

Cyclopropanations and cycloadditions of transition metal carbene complexes

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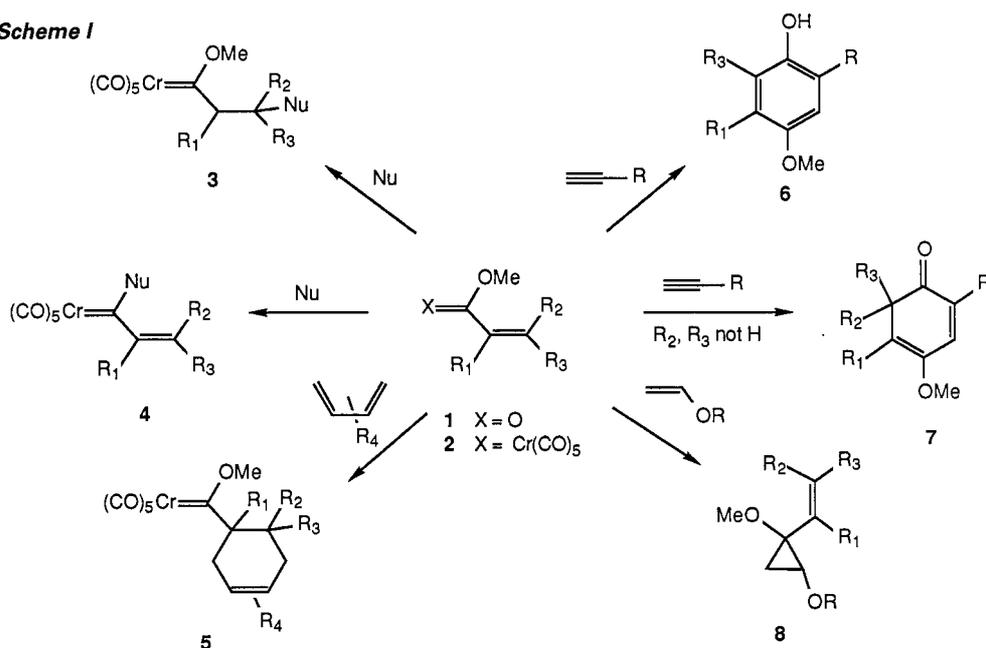
Abstract - The first examples of the cyclopropanation of 1,3-dienes with transition metal carbene complexes is reported for the heteroatom-stabilized pentacarbonyl complexes of the group 6 metals. The reaction of the chromium phenylmethoxymethylene complex **36** with Danishefsky's diene gives varying amounts of cyclopropanes and metathesis products whose distribution is carbon monoxide dependent. The reactions of the cyclohexenylmethoxymethylene complexes is metal dependent. The chromium complex **12a** gives a chemoselective reaction with Danishefsky's diene resulting in the formation of cyclopropanes, whereas, the same reaction of the tungsten complex **12b** chemoselectively gives Diels-Alder cycloadducts. Some cyclopropanation reactions of the phenylmethoxymethylene complex **36** with silyl enol ethers and enamines are also presented.

INTRODUCTION

The synthetic applications and methodology based on the reactions of transition metal carbene complexes can be found in the literature with increasing regularity.² The heteroatom-stabilized complexes of the group 6 metals in particular have a broad range of applications in synthetic organic chemistry. One of the reasons for this is likely due to the extensive and dual-nature of the reaction chemistry of these complexes. As illustrated by the three reactions on the left half of Scheme I, one part of the reaction chemistry of the pentacarbonyl carbene complexes of the group 6 metals can be anticipated from the reaction chemistry of esters. This is illustrated for the α,β -unsaturated chromium complex **2** in which the carbene carbon has a vinyl and a methoxyl substituent and for which the corresponding ester is the substituted acrylate **1**. Unsaturated carbene complexes such as **2** will undergo Michael addition reactions.³ As is the case with esters of the type **1**, the complex **2** will also undergo 1,2 addition with substitution for the methoxyl group.⁴ We reported four years ago that unsaturated carbene complexes of the type **2** will also undergo cycloaddition reactions.⁵ The chromium pentacarbonyl group is a reactivity and selectivity auxiliary and the complex **2** can function as a synthon for the acrylate **1** in the Diels-Alder reaction since the metal unit in the adduct **5** can be easily oxidatively removed to give the corresponding methyl ester. For those reactions that are mirrored in the reaction chemistry of esters, it is often observed that the reactions of carbene complexes are greatly accelerated with respect to those of their ester counterparts. For example, a Diels-Alder reaction of a chromium carbene complex has been found to be over 10^4 times faster than that of its corresponding ester with the same diene.⁵

There is another part of the reaction chemistry of group 6 carbene complexes that bears no relationship to the reaction chemistry of esters whatsoever and is illustrated by the three examples on the right half of Scheme I. The reaction of unsaturated carbene complexes of chromium with acetylenes produces benzannulated products of the type **6**. This reaction which was first reported by Dotz twelve years ago,⁶ and at the present time its importance in synthetic organic

Scheme I

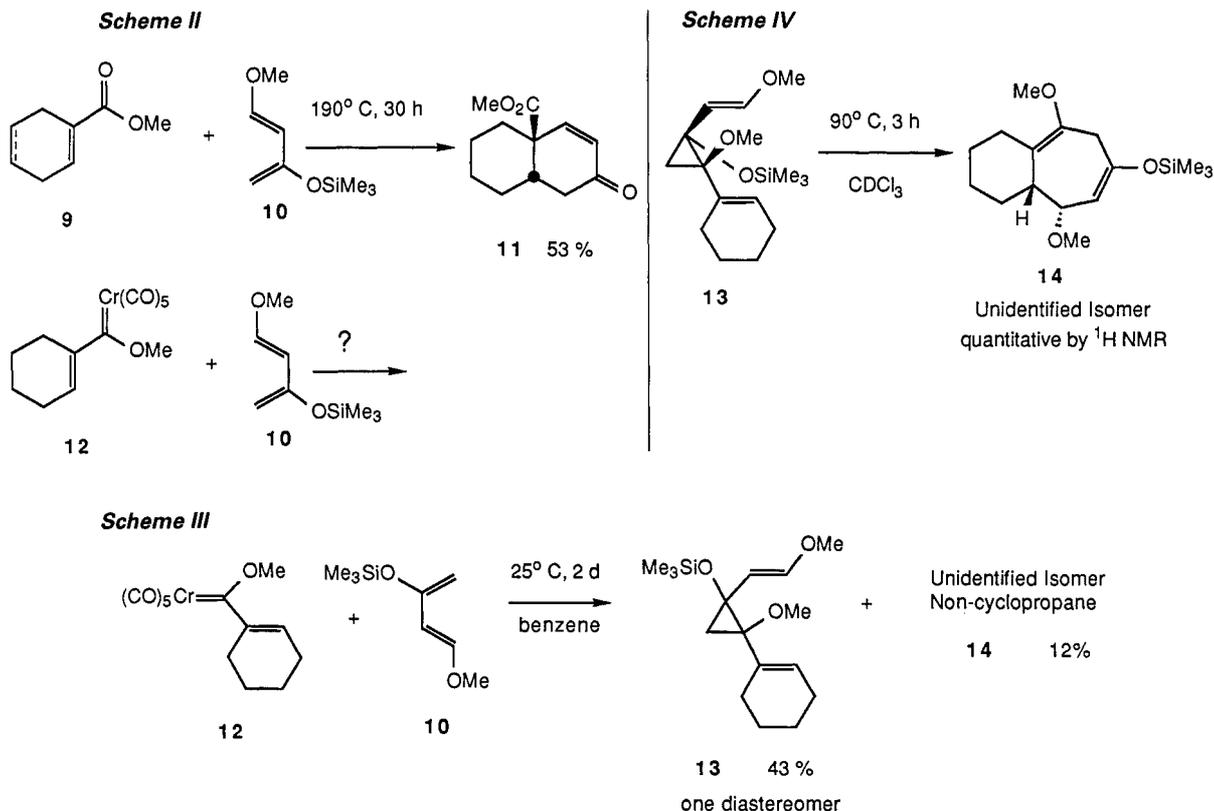


chemistry is well established and has been incorporated in a number of natural product syntheses.² Three years ago we introduced a variant of this reaction that produces cyclohexadienones if R_2 and R_3 in complex **2** are groups of low migratory propensity.⁷ Another example of a reaction that is not possible for esters is the cyclopropanation of olefins by transition metal carbene complexes.⁸ Cyclopropanations reactions of a variety of metal carbene complexes have been investigated, and was one of the first reactions of group 6 complexes that was examined with respect to synthetic applications. For the group 6 heteroatom-stabilized complexes, this reaction was found to produce useful amounts of cyclopropanes only with electron rich and with electron deficient olefins. For as long as this reaction has been known, there has not yet been appeared any synthetic applications of the cyclopropanation of olefins with group 6 carbene complexes. This review will mainly center on several aspects of the cyclopropanation reaction, but will begin with the Diels-Alder reactions of group 6 pentacarbonyl carbene complexes.

REACTION OF GROUP 6 CARBENE COMPLEXES WITH 1, 3-DIENES

The Diels-Alder reactions of α,β -unsaturated carbene complexes of the type **2** with dienes was first reported in 1983 and is a reaction that as of yet has not been completely explored, but the early results suggest that it may prove to be very important with regard to synthetic applications in organic chemistry.⁵ The first reports described the cycloadditions of relatively unsubstituted examples, but which nonetheless were found to occur with rates that were greatly accelerated with respect to their ester analogs.⁹ After finding that the greatly enhanced rates for these Diels-Alder reactions extends to a number of different carbene complexes and dienes, we became interested in determining the limits of the synthetic potential of these reactions. The reaction of the ester **9** with Danishefsky's diene is on the edge of the limits for the Diels-Alder reactions of esters with this diene.¹⁰ The cyclohexenyl ester **9** gave a 53 % yield of the hydrolyzed adduct **11** in 30 hours at 190° C. The reaction of the cyclohexa-1,4-dienyl ester corresponding to **9** gave similar results and was the first step in Danishefsky's synthesis of vernolepin and thus high throughput for this reaction was needed.¹¹ If not the ultimate, then certainly a most challenging test of the accelerating effect of the chromium pentacarbonyl group would thus be the reaction of the cyclohexenyl complex **12** with Danishefsky's diene. In view of the high thermal requirement for the reaction of **9** with **10**, it is not clear that even if the complex **12** displays the typical rate enhancement over esters, the reaction with the diene **10** may still have a thermal requirement that is at a point higher than the thermal stability of the starting carbene complex.

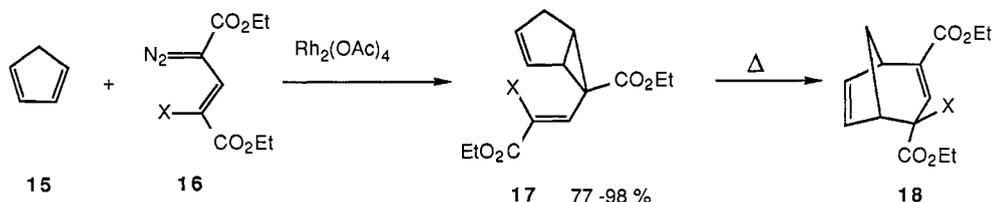
Our expectations were exceeded when it was found that the rate of the reaction of the cyclohexenyl complex **12** with Danishefsky's diene was such that the reaction was complete at room temperature in 48 hours, however, it came as a complete surprise that the major product from this reaction was the cyclopropane **13** and not a Diels-Alder adduct. A second product was obtained from this reaction in 12 % yield which was not immediately characterized other than it was determined not to be a Diels-Alder product, and was an isomer of **13** but was not a cyclopropane. The cyclopropane **13** was obtained as a single diastereomer and is the result of the regioselective transfer of the carbene ligand to the most electron-rich double bond of the diene **10**. The cyclopropanation of 1,3-dienes with transition metal carbene complexes has not previously been reported although a metathesis reaction has been observed.¹²



The stereochemistry of the cyclopropane **13** was assigned as *trans* on the basis of the fact that it had to be heated to 90 °C before it would undergo a Cope rearrangement. It is known that *cis*-divinylcyclopropanes undergo Cope rearrangements at or below room temperature and that they are not normally isolable.¹³ The Cope rearrangements of the *trans*-isomers of divinylcyclopropanes have been demonstrated to occur with initial isomerization to the *cis*-isomers followed by a Cope rearrangement *via* a boat transition state.¹⁴ This is consistent with the stereochemistry observed for the Cope product **14**. The Cope product **14** was found to have spectral properties identical with those of the unidentified isomer of **13** produced in the reaction of complex **12** and diene **10**.

The overall sequence to the seven-membered ring product **14** involves a tandem cyclopropanation/Cope rearrangement. The cyclopropanation of 1,3-dienes with transition metal carbene complexes is unknown and the closest reaction sequence known in the literature is that of the rhodium catalyzed reaction in Scheme V.¹⁵ The diazo compound **16** may react with cyclopentadiene *via* the intermediacy of a rhodium carbene complex, but in any event the reaction gives the *cis*-divinylcyclopropane **17** which is only isolable in the case where the substituent R is non-hydrogen and can be converted by mild thermolysis to the Cope rearrangement product **18**.

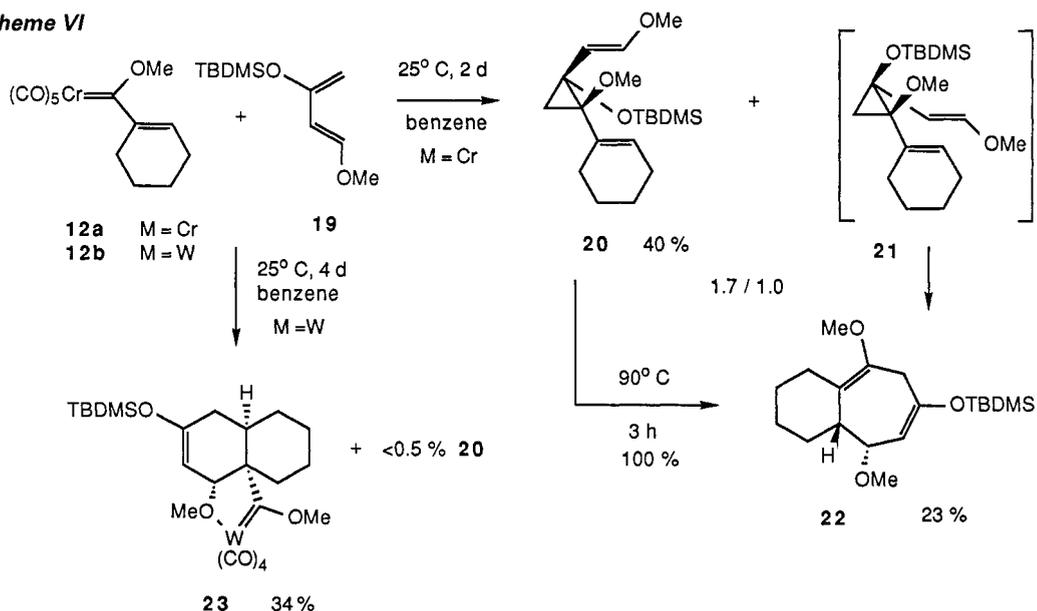
Scheme V



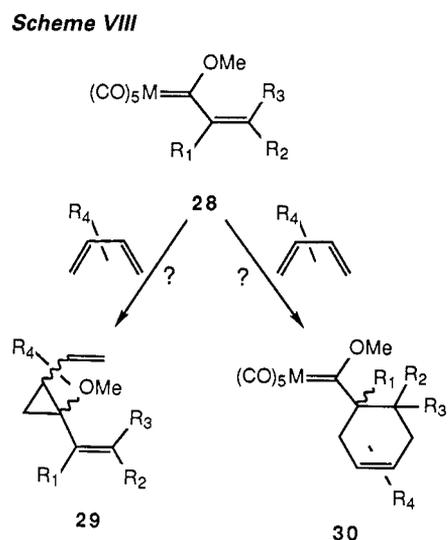
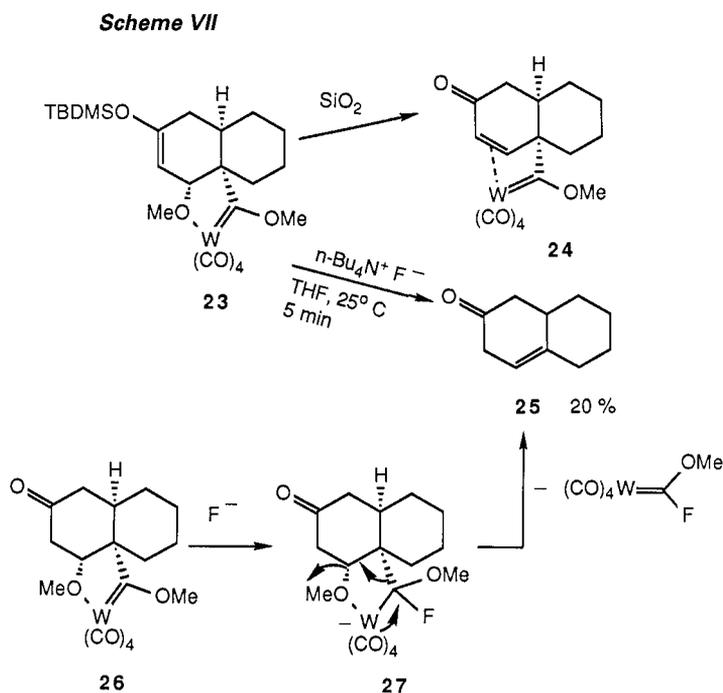
Since *cis*-divinylcyclopropanes undergo Cope rearrangement much faster than their corresponding *trans* isomers, it can be deduced that the ratio of the *trans*-cyclopropane product and the Cope product from the reaction of the cyclohexenyl carbene complex **12a** and Danishefsky's diene is a reflection of the stereoselectivity of the cyclopropanation reaction. This is illustrated in Scheme VI for the reaction with 3-*t*-butyldimethylsiloxy-1-methoxybutadiene **19** which produces a more chromatographically stable derivative of the Cope product. In this reaction the cyclopropane **20** is obtained in 40% yield and the Cope product **22** is obtained in 23% yield and therefore the stereoselectivity of the cyclopropanation reaction is 1.7:1.0. Since the thermal rearrangement of the cyclopropane **20** is nearly quantitative, this reaction can be utilized for the preparation of highly functionalized fused seven-membered rings in good overall yield. This investigation came full circle with another surprise when it was found that the tungsten complex **12b** gives the Diels-Alder adduct **23** at room temperature! The yield of the Diels-Alder reaction is only 34% but the increased rate of this reaction compared to that of the cyclohexenyl ester **9** (Scheme II) is quite remarkable.

From the point of view of the synthetic methodological development of transition metal organometallics, the two reactions indicated in Scheme VI represent an ideal situation. The reaction of the carbene complex **12** with Danishefsky's diene can be fine tuned to give either the tandem cyclopropanation / Cope product **22** or the Diels-Alder product **23** by adjusting the nature of the metal in the complex. These reactions are highly chemoselective in their reactions with Danishefsky's diene as the chromium complex **12a** gave no detectable amounts of the Diels-Alder product, and the tungsten complex **12b** gave less than 0.5% of the cyclopropane **20**. There were a few other minor products produced from the reaction of the tungsten complex that as of yet have not been identified.

Scheme VI

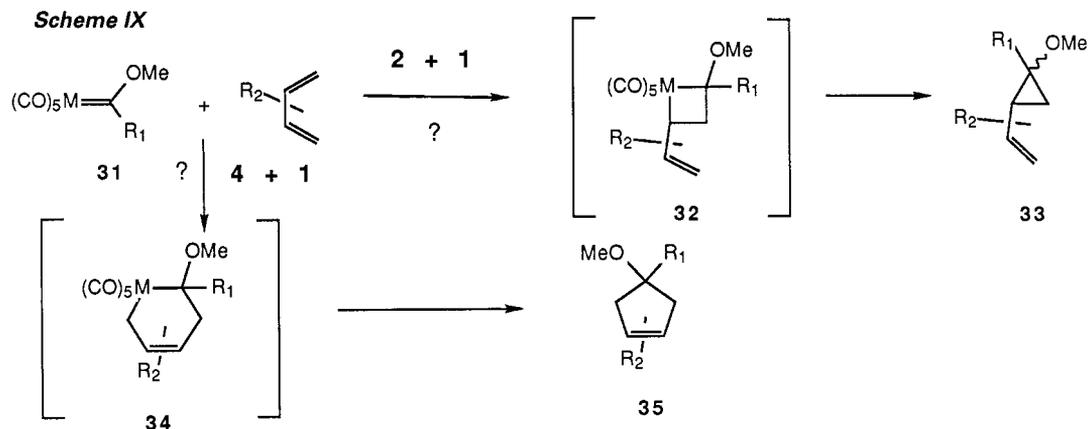


Two interesting transformations of the Diels-Alder adduct **23** are indicated in Scheme VII. Hydrolysis of the silyl enol ether of the cycloadduct **23** gives rise to the carbene complex **24** in which the enone double-bond is coordinated to the tungsten. Several examples of alkene-carbene complexes are known and most have been shown to give cyclopropanes upon thermolysis.¹⁶ In an attempt to prepare the complex **26** which requires the cleavage of the silyl enol ether without elimination of the methoxy group, the cycloadduct **23** was treated with tetrabutylammonium fluoride. The only product to be isolated from this reaction (not-optimized) was the decalene **25**. This type of reaction has not been observed before for transition metal carbene complexes, but in ester chemistry would be analogous to a reductive decarboxylation. The mechanism for this reaction is not known, but two possibilities are likely. It is possible that fluoride attacks the carbene carbon to give the intermediate **27**, and then a reductive fragmentation would account for the product. At this time there is no evidence for the formation of a fluoromethoxy carbene complex of tungsten. An alternative mechanism begins with the nucleophilic cleavage of the methyl-oxygen bond of the methoxy group on the carbene carbon of the intermediate **26**.

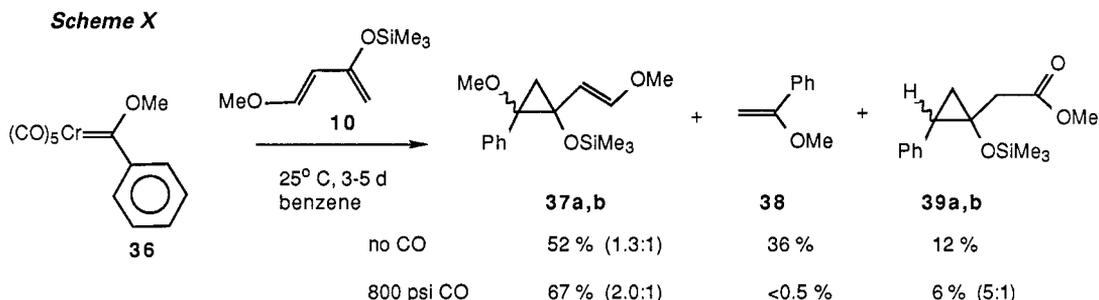


The tandem cyclopropanation / Cope rearrangement sequence and the Diels-Alder reaction in Scheme VI have obvious potential in natural product synthesis. A key factor in their successful implementation will be the understanding of the reasons for the extreme sensitivity of the chemoselectivity of the reactions of group 6 carbene complexes with dienes to the nature of the metal in the complex. General studies are in progress to determine how the distribution between Diels-Alder and cyclopropanation products will vary with the substitution pattern and functionality in the diene and in the carbene complex.

There is a third possible outcome for the reactions of group 6 carbene complexes and 1,3-dienes that is not indicated in Scheme VIII. An initial cycloaddition of the diene and the chromium carbon double-bond would give an intermediate of the type **34** in Scheme IX, and the most likely consequence of this event would be a reductive elimination and the isolation of the cyclopentene derivative **35**. This transformation is formally a [4 + 1] cycloaddition and is an as of yet unprecedented reaction. The likelihood of this outcome can perhaps be enhanced by removing the possibility of a cycloaddition on the carbene carbon substituent ($R_1 \neq \text{vinyl}$), however, there would still remain the possibility of a [2 + 1] cycloaddition leading to cyclopropanes.

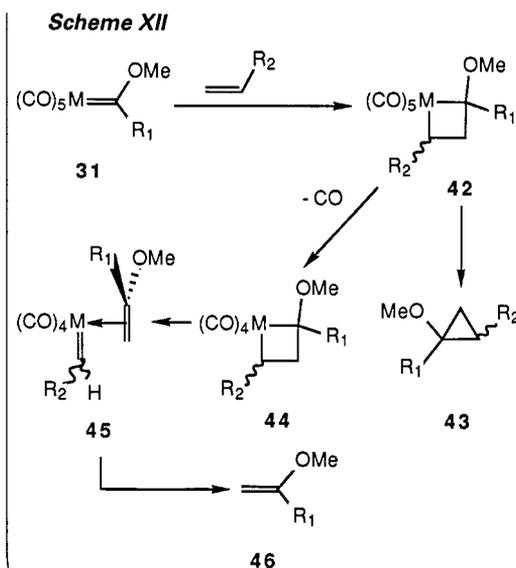
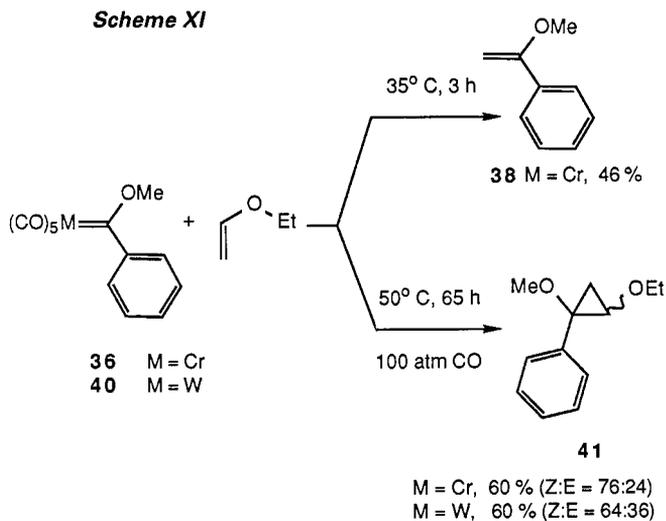


The reaction of the phenyl chromium complex **36** with Danishefsky's diene at room temperature in benzene went to completion in 5 days and gave a 52 % yield of the vinylcyclopropanes **37a** and **37b** (stereochemistry not assigned) and a 36 % yield of α -methoxystyrene which is the metathesis product resulting from the fragmentation of the metallacyclobutane intermediate **32**. The yield of the cyclopropane products **37** can be increased and the amount of metathesis product can be essentially eliminated if the reaction is carried out under 800 psi of carbon monoxide. No cyclopentene products could be found from this reaction and thus there is no evidence for the reaction pathway indicated in Scheme IX that begins with a [4 + 2] cycloaddition on the chromium carbon double-bond. The reaction did unexpectedly produce the cyclopropane **39** which is related to the expected cyclopropanation product **37** but has suffered a reduction of the cyclopropyl methoxy and an oxidation of the β -vinyl carbon. Labelling studies conducted to elucidate the mechanism by which this abnormal cyclopropanation product is formed will be presented elsewhere.¹⁷



REACTION OF GROUP 6 CARBENE COMPLEXES WITH ELECTRON RICH OLEFINS

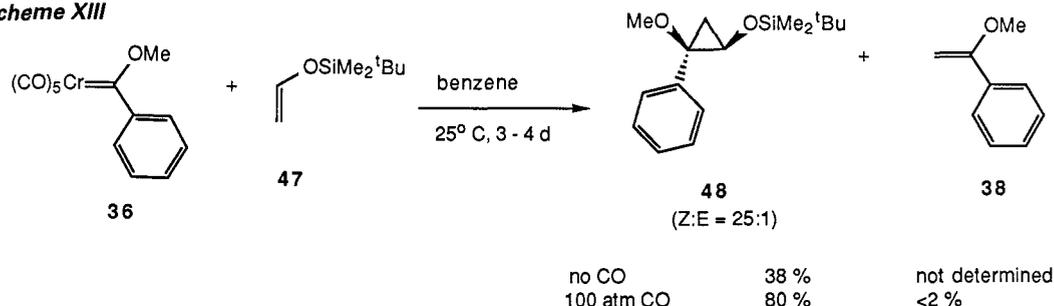
The stoichiometric cyclopropanation of olefins with Fischer carbene complexes was one of the first reactions investigated subsequent to the discovery of transition metal carbene complexes. The reaction fails with unactivated olefins, but can give useful yields with electron rich¹⁸ and electron deficient¹⁹ olefins. The reaction of the phenyl complex **36** with ethyl vinyl ether gives the metathesis product **38**. The cyclopropane **41** can only be obtained if the reaction is carried out under 100 atmospheres of carbon monoxide. The chromium and the tungsten complexes both give 60 % yield of the cyclopropane with only slightly different stereoselectivities. In light of these early observations it is curious that the cyclopropanation of the cyclohexenyl chromium complex **12a** with Danishefsky's diene gives essentially the same yield of cyclopropane products (**20** + **21**) but in the absence of carbon monoxide. It is likewise curious that the reaction of the phenyl complex **36** with Danishefsky's diene also gives a comparable yield of cyclopropanes (52 + 12 %) in the absence of carbon monoxide.



The cyclopropanation reactions of carbene complexes have been shown not to involve free carbenes. One supporting piece of evidence is the transfer of chirality from a complex bearing a chiral phosphine ligand to the cyclopropane product.²⁰ The dependence of the stereochemistry of the cyclopropane product **41** on the nature of the metal also suggests that a free carbene is not an intermediate.¹⁸ Casey has proposed the mechanism in Scheme XII to account for the affect of carbon monoxide on the distribution between metathesis and cyclopropane products.²¹ Addition of the olefin to the carbene complex generates the metallacyclobutane **42** as the key intermediate. Reductive elimination leads directly to the cyclopropane. In the absence of an external pressure of carbon monoxide, ligand dissociation occurs to give the unsaturated metallacyclobutane intermediate **44**. As a consequence of its open coordination site, this intermediate can undergo carbon-carbon bond rupture to give the olefin carbene complex **45** and hence produce the metathesis product **46**. It has not yet been resolved whether this or other mechanistic possibilities actual pertain for these or any other cyclopropanation reactions of carbene complexes, particularly with non-heteroatom stabilized or cationic complexes.⁸

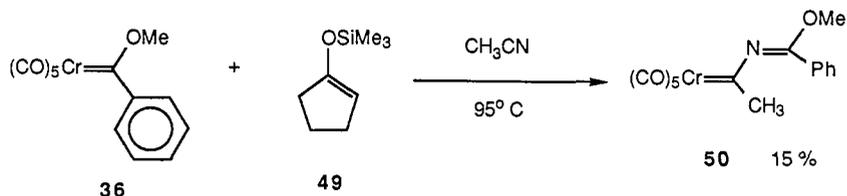
In the absence of data which can distinguish between the various mechanisms for cyclopropane formation, the general observations are that Danishefsky's diene will give cyclopropane products in the absence of carbon monoxide, whereas, the presence of carbon monoxide is a necessary condition for the formation of cyclopropanes from the reactions with ethyl vinyl ether. One question to be asked is whether this carbon monoxide dependence correlates with the electron density of the diene. In other words, how much of the functionality of Danishefsky's diene is needed in order to see cyclopropane products in the absence of carbon monoxide? Are both oxygen substituents necessary and/or are both double-bonds necessary? These questions are currently being addressed, and in a preliminary result shown in Scheme XIII the answer is that not much of the functionality of Danishefsky's diene is needed. The silyl enol ether **47** will react with the phenyl chromium complex **36** to give the cyclopropane **48** in 38 % yield along with substantial amounts (not yet quantified) of the metathesis product **38** in the absence of carbon monoxide. Under 100 atmospheres of carbon monoxide, the cyclopropane **48** is obtained in 80 % yield as a 25:1 mixture of diastereomers in favor of the Z-isomer with less than detectable amounts of the metathesis product being formed.

Scheme XIII



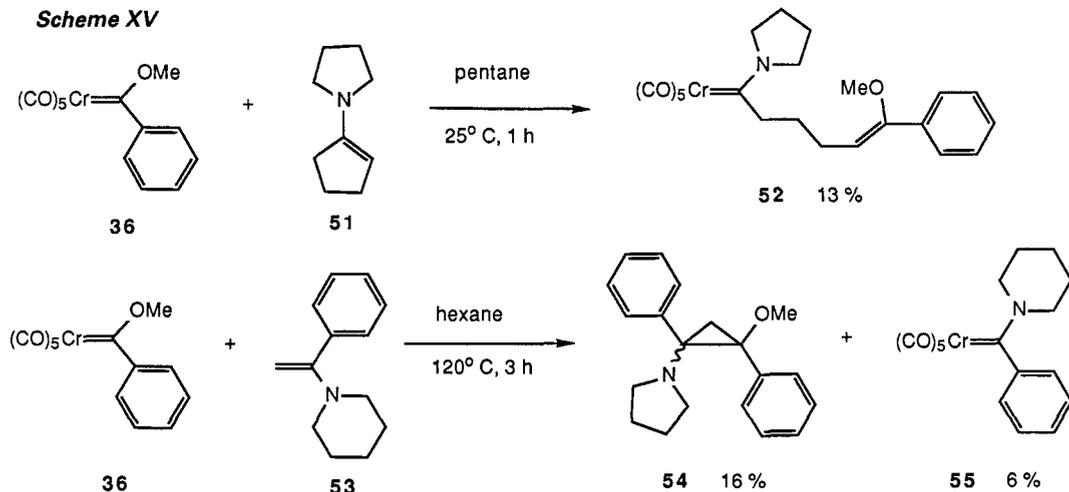
Investigations of the scope, stereoselectivity, and synthetic applications of the cyclopropanations of carbene complexes with silyl enol ethers are continuing, but the reaction shown in Scheme XIV gives an idea of the upper limit of this reaction. The reaction of the silyl enol ether of cyclopentanone with the phenyl complex **36** did not go until the reaction was heated to 95° C for several days. Under these conditions the reaction went to completion, but no cyclopropanation products could be isolated from the reaction mixture. The only reaction observed was that of the carbene complex with the solvent acetonitrile to give the insertion product **50**. Insertion reactions of this type have been observed before, but only with electron rich nitriles such as cyanamides.²² This is the first example of the insertion of an organonitrile into the chromium carbon bond of a group 6 carbene complex.²³

Scheme XIV



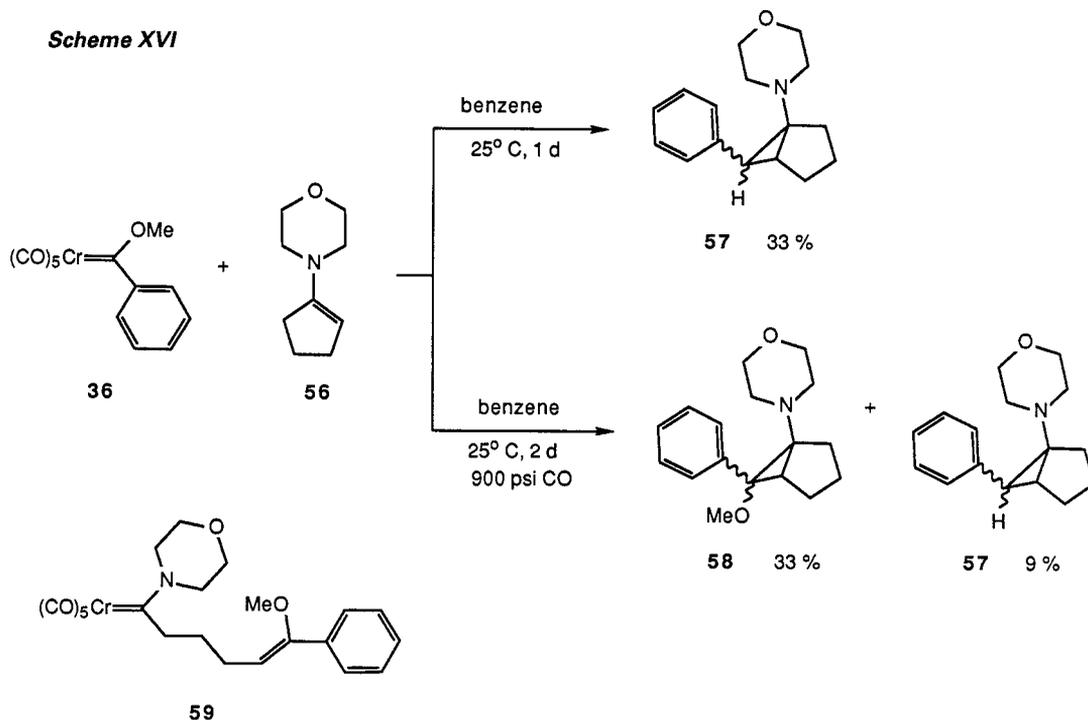
Conceptually, it should be possible to extend the scope of the cyclopropanation reactions to more highly substituted olefins by employing the more electron rich enamines. There are two reports²⁴ of the reactions of group 6 carbene complexes with enamines in the literature and in one example it was found that the pyrrolidine enamine of cyclopentanone **51**, unlike its silyl enol ether analog **49**, will react with the phenyl carbene complex **36**, however, under the conditions reported only the metathesis product **52** was obtained and no cyclopropane was reported.^{24b} The phenyl complex **36** was reported to cyclopropanate the piperidine enamine of acetophenone in low yield to give the cyclopropane **54** with unspecified stereochemistry. A small amount of the metathesis product **55** was also observed for this reaction.^{24b}

Scheme XV



Although the reaction of the enamine **51** with complex **36** does not produce cyclopropane products, we were encouraged by its high reactivity reflected in the fact the reaction with the phenyl complex **36** occurs in one hour at room temperature. We found that the reaction of the morpholino enamine of cyclopentanone **56** occurs at a slightly slower rate but still at room temperature in a reasonable period of time to give the cyclopropane **57** in 33 % yield as a single diastereomer whose stereochemistry has not yet been assigned. This is a reduced derivative of the expected cyclopropanation product **58** where the methoxyl group on the cyclopropyl carbon bearing the phenyl group has been replaced by a hydrogen. The expected cyclopropanation product **58** can be obtained from this reaction also as a single diastereomer if the reaction is carried out under 900 psi of carbon monoxide, conditions under which still small amounts of the reduced cyclopropane **57** is still produced. Both reactions also gave the metathesis product **59**, but the amount from each reaction has not yet been quantified. The mechanism for the formation of the reduced cyclopropane **57** is not known at this time, but the structure of this cyclopropane is related to the reduced cyclopropane **39** obtained from the reaction of the phenyl complex **36** with Danishefsky's diene.

Scheme XVI



CONCLUSIONS

The cyclopropanations of the group 6 pentacarbonyl carbene complexes have been known and studied for fifteen years yet they have not been utilized in synthesis. The initial studies on the cyclopropanations of silyl enol ethers and enamines described herein suggest that further studies are needed to determine the scope of the cyclopropanations of electron rich olefins with group 6 carbene complexes. The first examples of the reactions of group 6 carbene complexes with 1,3-dienes reveal that the preferred reaction path leads to cyclopropanes rather than cyclopentenones, i.e., [2 + 1] rather than [4 + 1] cycloaddition. The reaction is regioselective leading to addition to the most electron rich double-bond of an unsymmetrical diene. The reactions of α,β -unsaturated carbene complexes with 1,3-dienes have the additional option of [4 + 2] cycloaddition and the cyclohexenyl complexes **12** provide a dramatic example of chemoselective control in an organometallic reaction. The chromium cyclohexenyl chromium complex **12a** gives exclusively cyclopropanation products, whereas, the tungsten complex **12b** gives the Diels-Alder product to the exclusion of cyclopropanes. Further studies will be needed to examine this remarkable affect of the nature of the metal on the product distribution in these reactions.

Acknowledgements

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