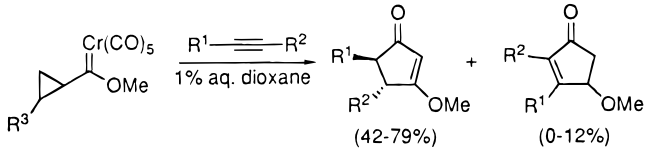
Relatively minor modifications to the structure of the carbene complex, the alkyne, or the reaction conditions can dramatically alter the observed reaction pathway. Since Dötz's initial observations, several groups have investigated reactions of group VI carbene complexes with alkynes. In their extensive studies of the reactions of alkylalkoxy chromium carbene complexes, Wulff and colleagues observed that when methylmethoxy chromium carbene complex **29** is treated with simple alkynes in hexane, cyclopentenones are produced (eq 7).[19,20] Tethering the alkyne to the alkyl substituent of the chromium carbene complex leads to vinylcyclopentenediones (eq



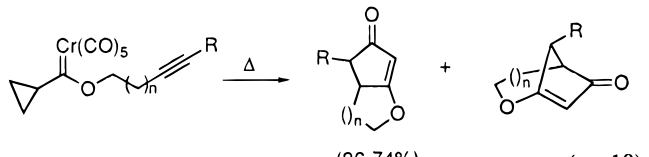
(eq. 7)



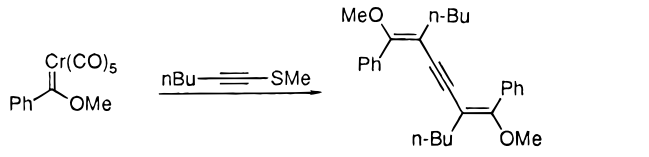
(eq. 8)



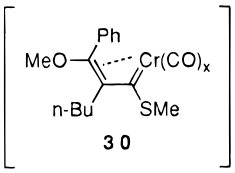
(eq. 9)



(eq. 10)



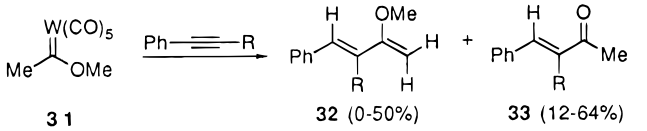
(eq. 11)



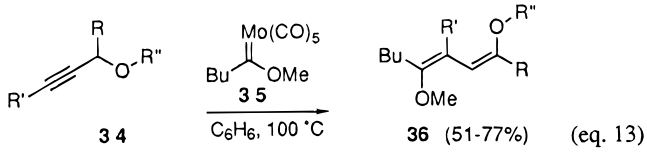
8).[21] Herndon and co-workers have reported that cyclopentenone products are obtained upon reaction of cyclopropyl-substituted chromium complexes with alkynes (eq 9).[22,23] When the alkyne is tethered to the carbene via the alkoxy substituent, intramolecular cyclization gives cyclopentenone-fused oxygen heterocycles (eq 10).[24] Katz has recently reported the transformation of an alkynyl thioether into a disubstituted acetylene using a chromium carbene complex (eq 11).[25] Despite the presumed intermediacy of **30**, which is analogous to that accepted in the Dötz reaction, it does not yield naphthol or indene products.

Effect of the Metal

The metal employed in the Fischer carbene complex has been found to play a major role in determining which reaction pathway is followed.[26] Tungsten carbene complexes, such as **31**, generally do not incorporate CO upon reaction with alkynes under thermal conditions as readily as do chromium carbene complexes. Instead vinyl ethers (**32**) and enones (**33**) are produced.[27] A related reaction has been observed upon treatment of butylmethoxy molybdenum carbene complex **35** with propargyl ethers (eq 13).[28] This process was found to proceed smoothly only with molybdenum carbene complexes.



(eq. 12)



(eq. 13)

The reactivity of phenylmethoxy Fischer carbene complexes of group VI metals with alkynes has been extensively investigated. When the metal is chromium, hydroquinone formation is generally favored over indene formation. When molybdenum or tungsten is employed in place of chromium, indene formation is generally favored. The order of selectivity for the CO-insertion product is Cr > W > Mo, which correlates with the metal−CO bond strengths of the metal hexacarbonyls for chromium (ΔH_{Cr-CO} = 36.8 kcal/mol) and tungsten (ΔH_{W-CO} = 46.0 kcal/mol), but not for molybdenum (ΔH_{Mo-CO} = 40.5 kcal/mol).[29] This difference is attributed to the tendency of molybdenum to undergo ligand substitution at a faster rate than either chromium or tungsten.[30]

A greater proportion of hydroquinone to indene/cyclopentadiene formation is seen when an alkenyl substituent is used in place of the aryl group. As in the phenyl case, hydroquinones are the major product with chromium, with only trace amounts of cyclopentadiene or cyclopentadiene-derived products observed. With tungsten, again, hydroquinone derivatives are obtained as the major products, however, significant amounts of cyclopentadiene-derived products are also produced. With molybdenum, hydroquinone formation is the dominant pathway in heptane and in concentrated (0.5 M) solutions of THF, but substituted cyclopentadienes are the major product when the THF solution is dilute (0.005 M) or the solvent is acetonitrile. A greater proportion of hydroquinone to indene is obtained when a terminal alkyne is used in place of an internal alkyne.[28]

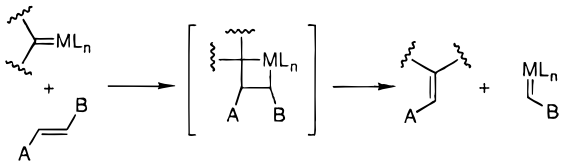
III. Reactions of Carbene Complexes with Alkenes

Transition metal carbene complexes are capable of reacting with alkenes in a number of different ways. The two major reaction pathways that have been reported are olefin metathesis and alkene cyclopropanation. As with the reaction of carbene complexes with alkynes, in the presence of carbon monoxide, CO insertion pathways often occur.

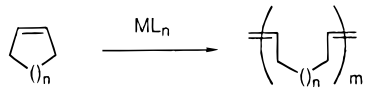
Olefin Metathesis

It has been amply demonstrated that a variety of transition metal complexes are capable of catalyzing olefin metathesis reactions.[31,32] The general mechanism for this reaction involves [2+2] cyclization of the alkene with the metal−carbon double bond to

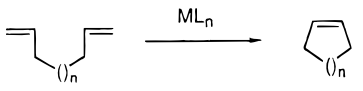
Scheme 7



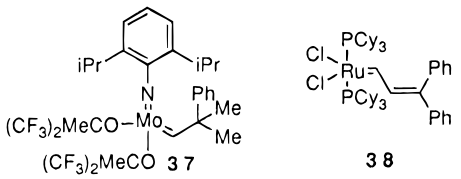
form a metallacyclobutane intermediate. Subsequent retro [2+2] cyclization leads to a new alkene and a new alkylidene complex (Scheme 7). When applied to cycloalkenes, polymers are produced (eq 14).

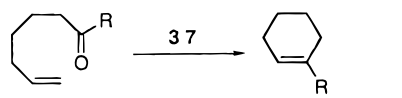


(eq. 14)

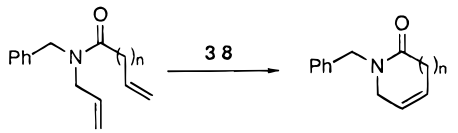


(eq. 15)





(eq. 16)



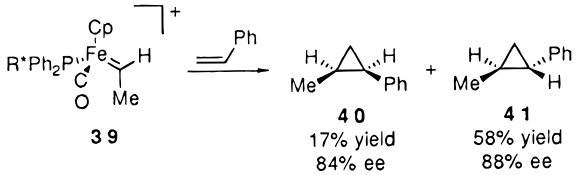
(eq. 17)

Conversely, metathesis of 1,*n*-dienes ($n = 6-9$) leads to cycloalkenes (eq 15). Molybdenum carbene complex **37** metathesizes olefins more rapidly than it olefinates ketones and has proven to be effective in synthesizing unsaturated five-, six-, and seven-membered carbocycles and heterocycles from the appropriate alkenones (eq 16). Ruthenium carbene complex **38** expands the scope of the ring-closing diene metathesis reaction. It has a high tolerance to atmospheric oxygen and moisture and an increased tolerance to most functional groups in comparison to the molybdenum-based catalyst. The ruthenium catalyst can cyclize dienes in the presence of air in reagent-grade solvents to give five-, six-, seven-, and some eight-membered ring systems (eq 17).

Cyclopropanation of Alkenes

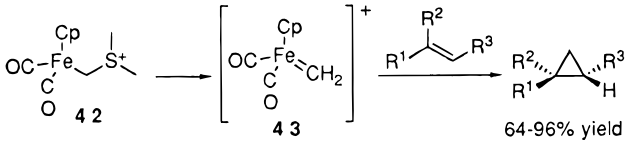
The ability of metallocarbenoids, generally produced by treatment of α-diazocarbonyl compounds with a variety of transition metal complexes, to cyclopropanate alkenes has been extensively investigated, and the ability of such complexes to participate in cascade-type reactions has recently been reviewed.[33]

Both chiral and achiral iron carbene complexes have been found to readily react with alkenes to form cyclopropanes. For example, chiral cationic iron carbene complex **39** reacts with styrene to form



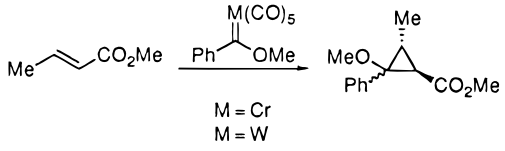
(eq. 18)

cyclopropanes **40** and **41**.[34] Similarly, sulfonium salt **42** is a stable, isolable reagent that cyclopropanates alkenes in good to excellent yields (64−96%).[35] The reactive species is presumed to be iron carbene complex **43**, produced via dissociation of dimethyl sulfide from **42**.

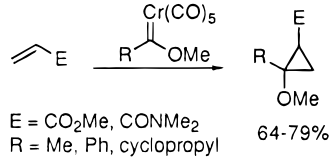


(eq. 19)

Fischer and Dötz described the first reactions of chromium and tungsten arylalkoxycarbene complexes with electron-rich and electron-deficient alkenes to produce substituted cyclopropanes.[36] The scope and limitations of these original observations have since been further explored and it has been found that a broad variety of substituted cyclopropanes are accessible by this approach.[37] Monosubstituted alkenes bearing ester, amide, nitrile, phosphonic ester and sulfone functionality all react smoothly to give substituted cyclopropanes in good yield. It was also demonstrated that the carbene complex need not be restricted to a phenyl substituent, as methylmethoxy chromium carbene complex also participates in the cyclopropanation reaction. A cyclopropyl substituted chromium carbene complex was found to react with alkenes to produce dicyclopropanes.[38]



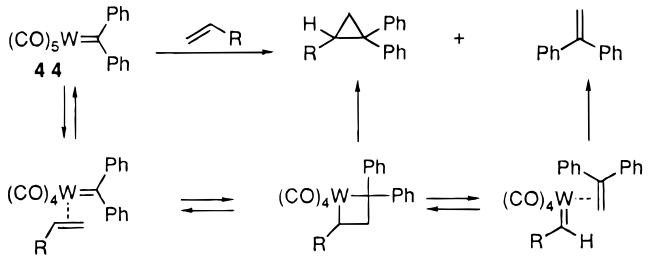
(eq. 20)



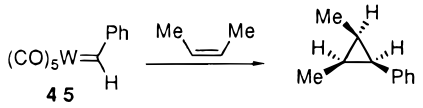
(eq. 21)

Casey has shown that diaryl tungsten carbene complex **44** reacts with alkenes to give mixtures of cyclopropane and olefin metathesis products, presumably through a metallacyclobutane intermediate[39] (Scheme 8). In contrast, monoaryl tungsten carbene complex **45**, which is considerably more electrophilic than **44**, reacts with alkenes to give only cyclopropanes and no olefin metathesis products.[40] Both *cis*- and *trans*-2-butene react with complex **45**

Scheme 8



to give cyclopropanes with retention of alkene geometry in high yield.[11,41]

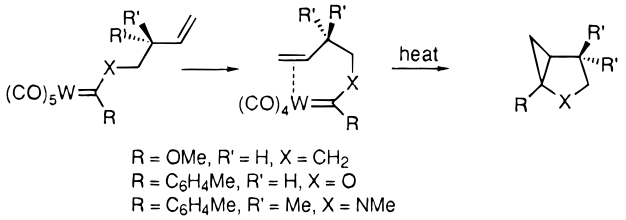


(eq. 22)

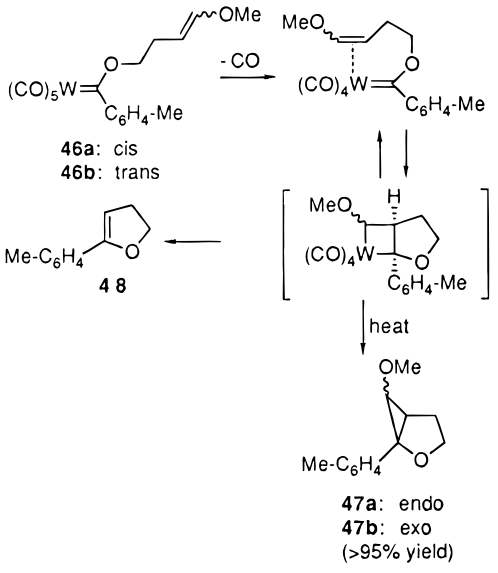
In 1984, Casey[41b] and Rudler[42] reported studies of the reactivity of chelated alkenyl, alkenyloxy, and alkenylamino tungsten carbene complexes. Thermolysis of these complexes led to the formation of cyclopropanes (Scheme 9). Subsequent reports indicated that in coordinating solvents, such as acetonitrile and THF, *cis* and *trans* tungsten carbene complexes **46a,b** were stereospecifically converted to *endo*- and *exo*-cyclopropanes **47a,b** in >95% yield. In benzene, and other noncoordinating solvents, reductive elimination led to the nonstereospecific formation of cyclopropanes **47a,b** and to olefin metathesis product **48**[41c] (Scheme 10).

The absence of early examples of cyclopropanations with molybdenum carbene complexes has been attributed to their relative instability compared to

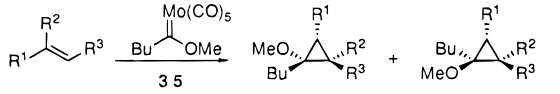
Scheme 9



Scheme 10



Scheme 11

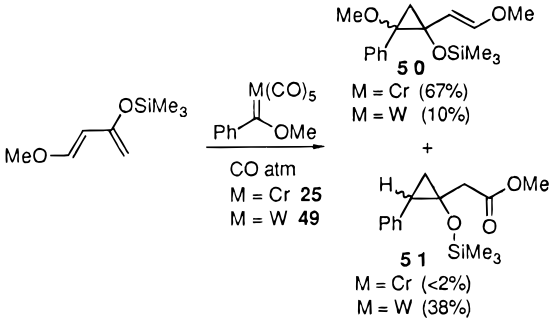


R1	R2	R3	M	Yield (%)	
H	H	CN	Mo	32	23
H	H	CN	Cr	26	24
H	H	CN	W	39	30
H	H	CO_2Me	Mo	51	27
H	H	$PO(OMe)_2$	Mo	47	33
H	Me	CO_2Me	Mo	44	13
Me	H	CO_2Me	Mo	51	8

chromium and tungsten.[43] The instability of the methylmethoxy and phenylmethoxy molybdenum carbene complexes was thought to make their synthetic utility somewhat low.[39] Harvey and Brown investigated the viability of this process using a molybdenum carbene complex and found that butylmethoxy molybdenum carbene complex **35** is considerably more stable than the analogous methyl complex and readily cyclopropanates electron-deficient alkenes. Not only does it react in good yield, but the reaction conditions are considerably milder than those required for the corresponding chromium and tungsten complexes[43] (Scheme 11).

Cyclopropanation of 1,3-Dienes

The first cyclopropanation of a 1,3-diene by a Fischer carbene complex was reported in 1988.[44] Reaction of 1-methoxy-3-(trimethylsiloxy)-1,3-butadiene (Danishefsky's diene) with phenylmethoxy chromium (**25**) and tungsten (**49**) carbene complexes in benzene gave a mixture of vinylcyclopropane **50** and cyclopropane **51**.[45] In the absence of a carbon

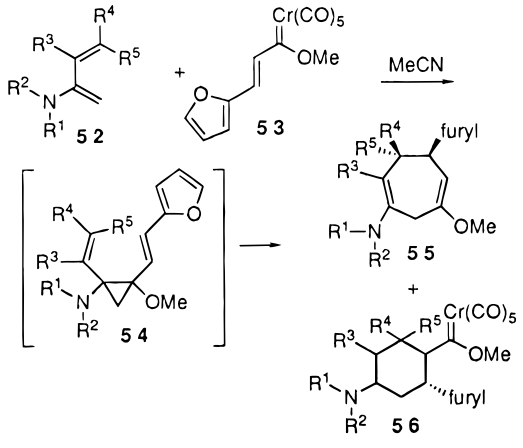


(eq. 23)

monoxide atmosphere, the chromium carbene complex also produces a metathesis product, α-methoxystyrene, which is the result of retro [2+2] cycloaddition of the metallacyclobutane intermediate. No metathesis products are observed when tungsten carbene complex **49** is employed.

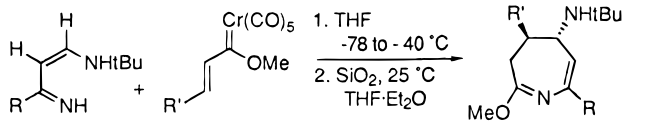
Reaction of dienes with vinyl-substituted chromium carbene complexes, such as **53**, has been reported to regio- and stereoselectively produce cycloheptadiene derivatives via in situ Cope rearrangement of a cis-divinylcyclopropane intermediate[46,47] (Scheme 12). Cyclohexyl chromium carbene complexes (**56**) arising from [4+2] cycloaddition of the electron-rich diene with the electron-deficient alkene of the vinylcarbene complex, are produced in low yield. Similarly, the reaction of **57** with chromium carbene complexes **53**

Scheme 12



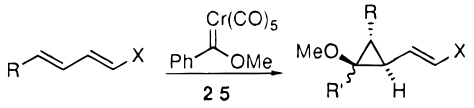
R^1	R^2	R^3	R^4	R^5
Ph	Me	Me	CH_2OMe or H	CH_2OMe or H
Ph	Me	$-(CH_2)_4-$		H
$-(CH_2)_2O(CH_2)_2-$		Me	CH_2OMe	H

and **58** stereoselectively leads to substituted 5*H*-6,7-dihydroazepines (**59**).[48]



(eq. 24)

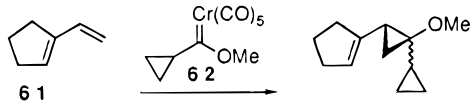
Cyclopropanation of electron-deficient 1,3-dienes generally occurs with much higher regio- and stereoselectivity than does cyclopropanation of analogous electron-deficient alkenes. Reissig has shown that thermolysis of dienes with chromium carbene complex **25** produces cyclopropanes **60a**,**b** with the carbene carbon transferred to the more electron-rich double bond and the diastereomer with the alkoxy group cis to the olefinic moiety as the major product.[49]



(eq. 25)

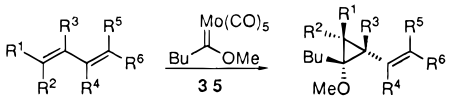
R	X	Yield (%)	cis:trans
Me	CO_2Me	79	90:10
Ph	CO_2Me	36	100:0
CO_2Me	CO_2Me	40	95:5
Me	CN	58	87:13

Examples of the cyclopropanation of electronically neutral 1,3-dienes are relatively limited. Herndon reported that diene **61** can be cyclopropanated by cyclopropyl chromium carbene complex **62** in 60% yield.[38,50,51]



(eq. 26)

The reactivity of molybdenum complex **35** with simple, substituted 1,3-dienes showed surprisingly high levels of regio- and diastereoselectivity (eq 27).[52]

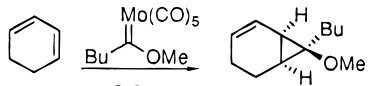


(eq. 27)

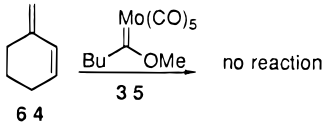
R1	R2	R3	R4	R5	R6	Yield (%)
H	H	Me	Me	H	H	71
H	H	H	H	H	Et or Ph	76
H	H	Me	H	H	Me	75 (6.3:1 regioisomers)
Me	H	H	H	H	Me	65
Me	H	H	H	Me	H or Me	no reaction
Me	Me	H	H	Me	Me	no reaction

Cyclopropanation occurs preferentially at the least sterically hindered double bond and, in all but one case, only a single diastereomer is obtained. A high level of chemoselectivity is also achieved. The *E*,*E*-isomer of 2,4-hexadiene is readily cyclopropanated, while the *E*,*Z*-isomer fails to react at either alkene position.

It was concluded from these studies that dienes with a readily accessible *s-cis* conformation are capable of participating in this reaction. This hypothesis is supported by the observation that 1,3-cyclohexadiene (**63**), which is locked in an *s-cis* conformation, is readily cyclopropanated in 67% yield while methylenecyclohexene (**64**), which is locked in an *s-trans* conformation, does not react. A mechanism involving formation of an η^1,η^3-intermediate accounts for these results.



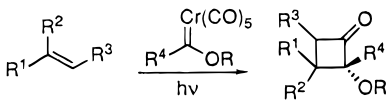
(eq. 28)



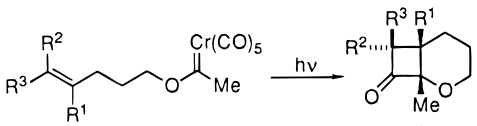
(eq. 29)

Reactions of Carbenes with Alkenes and CO

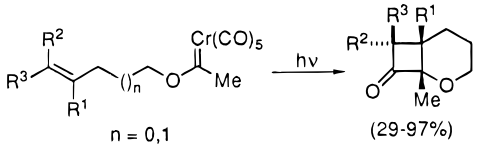
Photolysis of chromium carbene complexes in the presence of simple olefins produces cyclobutanones in a stereoselective and regioselective fashion (eq 30).[45a] Intramolecular versions of this reaction have also been reported (eq 31).[45a] The photochemically generated ketene complex can be trapped by other



(eq. 30)



(eq. 31)



(eq. 32)

ketenophiles. For example, with imines, β-lactams are generated in a stereoselective fashion (eq 32).[53,54]

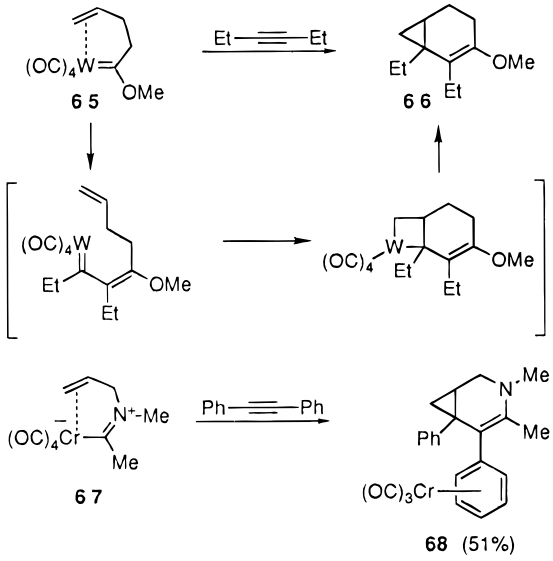
IV. Carbene–Alkyne–Alkene Reactions

As outlined in sections II and III, reactions of carbene complexes with both alkynes and alkenes are well-precedented. In order for the desired carbene to vinylcarbene to vinylcyclopropane reaction pathway to occur (Scheme 1), many of the other reaction pathways described above, such as olefin metathesis and CO insertion, must be avoided. By tethering the various components of this three-component coupling reaction in different ways, entropy constraints allow the desired reaction pathway to occur.

Carbene Tethered to Alkene

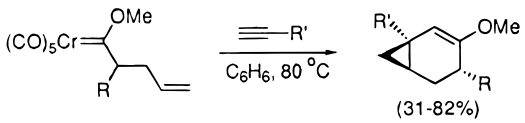
Rudler and co-workers were the first to demonstrate that alkynes would react with alkenylcarbene complexes to produce bicyclo[4.1.0]heptane derivatives (Scheme 13).[55] The high reactivity of these

Scheme 13



complexes is ascribed to the presence of a coordinated double bond in the γ-position with respect to the carbene carbon.[56] When treated with an alkyne, the intramolecularly coordinated alkene dissociates and the carbene complex reacts with the alkyne to form a vinylcarbene intermediate. Subsequent intramolecular cyclopropanation of the tethered alkene leads to **66** and **68**.[57] Direct intramolecular cyclopropanation of the tethered alkene of **65** and **67** is not likely to occur since a highly strained substituted bicyclo[2.1.0]pentane ring system would be produced.

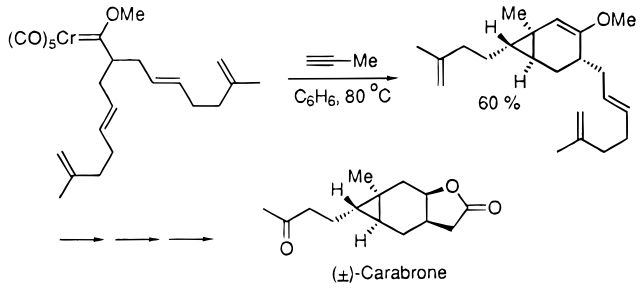
Hoye and Vyvyan have reported the reaction of alkene-containing Fischer carbene complexes with alkynes to be an efficient and stereoselective route to functionalized bicyclo[4.1.0]heptane derivatives.[58]



(eq. 33)

They have demonstrated the synthetic utility of this cyclization reaction in a formal synthesis of (±)-carabrone (Scheme 14).

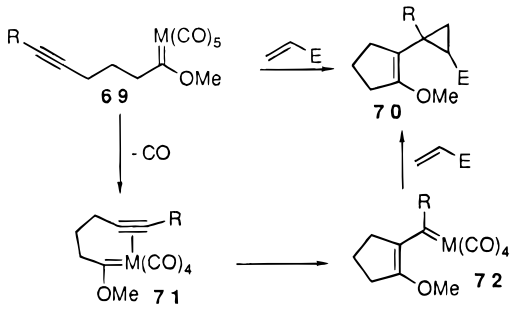
Scheme 14



Carbene Tethered to Alkyne

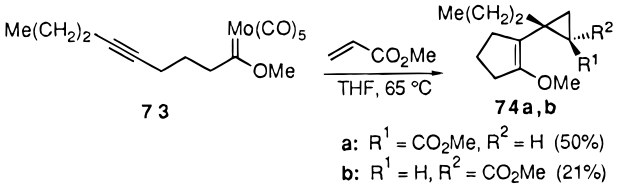
Studies by Harvey and Brown have demonstrated that, by tethering the alkyne to the carbene, cyclopentenylcyclopropanes are readily generated.[59] The presumed reaction pathway involves initial exchange of the tethered alkyne for carbon monoxide to form alkyne coordination complex **71** (Scheme 15). In-

Scheme 15



tramolecular cyclization and ring opening generates vinylcarbene complex **72**. Subsequent intermolecular cyclopropanation of the alkene by the vinylcarbene complex, presumably via metallacyclobutane formation and reductive elimination, leads to cyclopropanation product **70**.

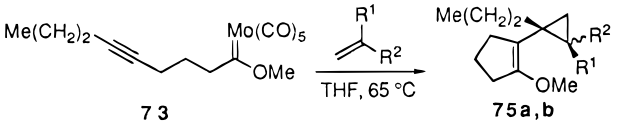
Mild thermolysis of carbene complex **73** in the presence of methyl acrylate led to a mixture of vinylcyclopropane stereoisomers **74a**,**b** in 71% yield.



(eq. 34)

The stereoselectivity observed in this process is similar to that seen in previous cyclopropanation studies.[60] Several other electron-deficient alkenes also readily participate in this process. Reaction of carbene complex **73** with acrylonitrile, dimethyl vinylphosphonate, and methyl methacrylate all lead to cyclopropanation products as mixtures of diastereomers.

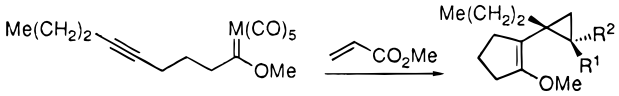
Thermolysis of the analogous tungsten carbene complex (**76a**) in the presence of methyl acrylate requires higher temperatures for reaction to occur (110 °C versus 65 °C) and produces vinylcyclopro-



73 75a,b (eq. 35)

R^1	R^2	% Yield (anti:syn)
CN	H	40:26
$PO(OMe)_2$	H	47:32
CO_2Me	Me	23:11

panes in considerably lower yield (27%, 3:1). Analogous thermolysis of chromium carbene complex **76b** led to a complex mixture of products.

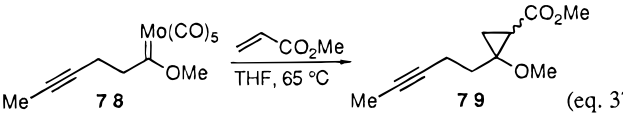


76 **a** M = W **b** M = Cr

77a,b **a:** $R^1 = CO_2Me$, $R^2 = H$ **b:** $R^1 = H$, $R^2 = CO_2Me$ (eq. 36)

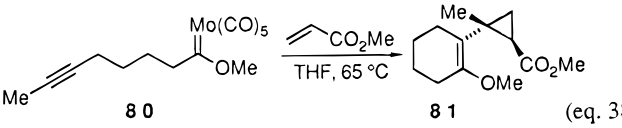
M	Yield (%) (a:b)
W	27% (3:1)
Cr	--

The success of this cyclization was found to be dependent upon the length and composition of the tether between the alkyne and the carbene complex. When carbene complex **78**, which has a shorter



78 **79** (eq. 37)

ethylene tether, was heated in the presence of methyl acrylate, it did not give the desired cyclopropanation product, or any identifiable products derived therefrom. Instead, the only identifiable product was cyclopropane **79**, isolated as a 3:1 mixture of diastereomers in only 6% yield. Cyclopropane **79** is the result of direct cyclopropanation of the alkene by the carbene complex without initial reaction with the alkyne. Thermolysis of carbene complex **80**, which

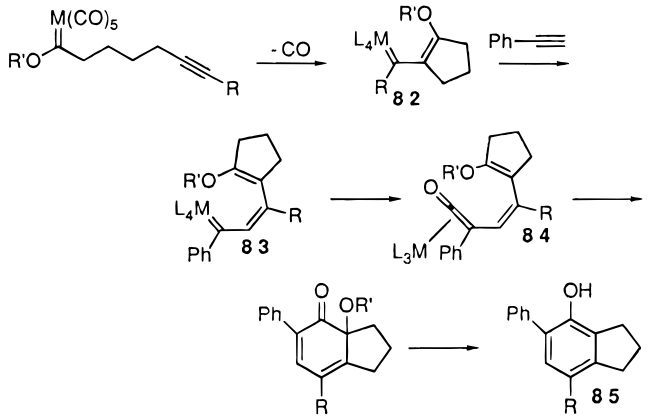


80 **81** (eq. 38)

has a longer four-carbon tether, in the presence of methyl acrylate was found to give the desired cyclohexenylcyclopropane (**81**), albeit in only 6% yield. This was the only identifiable product isolated from this reaction.

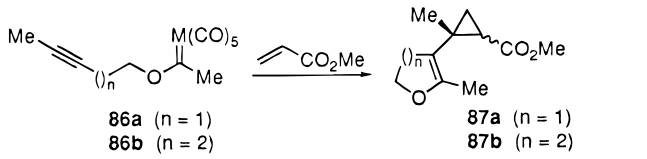
In-situ-generated vinylcarbene complexes can also be trapped intermolecularly by another equivalent of alkyne.[15,61,62] The proposed mechanism for this intraintermolecular two-alkyne annulation is similar to that believed to be operative for normal carbene-mediated benzannulation reactions. Initial alkyne for CO ligand exchange and subsequent intramolecular cyclization lead to complex **82** (Scheme 16). Repetition of this process in an intermolecular fashion with phenylacetylene generates a dienylcarbene

Scheme 16



complex (**83**) from which, after CO insertion to form **84** and in situ reduction and elimination, hydroquinone **85** is produced.

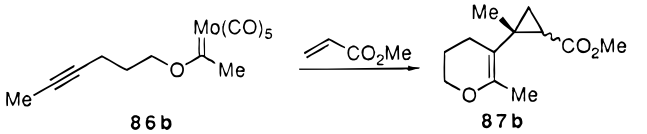
The alkyne can also be tethered to the carbene via the alkoxy substituent of the Fischer carbene complex.[63] Thermolysis of molybdenum carbene complex **86**, with excess methyl acrylate, generates a 1:1 mixture of dihydrofurans **87** (eq 39).[59] Under similar



86a (n = 1) **86b** (n = 2) **87a** (n = 1) **87b** (n = 2) (eq. 39)

M	Conditions (n = 1)	Yield (%)
Mo	C_6H_6, 60 °C, 2 h	49
Cr	C_6H_6, 70 °C, 3h	20
W	$PhCH_3$, 110 °C, 4h	trace

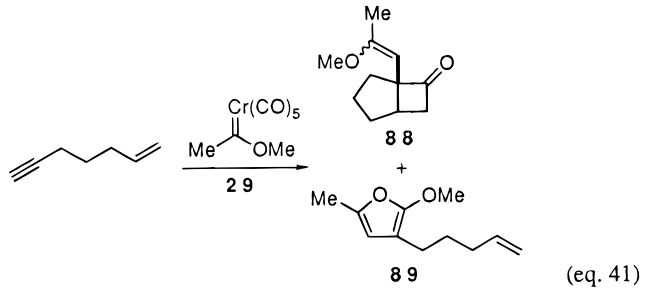
conditions, the analogous chromium and tungsten carbene complexes also produce dihydrofurans, but in significantly lower yield. Dihydropyranylcyclopropanes are also prepared in this fashion (eq 40).



86b **87b** (eq. 40)

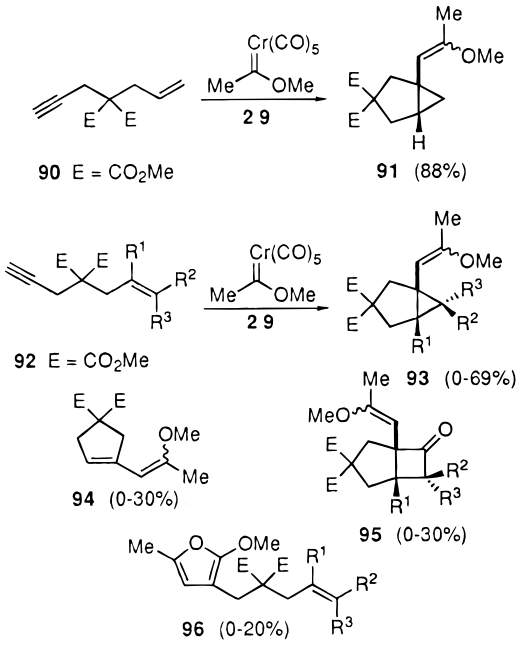
Alkyne Tethered to Alkene

Several groups have investigated the reactivity of 1,6- and 1,7-enynes with group VI Fischer carbene complexes. Wulff and Kaesler initially demonstrated that thermolysis of 6-hepten-1-yne and methylmethoxy chromium carbene complex **29** in acetoni-



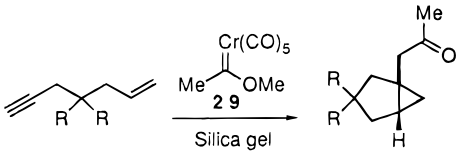
(eq. 41)

Scheme 17



trile produced cyclobutanone **88** as a mixture of enol ether isomers in 45% yield.[64] When THF was used as the solvent, a complex mixture of products, including cyclobutanone **88** (13%) and furan **89** (10%), was produced. The reaction failed when the corresponding tungsten carbene complex was employed. Both **88** and **89** result from reaction of the carbene complex with the alkyne to form a vinylcarbene complex followed by CO insertion to form the corresponding vinyl ketene complex. Intramolecular [2+2] alkene/ketene cyclization leads to cyclobutanone **88** while metal-mediated rearrangement of the vinylketene complex produces furan **89**.[64]

Hoye and co-workers demonstrated that cyclization reactions of chromium carbene complexes with enyne substrates proceeds smoothly when *gem*-carbomethoxy groups are situated on the tether between the alkyne and the alkene (Scheme 17).[65] As the substitution pattern on the alkene is varied, cyclobutanones (**95**),



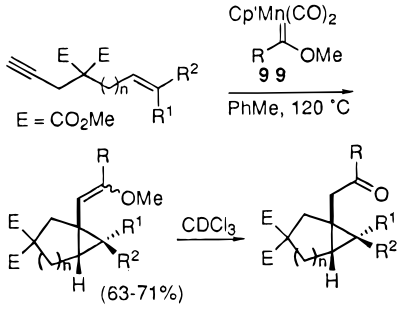
(eq. 42)

R	Yield (%)
CO_2Me	94
Me	85

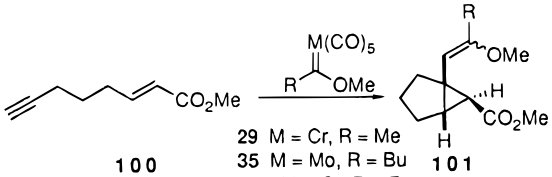
furans (**96**), and 1,3-dienes (**94**) are also obtained. Enynes can also be cyclopropanated by chromium carbene complex **29** in a solid phase reaction via adsorption on silica gel.[66] Silica gel-catalyzed hydrolysis of the enol ether leads to the ketone **98**.

Hoye and Rehberg have investigated the reactivity of manganese carbene complexes with enynes.[67] Treatment of manganese complex **99** with a series of enyne diesters gave alkoxy-substituted bicyclic vinylcyclopropanes which hydrolyzed to the corresponding ketones upon standing (Scheme 18). Unlike the chromium carbene complex, no evidence of cyclobutanone, furan, or metathesis products was detected.

Scheme 18



Studies by Harvey and co-workers have demonstrated that molybdenum carbene complexes react smoothly with a variety of enynes to form vinylcyclopropane products. For example, treatment of enyne **100** with molybdenum carbene complex **35** led



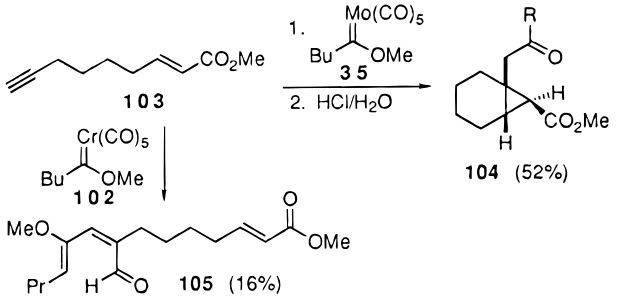
(eq. 43)

M	R	Yield (%)	(E:Z)
Mo	Bu	76	(10:1)
Cr	Bu	34	(4:1)
Cr	Me	33	(3:1)

to cyclopropanation product **101** as a 10:1 mixture of enol ether isomers in 76% yield.[68] The analogous chromium carbene complex produced a 4:1 mixture of the cyclopropanated products in significantly lower yield (34%). When enyne **100** was treated with methylmethoxy chromium carbene complex **29**, as used previously by Wulff, Hoye, and Katz, a 3:1 mixture of vinylcyclopropanes was produced in 33% yield. Careful examination of each of these cyclizations revealed no evidence of CO insertion or olefin metathesis products. Since both the butyl and methyl chromium complexes behaved similarly, the dramatic improvement in yield with molybdenum complex **35** is attributed to the metal rather than to the alkyl substituent.

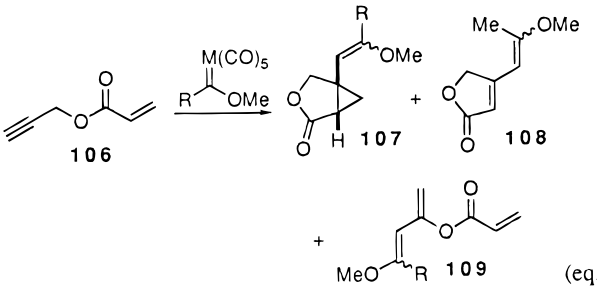
The success of this type of cyclization reaction was found to be highly dependent on the length and composition of the tether between the alkyne and the alkene. Thermolysis of enyne **103**, containing a longer 4-atom tether, with molybdenum carbene complex **35** gave a mixture of vinylcyclopropane enol ether isomers which were hydrolyzed directly to the corresponding ketone (Scheme 19). The lower yield of **104** compared to **101** was attributed to the slower rate of olefin coordination with the longer tether. When enyne **103** was treated with chromium carbene complex **102**, none of the desired cyclopropanation products were obtained. Instead, only aldehyde **105**, resulting from CO insertion into the intermediate vinylcarbene complex followed by 1,5-hyrogen shift,

Scheme 19



was produced in 16% yield. The three-atom tether was shown to produce the best results, and any increase or decrease in the tether length generally resulted in reduction of the efficacy of this reaction.

6-Hepten-1-yne, lacking the electron-withdrawing group on the alkene, failed to give any cyclization product. Instead, only intractable material, likely the result of oligomerization/polymerization of the alkyne, was produced. It therefore appeared that in the absence of substituents on the tether, successful reaction with the alkene component required that an electron-withdrawing group be present on the alkene so that metal coordination to the coordinatively unsaturated vinylcarbene complex intermediate, which is likely to involve considerable d$-\pi^*$ back-bonding, would be more favorable. Alkene activation with the electron-withdrawing group as part of the tether (**106**) also led to vinylcyclopropane products (**107** in

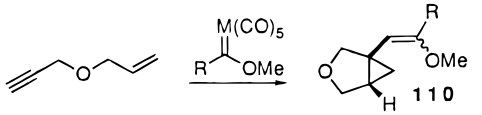


(eq. 44)

M	R	107 (E:Z)	108	109
Mo	Bu	24% (1:3)	--	--
Cr	Bu	5% (5:1)	9%	--
Cr	Me	4%	10%	13%

24% yield) upon thermolysis with molybdenum carbene complex **35**. Treatment of **106** with chromium carbene complexes gave the expected cyclopropanation products in lower yields, as well as significant quantities of olefin metathesis product **108** and diene ester **109**. Diene **109** appears to be the result of rearrangement of the in-situ-generated vinyl carbene complex.

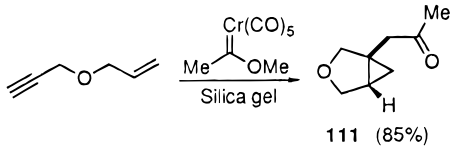
The feasibility of incorporating heteroatom functionality on the tether between the alkene and the alkyne was also investigated. Treatment of allyl propargyl ether with molybdenum carbene complex **35** produced vinylcyclopropane **110** in excellent yield.[69] Unlike the ester linked enyne, no CO insertion or metathesis products were obtained even when the solvent was changed from benzene to THF or acetonitrile. The analogous chromium carbene complexes also produced exclusively cyclopropanation products, though in reduced yield. Subsequently, Katz and



(eq. 45)

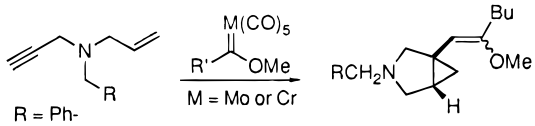
M	R	XX	(E:Z)
Mo	Bu	81%	(3:1)
Cr	Bu	55%	(4:1)
Cr	Me	46%	(10:1)

Yang showed that allyl propargyl ether is cyclopropanated by methylmethoxy chromium carbene complex **29** to produce ketone **111** in 85% yield when the thermolysis is carried out on a solid support.[70]

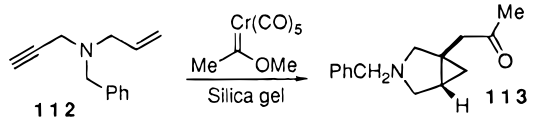


(eq. 46)

Harvey and Sigano have shown that treatment of allylpropargyl amine derivatives with both molybdenum and chromium carbene complexes does not give cyclopropyl derivatives. Under a variety of



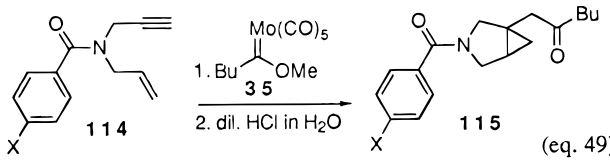
(eq. 47)



(eq. 48)

conditions, thermolysis gave only a mixture of nonisolable products, possibly the result of alkyne oligomerization/polymerization.[71] The power of the solid phase conditions developed by Katz is amply demonstrated in this case, as amine derivative **112** produced cyclopropane **113** when treated with chromium complex **29**.[70]

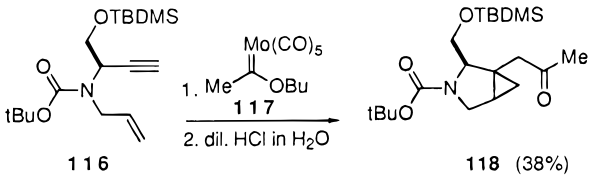
In contrast to allylpropargyl amines, allylpropargyl amide derivatives, such as **114**, readily react with



(eq. 49)

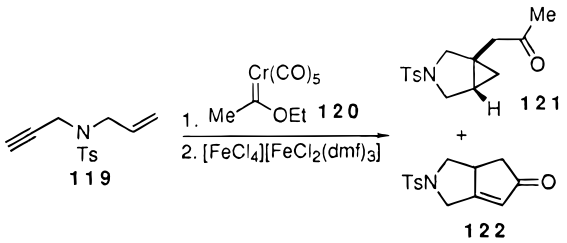
	X	Yield (%)
138a:	NO_2	74
138b:	H	56
138c:	OMe	58

complex **35** to give cyclopropanation products in good to excellent yield.[71] The 4-nitro derivative was found to give a somewhat better yield than the corresponding unsubstituted and 4-methoxy derivatives. Allylpropargyl carbamate derivative **116** can also be smoothly cyclopropanated by molybdenum carbene complex **117** in 38% yield.[72] Mori and Watanuki have demonstrated that allylpropargyl sulfonamide **119** in



(eq. 50)

acetonitrile readily reacts with chromium carbene complex **120** to give cyclopropane derivative **121** in 91% yield after treatment with $[FeCl_4][FeCl_2(dmf)_3]$.[73] When THF is used in place of acetonitrile, a bicyclic cyclopentenone derivative (**122**) is obtained in 18% yield along with **121** in 47% yield.

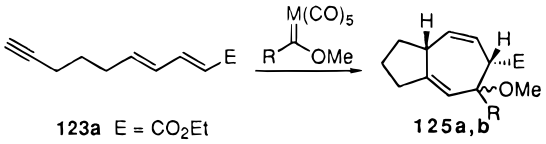


(eq. 51)

These studies, carried out by three independent groups, clearly show that relatively minor changes in the substrate, the carbene complex, or the reaction conditions can have a dramatic impact on whether CO insertion, olefin metathesis, or cyclopropanation products are produced.

Alkyne Tethered to 1,3-Diene

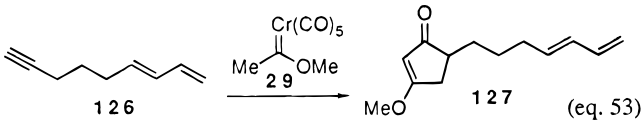
On the basis of the observed reactivity of enynes, it was anticipated that treatment of dienynes, such as **123**, with carbene complexes would lead to divinylcyclopropane products which, under the reaction conditions, would be expected to undergo [3,3] sigmatropic rearrangement to produce a hexahydroazulene ring system (Scheme 20). The feasibility of such a process was first demonstrated by Harvey and Lund.[74] Thermolysis of dienyne **123a** with molybdenum complex **35** (R = Bu, M = Mo) produced hexahydroazulenes **125a** (1:4.8 ratio) in 87% overall yield. The corresponding divinylcyclopropanes, **124**, were not detected. When dienyne **123a** was treated with chromium carbene complexes, hexahydroazulenes **125a**,**b** were produced in much lower yield.



(eq. 52)

M	R	Yield (%)	(E:Z)
Mo	Bu	87	(1:4.8)
Cr	Bu	22	(1.2:1)
Cr	Me	24	(1.2:1)

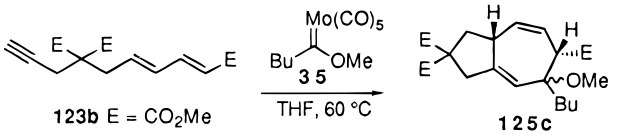
Thermolysis of dienyne **126**, lacking an electron-withdrawing group on the diene and any substituents on the tether, failed to give any of the anticipated hexahydroazulenes with either molybdenum or chromium carbene complexes. The only isolable product



(eq. 53)

obtained with this substrate was cyclopentenone **127** from treatment of **126** with methylmethoxy chromium carbene complex **29**.[74] The failure of dienyne **126** to participate in the cyclopropanation pathway was attributed to the absence of an electron-withdrawing group on the 1,3-diene.

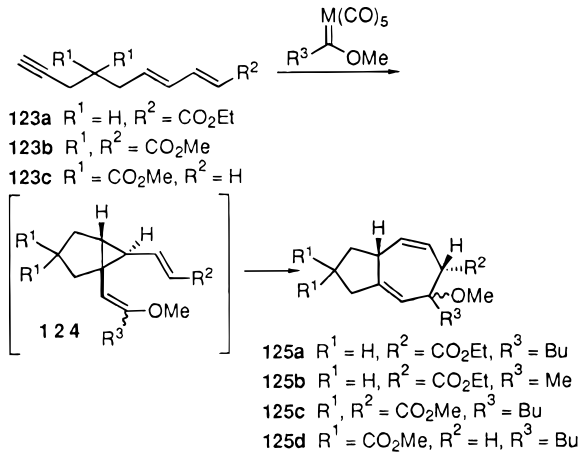
Hoye et al. have shown that when *gem*-carbomethoxy substituents are situated on the tether between the alkene and the alkyne, cyclopropanation products are readily generated.[65] Additionally, thermolysis of dienynes containing *gem*-carbomethoxy groups on the tether gives exclusively hexahydroazulenes, provided that an electron-withdrawing group is attached to the diene.[74] Thermolysis of **123b** in the presence of molybdenum complex **35** proceeds smoothly to give hexahydroazulenes **125c** in 81% yield. When the dienyne lacks the activating electron-



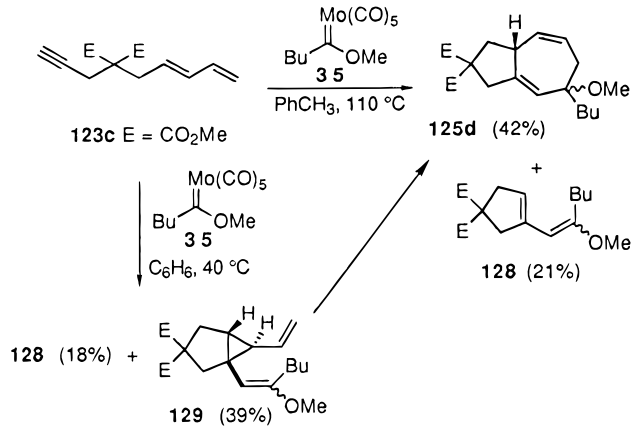
(eq. 54)

withdrawing group (**123c**) and only possesses the *gem*-carbomethoxy groups on the tether, hexahydroazulenes (**125d**) are produced, but they are accompanied by olefin metathesis product **128**. When dienyne **123c** is treated with molybdenum complex **35** in benzene at lower temperature (40 °C), divinylcyclopropanes **129** are isolated along with metathesis product **128** (Scheme 21). Divinylcyclopropanes **129** smoothly rearrange to the corresponding cycloheptadienes upon thermolysis at slightly higher temperature. The electron-withdrawing substituent on the diene appears to both activate the alkene component toward coordination to the coordinatively unsaturated metal, as well as cause the cyclopropanation pathway to be preferred over olefin metathesis.

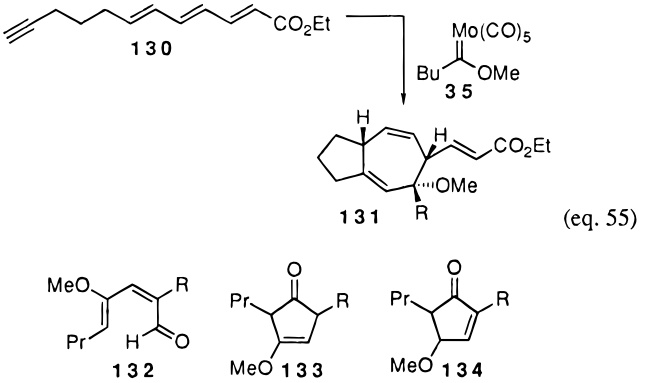
Scheme 20



Scheme 21



The influence of additional olefinic functionality on this reaction has been investigated.[75] Thermolysis of trienyne **130** in the presence of complex **35**

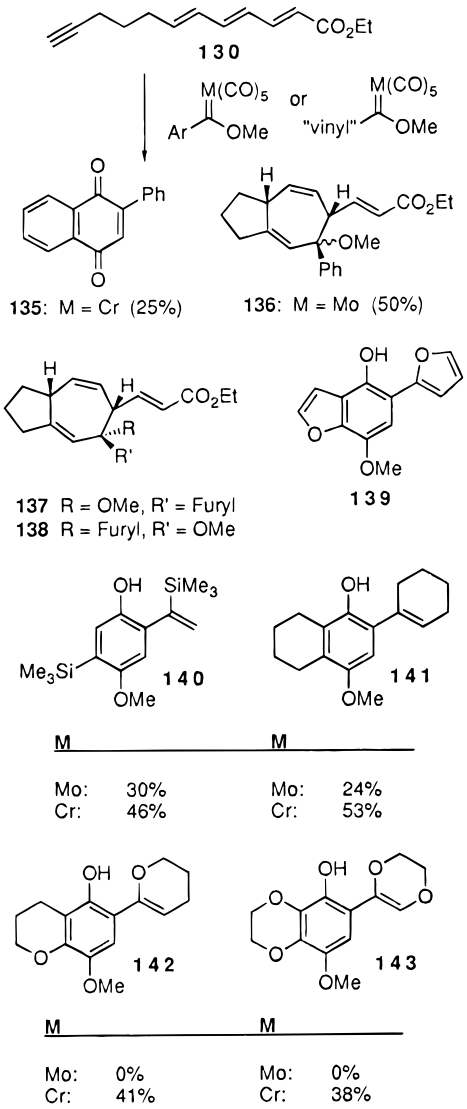


produces hexahydroazulene **131** in 66% yield as a single diastereomer. The analogous butylmethoxy chromium complex gives a mixture of CO insertion products that includes dienal **132** (17%) and cyclopentenones **133** (14%) and **134** (10%).

Replacement of the butyl group with a phenyl substituent leads to formation of hexahydroazulene **136** in 50% yield as a 2:1 mixture of isomers (Scheme 22). The analogous chromium complex follows the Dötz reaction pathway to give, after oxidation, benzoquinone **135** in 25% yield. Similar results are obtained using a furylmethoxy molybdenum carbene complex. Hexahydroazulene **137** is produced as a single diastereomer in 42% yield, and no CO insertion products are isolated. The analogous chromium complex gives benzofuran **139** in 52% yield and hexadydroazulene **138** in 10% yield. Replacement of the aryl group with a vinyl substituent dramatically changes the reaction pathway. Only trace amounts (3%) of cyclopropane-derived products are produced. When (trimethylsilyl)ethenyl-, cyclohexenyl-, dihydropyranyl-, or 1,4-dioxenyl-substituted chromium carbene complexes are employed, hydroquinone derivatives are produced instead.

Upon treatment of **130** with cyclohexenyl, dihydropyranyl, and dioxenyl molybdenum carbene complexes, cyclopentadiene-derived products **144**, **145** and **146** are generated (Scheme 23). Cyclization product **146** is the result of intramolecular Diels–Alder reaction of an initial substituted cyclopentadiene product.[76]

Scheme 22

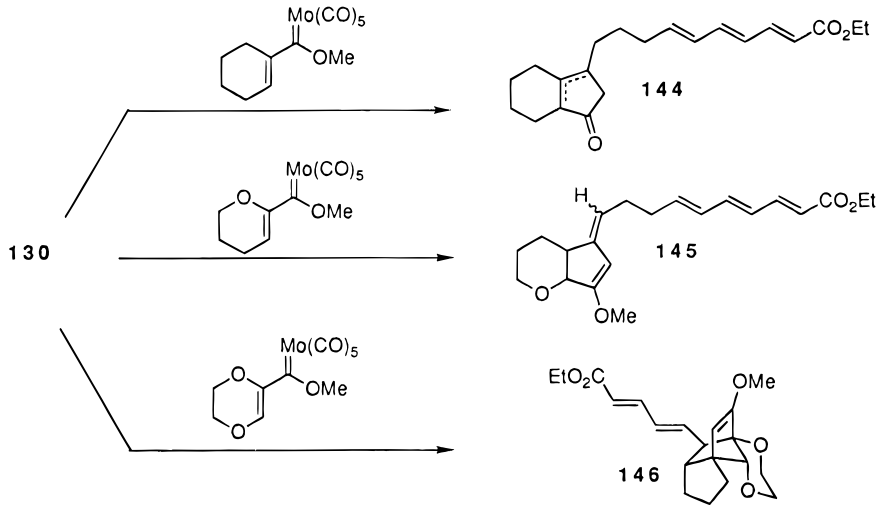


Two general conclusions were made from these studies. First, though aryl- or alkylcarbene complexes give cyclopropanation products, alkenyl substituents at this position cause the cyclopropanation pathway to be disfavored and hydroquinone or cyclopentadiene formation to occur instead. Second, the ratio of hydroquinone to cyclopentadiene products appears to be a function of the electronic nature of the substituents on the alkene, with electron-donating substituents causing cyclopentadiene products to be favored while less electron-donating substituents cause CO insertion pathways to be preferred.

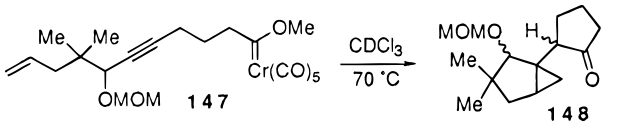
All-Intramolecular Cyclizations

On the basis of some of the initial studies in this area, it was envisioned that attachment of an appropriately functionalized enyne or dienyne to a carbene complex would provide direct access to polycyclic frameworks via an all-intramolecular cyclization reaction. To date, a relatively limited number of examples of this type of cyclization have been reported. Hoye and co-workers initially demonstrated the feasibility of such a process by tether-

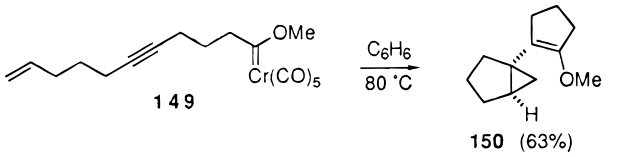
Scheme 23



ing a methoxy chromium carbene complex to an enyne (**147**).[65c] Preliminary studies showed that,



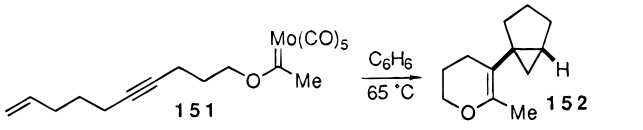
(eq. 56)



(eq. 57)

upon warming, two diastereomeric ketones were formed of undetermined relative stereochemistry. Unsubstituted chromium carbene complex **149** was also prepared and, upon warming in benzene, gave the tricyclic enol ether **150**.[77]

Harvey and Brown explored all-intramolecular versions of this reaction with molybdenum carbene complexes wherein the enyne or dienyne component was tethered through the alkoxy substituent.[78] Thermolysis of complex **151** gave vinylcyclopropane **152**

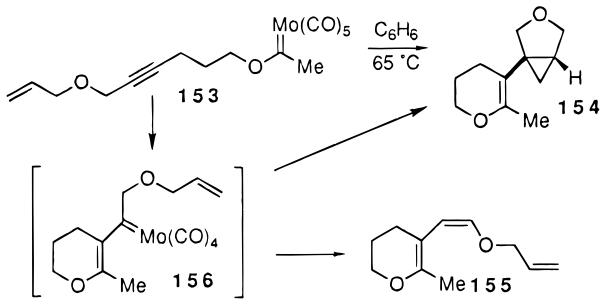


(eq. 58)

as the only isolable product in 51% yield. As with Hoye's unsubstituted chromium carbene complex **149**, the success of this cyclization was somewhat surprising since earlier studies had suggested that appropriate substitution on the olefin is required for activation toward this type of cyclization.

Since allylic ethers had been found to function well as the alkene component of this type of cyclization,[68,69] molybdenum carbene complex **153** was prepared and its reactivity investigated (Scheme 24). Thermolysis of **153** produced the highly functional-

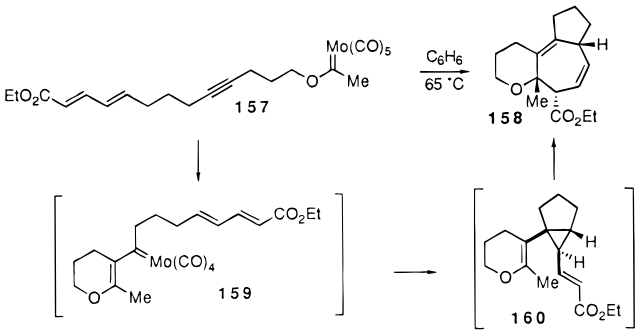
Scheme 24



ized vinylcyclopropane system **154** in 39% yield, as well as triene **155** in 3% yield. Triene **155** is thought to be the product of a 1,3-hydrogen shift from vinylcarbene intermediate **156**, followed by reductive elimination. This reaction was later found to be fairly general and readily occur in good yield with a variety of propargyl ethers.[30] In the case at hand, intramolecular cyclopropanation of the allyl group is favored over rearrangement and reductive elimination to form the conjugated diene framework.

Ester substituents have been found to activate 1,3-dienes toward cyclopropanation.[68,69] Accordingly, thermolysis of ester-activated dienyne complex **157** produced tricyclic product **158** in 55% yield as a single diastereomer (Scheme 25). This product is believed to be produced via in situ generation of vinylcarbene complex **159**, followed by cyclopropanation to form **160**, and [3,3] sigmatropic rearrangement to give **158**.

Scheme 25



V. Factors Influencing the Carbene–Alkyne–Alkene Cyclization Reaction

The variety of studies described above have demonstrated that the carbene−alkyne−alkene cyclization approach to vinylcyclopropanes, and products derived therefrom, is quite feasible. However, in many cases, other reaction pathways have been documented to be competitive with the desired reaction pathway. The factors which influence whether the desired reaction pathway or competing reaction pathways occur can be grouped into three categories: (1) steric effects associated with substituents on the tether between the alkyne and the alkene component, (2) electronic effects due to functionality in the vicinity of the alkene, and (3) coordination effects due to functionality in the vicinity of the vinylcarbene intermediate.

Steric Effects

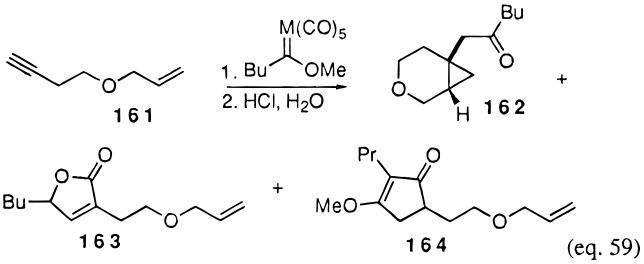
The ability of substituents on the tether between two reactive functionality to influence the rate of an intramolecular reaction is well-documented.[79] A variety of explanations for this effect have been advanced. Thorpe and Ingold initially proposed that alkyl substituents cause a compression of the internal angle of the carbon chain, thus causing the reactive centers to be closer together.[80] Bruice and Pandit described the increased reactivity as a "reactive rotamer effect".[81] Other rationalizations have also been advanced.[82] In the context of the studies summarized herein, this effect plays a role in the success of several cyclizations. For example, hept-6-en-1-yne fails to give any isolable cyclization products while closely related substrates studied by Hoye and co-workers cyclize smoothly (Scheme 17), though both cyclopropanation and olefin metathesis products are generated.

Electronic Effects

Electron-withdrawing substituents on the alkene increase the reactivity of the alkene component toward cyclopropanation quite significantly. Coordination of the alkene to the metal of the coordinatively unsaturated vinylcarbene complex intermediate has a large d−π* back-bonding component. Electron-withdrawing substituents on the alkene will strengthen this interaction.

Strongly electron-withdrawing groups, such as ester, aldehyde, sulfoxide, and nitro substituents, were found to sufficiently activate the alkene toward metal coordination for it to participate in the carbene−alkyne−alkene cyclization reaction.[83] Substrates with weaker electron-withdrawing substituents in the vicinity of the alkene, such as allylicly situated alkoxy- and acylamino substituents (see eqs 45−51), were also found to cyclize well.

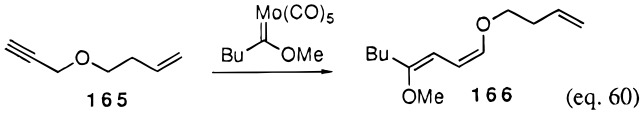
With a longer four-atom tether between the alkene and the alkyne, positioning the oxygen at the allylic/homopropargylic position, as in **161**, leads to a mixture of products derived from cyclopropanation of the alkene (**162**) and insertion of CO into the vinylcarbene complex (**163** and **164**). In contrast, positioning the oxygen at the homoallylic/propargylic position gives exclusively 1,4-dialkoxy-1,3-butadiene



161 162 163 164 (eq. 59)

M	192	193	194
Mo	37%	29%	0%
Cr	3%	8%	26%

derivative **166**.[30] With the oxygen positioned as it is



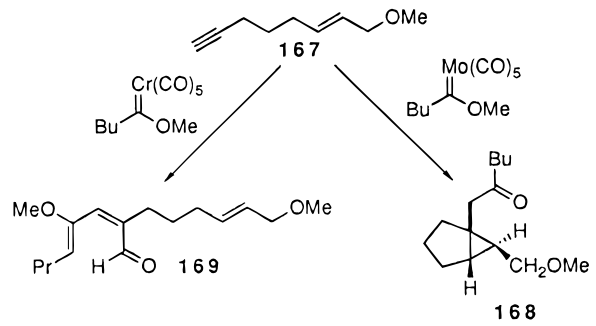
165 166 (eq. 60)

in **165**, it is not able to activate the alkene toward cyclopropanation since it is homoallylic rather than allylic. Additionally, since only propargyl ethers have been found to consistently react with carbene complexes to form butadiene derivatives, the propargylic positioning of the oxygen is believed to activate the propargylic hydrogens toward hydrogen migration at the vinylcarbene intermediate stage, rendering conversion to the 1,3-diene favored over intramolecular cyclopropanation of the alkene.

When the allylic oxygen is positioned outside of the tether, as in **167**, cyclopropanation product **168** is obtained in 45% yield, after hydrolysis of the corresponding enol ether.[84] No olefin metathesis or CO insertion products were detected. Treatment of **167** with the analogous chromium carbene complex did not give any cyclopropanation products. Instead, a CO insertion product, aldehyde **169**, is isolated in 14% yield (Scheme 26). In contrast with the all-carbon tethered enynes, the allylic ether, located either in the tether or as a substituent on the olefin, significantly increases the tendency of the alkene to participate in the cyclopropanation event. The σ-electron-withdrawing ability of the oxygen is thought to be responsible for this effect.

N-Benzyl-*N*-allyl-*N*-propargylamine derivatives do not readily participate in this reaction.[71] The only case where an allyl propargyl amine derivative has successfully participated in a carbene−alkyne−alkene cyclization reaction was reported by Katz with the reaction carried out on a solid support.[70] In solution, even with an additional 4-nitro group on the

Scheme 26

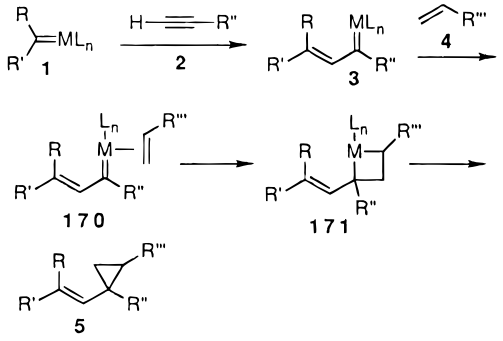


benzyl substituent, thermolysis with complex **35** gives only a complex mixture of nonisolable products.[71] The reduced activity of these systems may be attributed to the lower electronegativity of nitrogen in comparison to oxygen. When the amine is functionalized with stronger electron-withdrawing groups, such as amides,[71] carbamates,[72] and sulfonamides,[73] intramolecular cyclopropanation occurs smoothly (see eqs 49−51).

Coordination Effects

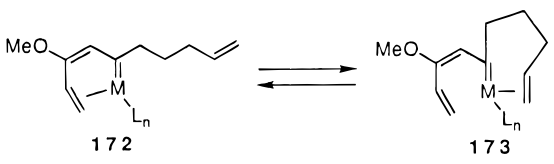
It appears that the critical step that determines whether the carbene−alkyne−alkene cyclization pathway will occur, is coordination of the alkene component, **4**, to vinylcarbene complex intermediate **3** to form complex **170** (see Scheme 27). Coordination of

Scheme 27



other ligands to intermediate **170** will interfere with coordination of the preferred alkene and inhibit the desired cyclization reaction. Several examples of this coordinative inhibition effect have been documented.

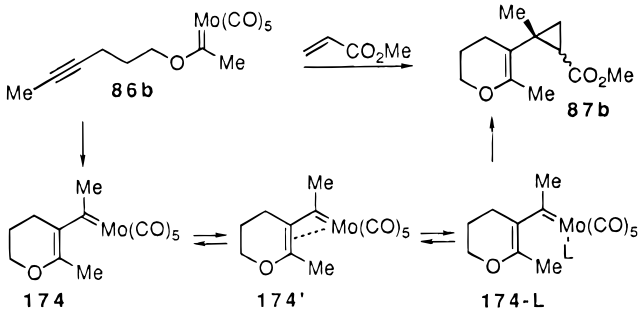
Both alkyl- and aryl-substituted carbene complexes give alkene cyclopropanation products. However, vinyl-substituted carbene complexes give a variety of products, none of which are the result of intramolecular reaction with the tethered alkene. Generally, when electron-donating groups are situated on the carbene vinyl substituent, cyclopentadiene-derived products are produced, while in the absence of such groups CO insertion occurs, leading to hydroquinone formation.[75] This has been suggested to be caused by coordination of the additional vinyl substituent, as in **172**, competing with coordination of the tethered alkene substituent, as in **173**.



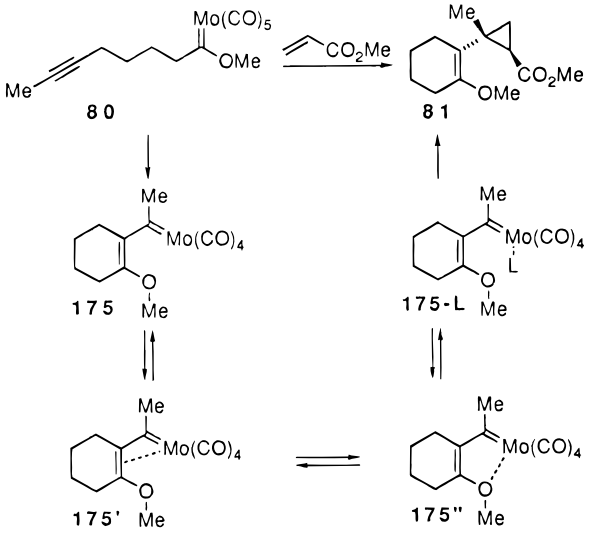
(eq. 61)

It has also been documented that coordination of alkoxy groups can dramatically effect the reactivity of in-situ-generated vinylcarbene complexes. For example, treatment of complex **86b** with methyl acrylate gave dihydropyranyl derivative **87b** in 59% yield[85] while complex **80** produced methoxycyclohexene derivative **81** in only 6% yield[61] (Schemes 28 and 29). This difference in reactivity is attributed to the different modes of coordination available at the vinylcarbene complex stage. Complex **175**, resulting

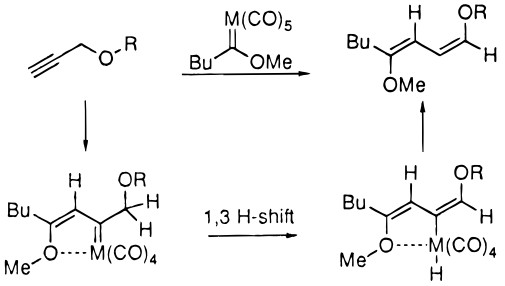
Scheme 28



Scheme 29



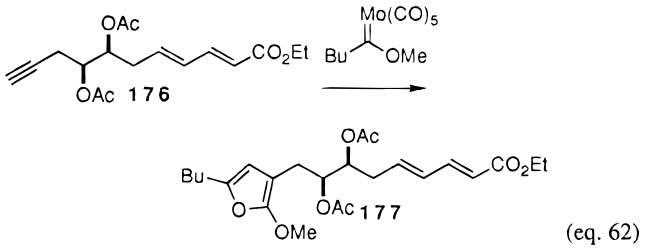
Scheme 30



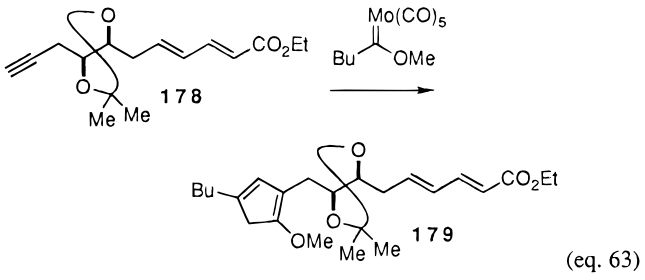
from intramolecular reaction of complex **80** with the pendant alkyne, can exist in a coordinatively unsaturated η^1,η^1-form (**175**), in the coordinatively saturated η^1,η^3-form (**175′**), or in the oxygen-bound coordinatively saturated η^1,η^1,η^1-form (**175″**). Coordination to methyl acrylate gives **175-L**, which leads to the observed products. Because of the ability of the oxygen to coordinate as in **175″**, **175** is expected to be considerable more stable than **174** and less likely to coordinate to the electron-deficient alkene of methyl acrylate. When the alkyne is tethered through the alkoxy-substituent of the carbene complex, ether coordination is not possible and the vinylcarbene intermediate **174** is expected to be considerably more reactive. Similar enol ether coordination has been suggested to be responsible for the high stereoselectivity obtained in the synthesis of 1,4-dialkoxy-1,3-butadienes (Scheme 30).

In connection with the application of this reaction to natural product synthesis, the reactivity of dienynes bearing alkoxy-substituents on the tether

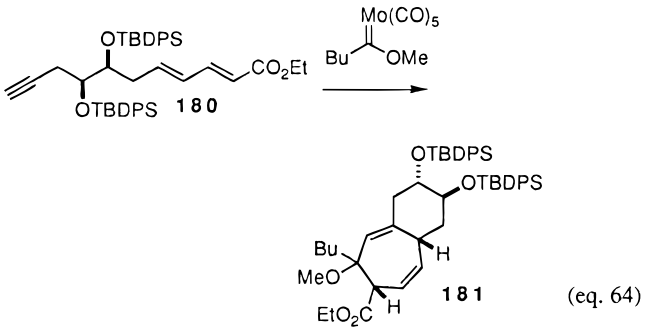
between the alkyne and the 1,3-diene was investigated.[86] Initial studies demonstrated that acetate and acetonide derivatives both failed to give the anticipated bicyclic ring system. Instead, substituted



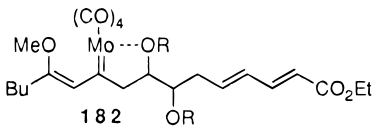
(eq. 62)



(eq. 63)



(eq. 64)



furan products, resulting from insertion of carbon monoxide into the vinylcarbene intermediate, are obtained. Only when the vicinal diol is protected as the bis-TBDPS ether is the cyclization successful, giving **181** in 72% yield. The failure of the acetate and acetonide derivatives to react is attributed to the ability of the alkoxyl substituents to coordinate to the coordinatively unsaturated metal of vinylcarbene intermediate **182** and thus inhibit coordination of the desired alkene. With the siloxyl substituents, the siloxyl oxygen is both sterically and electronically incapable of coordinating to the coordinatively unsaturated metal. Additionally, it is believed that coordination of the alkoxyl group induces CO insertion and, thus, furan formation since alkynes lacking alkoxyl substituents failed to give analogous CO-insertion-derived products.

VI. Conclusions

As the examples presented in this review demonstrate, the three-component carbene−alkyne−alkene approach to vinylcyclopropanes allows access to a wide variety of highly functionalized bi- and tricyclic ring systems. Studies completed to date have demonstrated that this reaction is capable of smoothly occurring in a variety of scenarios, though in some cases coordination of additional functionality to the in-situ-generated vinylcarbene intermediate has been shown to inhibit the cyclopropanation step and cause other reaction pathways to be favored.

References

(1) Wulff, W. D.; Yang, D. C.; Murray, C. K. *Pure Appl. Chem.* **1988**, *60*, 137−144.
(2) (a) Clarke, T. C.; Yannoni, C. S.; Katz, T. J. *J. Am. Chem. Soc.* **1983**, *105*, 7787−7789. (b) Katz, T. J.; Hacker, S. M.; Kendrick, R. D.; Yannoni, C. S. *J. Am. Chem. Soc.* **1985**, *107*, 2182−2183.
(3) (a) Fox, H. H.; Wolf, M. O.; O'Dell, R.; Lin, B. L.; Schrock, R. R.; Wrighton, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 2827−2843. (b) Schlund, R.; Schrock, R. R.; Crowe, W. E. *J. Am. Chem. Soc.* **1989**, *111*, 8004−8006. (c) Wallace, K. C.; Liu, A. H.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 644−654.
(4) (a) Katz, T. J.; Lee, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 422−424. (b) Katz, T. J.; Sivavec, T. M.; *J. Am. Chem. Soc.* **1985**, *107*, 737−738.
(5) See also: (a) Katz, T. J.; Han, C.-C. *Organometallics* **1982**, *1*, 1093−1095. (b) Han, C.-C.; Katz, T. J. *Organometallics* **1985**, *4*, 2186−2195.
(6) .(a) Parlier, A; Rudler, H.; Platzer, N.; Fontanille, M.; Soum, A. *J. Chem. Soc. Dalton Trans.* **1987**, 1041−1049. (b) Liaw, D.-J.; Soum, A.; Fontanille, M.; Parlier, A.; Rudler, H. *Makromol. Chem., Rapid Commun.* **1985**, *6*, 309−315.
(7) Wood, C. D.; McLain, S. J.; Schrock, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 3210−3222.
(8) Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074−5075.
(9) Doxsee, K. M.; Mouser, J. K. M. *Organometallics* **1990**, *9*, 3012−3014.
(10) For a discussion of titanacyclobutenes, see: (a) Doxsee, K. M.; Mouser *Tetrahedron Lett.* **1991**, *32*, 1687−1690. (b) Doxsee, K. M.; Mouser, J. K. M.; Farahi, J. B. *Synlett* **1992**, 13−21. (c) Doxsee, K. M.; Farahi, J. B.; Hope, H. *J. Am. Chem. Soc.* **1991**, *113*, 8889−8898. (d) Doxsee, K. M.; Juliette, J. J. J.; Mouser, J. K. M.; Zientara, K. *Organometallics* **1993**, *12*, 4682−4686. (e) Doxsee, K. M.; Juliette, J. J. J.; Mouser, J. K. M.; Zientara, K. *Oraganometallics*, **1993**, *12*, 4742−4744.
(11) Casey, C. P.; Polichnowski, S. W.; Shusterman, A. J.; Jones, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 7282−7292.
(12) Dötz, K. H.; Pruskil, I. *J. Organometallic Chem.* **1977**, *132*, 115−120.
(13) Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 644−645.
(14) For a review of carbene complexes in organic synthesis, see: Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 587−608.
(15) (a) Dötz, K. H. *J. Organometallic Chem.* **1977**, *140*, 177−186. (b) Wulff, W. D.; Tang, P.-C.; Chan, K.-S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813−5832.
(16) (a) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*, 5803−5812. (b) Hegedus, L. S.; Schultze, L. M.; Toro, J.; Yijun, C.; *Tetrahedron* **1985**, *41*, 5833−5838.
(17) Dötz, K. H.; Pruskil, L. I.; *Chem. Ber.* **1978**, *111*, 2059.
(18) Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616−7630.
(19) Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S.; 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.
(20) For related examples, see also: (a) McCallum, J. S.; Kunng, F.-A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346−2360. (b) Anderson, B. A.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 8615−8617.
(21) (a) Xu, Y.-C.; Challener, C. A.; Dragisich, V.; Brandvold, T. A.; Peterson, G. A.; Wulff, W. D.; Williard, P. G. *J. Am. Chem. Soc.* **1989**, *111*, 7269−7271. (b) Anderson, B. A.; Bao, J.; Brandvold, T. A.; Challener, C. A.; Wulff, W. D.; Xu, Y.-C.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 10671−10687.
(22) Herndon, J. W.; Tumer, S. U.; Schnatter, W. F. K. *J. Am. Chem. Soc.* **1988**, *110*, 3334−3335.
(23) For a complete study on the scope and limitations of this reaction see: Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394−8404.
(24) Herndon, J. W.; Matasi, J. J. *J. Org. Chem.* **1990**, *55*, 786−788.
(25) Katz, T. J.; Yang, G. X.-Q.; Rickman, B. H.; Iwashita, T. *J. Am. Chem. Soc.* **1993**, *115*, 2038−2039.
(26) 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.
(27) Macomber, D. W. *Organometallics* **1984**, *3*, 1589−1591.
(28) Harvey, D. F.; Niel, D. A. *Tetrahedron* **1993**, *49*, 2145−2150.

(29) Lewis, K. E.; Golden, D. M.; Smith, G. P. *J. Am. Chem. Soc.* **1984**, *106*, 3905−3912.
(30) (a) Principles and Applications of Organotransition Metal Chemistry, 2nd Ed.; pp. 249−151. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. **1987**, University Science Books, Mill Valley, CA. (b) Li, J.; Schreckenbach, G.; Ziegler, T. *J. Am. Chem. Soc.* **1995**, *117*, 486−494.
(31) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800−3801. (b) Fu, G. C.; Nguyen, S. B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857 (c) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.
(32) See also: (a) Nguyen, S. B. T.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 9858−9859. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426−5427. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325.
(33) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, 223−269 (in this issue).
(34) Brookhart, M.; Timmers, D.; Tucker, J. R.; Williams, G. D.; Husk, G. R.; Brunner, H.; Hammer, B. *J. Am. Chem. Soc.* **1983**, *105*, 6721−6723.
(35) Brandt, S.; Helquist, P.; *J. Am. Chem. Soc.* **1979,** *101*, 6473−6475.
(36) (a) Dötz K. H.; Fischer E. O. *Chem. Ber.* **1972**, *105*, 1356−1367. (b) Dotz K. H.; Fischer E. O. *Chem. Ber.* **1972**, *105*, 3966−3973. (c) Dotz K. H.; Fischer E. O. *Chem. Ber.* **1970**, *103*, 1273−1278.
(37) Wienand, A.; Reissig, H.-U. *Organometallics* **1990**, *9*, 3133−3142.
(38) Herndon, J. W.; Tumer, S. U. *Tetrahedron Lett.* **1989**, *30*, 4771−4774.
(39) (a) Casey, C. P.; Burkhart, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 7808−7809. (b) Casey, C. P.; Tuinstra, H. E.; Saeman, M. C. *J. Am. Chem. Soc.* **1976**, *98*, 608−609.
(40) Casey, C. P., *Reactive Intermediates-A, Vol II*, **1981**, 136−174.
(41) For a discussion of tungsten−carbene−alkene intermediates in cyclopropanation, see also: (a) Casey, C. P.; Shusterman, A. J. *Organometallics* **1985**, *4*, 736−744. (b) Casey, C. P., Vollendorf, N. W.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 3754−3764. (c) Casey, C. P.; Hornung, N. L.; Kosar, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 4908−4916.
(42) Toledano, C. A.; Rudler, H.; Daran, J. C.; Jeanin, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 574−576.
(43) Harvey, D. F; Brown, M. F. *Tetrahedron Lett.* **1990**, *31*, 2529−2532.
(44) Wulff, W. D.; Yang, D. C.; Murray, C. K. *J. Am. Chem.* **1988**, *110*, 2653−2655.
(45) For a discussion of photochemically induced cycloaddition reaction of chromium carbene complexes with 1,3-dienes, see: (a) Söderberg, B. C.; Hegedus, L. S.; Sierra, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 4364−4374. (b) Köbbing, S.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 927−930.
(46) Barluenga, J.; Aznar, F.; Martín, A.; García-Granda, S.; Salvadó, M. A.; Pertierra, P. *J. Chem. Soc., Chem. Commun.* **1993**, 319−321.
(47) See also: Barluenga, J.; Aznar, F.; Martín, A.; Barluenga, S.; García-Granda, S.; Paneque-Quevedo, A. *J. Chem. Soc., Chem. Commun.* **1994**, 843−844.
(48) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría J.; López-Ortiz, F. *J. Chem. Soc., Chem. Commun.* **1994**, 321−322.
(49) (a) Buchert, M.; Reissig, H.-U. *Tetrahedron Lett.* **1988**, *29*, 2319−2320. (b) Buchert, M.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2723−2729.
(50) Herndon, J. W.; Tumer, S. U. *J. Org. Chem.* **1991**, *56*, 286−294.
(51) See also: Fischer, H.; Hoffman, J. *Chem. Ber.* **1991**, *124*, 981−988.
(52) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916−8921.
(53) (a) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M.; Yijun, C.; Anderson, O. P. *J. Am. Chem. Soc.* **1984**, *106*, 2680−2687. (b) Borel, C.; Hegedus, L. S.; Krebs, J.; Satoh, Y. *J. Am. Chem. Soc.* **1987**, *109*, 1101−1105.
(54) See also: (a) Hegedus, L. S.; Imwinkelried, R.; Alarid-Sargent, M.; Dvorak, D.; Satoh, Y. *J. Am. Chem. Soc.* **1990**, *112*, 1109−1117. (b) Alcaide, B.; Dominguez, G.; Plumet, J.; Sierra, M. A. *J. Org. Chem.* **1992**, *57*, 447−451.
(55) Parlier, A.; Rudler, H.; Platzer, N.; Fontanille, M.; Soum, A. *J. Organomet. Chem.* **1985**, *287*, C8-C12.
(56) Alvarez, C.; Levisalles, J.; Rudler, M.; Rudler, H.; Daran J. C.; Jeannin, Y. *J. Organomet. Chem.* **1982**, *228*, C7.
(57) Alvarez, C.; Parlier, A.; Rudler, H.; Yefsah, R.; Daran, J. C.; Knobler. C. *Organometallics* **1989**, *8*, 2253−2259.
(58) Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995**, *60*, 4184−4195.
(59) Harvey, D. F.; Brown, M. F. *J. Am. Chem. Soc.* **1990,** *112*, 7806−7807.
(60) Wienand, A.; Reissig, H. U. *Tetrahedron Lett.* **1988**, *29*, 2315−2318.
(61) Wulff, W. D.; Xu, Y.-C. *Tetrahedron Lett.* **1988**, *29*, 415−418.
(62) See also: Xu, Y.-C.; Challener, C. A.; Dragisich, V.; Brandvold, T. A.; Peterson, G. A.; Wulff, W. D *J. Am. Chem. Soc.* **1989**, *111*, 7269−7271.
(63) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1991**, *32*, 5223−5226.
(64) Wulff, W. D.; Kaesler, R. W. *Organometallics* **1985**, *4*, 1461−1463.
(65) (a) Hoye, T. R.; Rehberg, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 2841−2842. (b) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070−2071. (c)Hoye, T. R.; Korkowski, P. F.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676−2678.
(66) Katz, T. J.; Yang, G. X. Q. *Tetrahedron Lett.* **1991**, *32*, 5895−5898.
(67) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1990**, *9*, 3014−3015.
(68) Harvey, D. F.; Lund, K. P.; Neil, D. A. *Tetrahedron Lett.* **1991**, *32*, 6311−6314.
(69) Harvey, D. F.; Lund, K. P.; Neil, D. A. J. *Am. Chem. Soc.* **1992**, *114*, 8424−8434.
(70) Katz, T. J.; Yang, G. X. Q. *Tetrahedron Lett.* **1991**, *32*, 5895−5898.
(71) Harvey, D. F.; Sigano, D. M., manuscript in preparation. Presented at the 207th National Meeting of the American Chemical Society, San Diego, CA, March, 1994, Organic paper 65.
(72) Sigano, D. M., unpublished results.
(73) Mori, M.; Watanuki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1082−1084.
(74) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 5066−5068.
(75) Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994,** *116*, 6719−6732.
(76) Harvey, D. F.; Grenzer, E. M., manuscript submitted for publication.
(77) See also: Hoye, T. R.; Chen, K.; Vyvyan, J. R. *Organometallics* **1993**, *12*, 2806−2809.
(78) Harvey, M. F.; Brown, M. F. *J. Org. Chem.* **1992**, *57*, 5559−5561.
(79) For a recent discussion, see: Parrill, A. L.; Dolata, D. P. *Tetrahedron Lett.* **1994**, *35*, 7319−7322.
(80) Schleyer, P. V. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368−1373.
(81) Bruice, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5828−5865.
(82) (a) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224−232. (b) Jung, M. E.; Trifunovich, I. D.; Lensen, N. *Tetrahedron Lett.* **1992**, *33*, 6719−6722.
(83) Lund, K. P.; Ph.D. Dissertation, University of California, San Diego, **1992**.
(84) Since the corresponding enol ethers were found to readily hydrolyze during isolation, this mixture was directly treated with dilute HCl in H_2O and smoothly converted to the ketone.
(85) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1991**, *32*, 5223−5226.
(86) Backenstrass, F., unpublished results.

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