# Chapter One

## Introduction

Since the discovery and synthesis of the first chromium-pentacarbonyl carbene complex (e.g. **1**) by E. O. Fischer and A. Maasbol in 1964, there has been a surge in their use in organic synthesis. Complexes of this type have been used as synthons in key steps in the total synthesis of a wide range of natural products, including; Vitamins E **2** and K1 **3**, as well as antibiotics such as nanaomycin **4**.

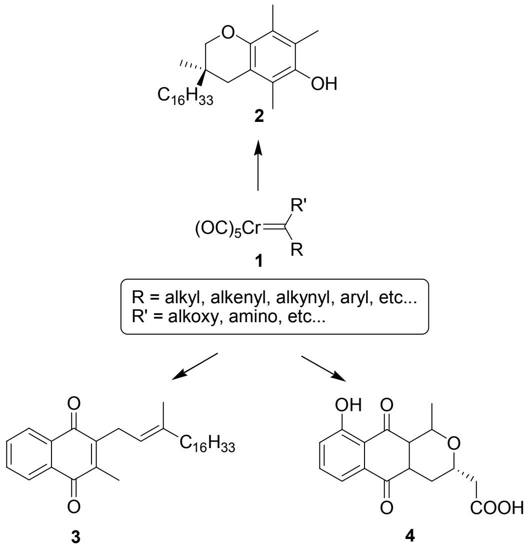

Figure One: Natural Products Prepared by Complexes

This review focuses on the use of such complexes in the synthesis of both carbocyclic and heterocyclic molecules through a plethora of cycloaddition and cyclization processes, concentrating on the synthesis of three- to seven-membered ring containing products. However, in addition to this, the structure and bonding of carbene complexes is also discussed. In particular, an analysis of information gained through computational analysis is provided. Such information has been used to rationalize most of the observed reaction pathways and hence is crucial to the total understanding of the chemistry of chromium-pentacarbonyl carbene complexes.

Fischer carbene complexes exhibit two characteristic features that are important in understanding their respective chemistry. The first of these features is the fact that these complexes tend to contain transition metals in low oxidation states. The most common Fischer carbene complexes are those of the group 6 transition metals (Cr, Mo, W), in which the metal moiety exists in a zero oxidation state.

However, more important is the fact that the carbene moiety in such complexes is electrophilic, hence it tends to react readily with nucleophiles as will be illustrated in later sections of this review.

These two properties set Fischer carbene complexes in stark contrast to the so-called “Schrock carbenes” which were discovered by Richard R. Schrock in 1974.

Whilst Fischer carbene complexes with ligands other than carbon monoxide are known and readily encountered, for the purposes of this review, only pentacarbonyl-substituted complexes will be investigated, and furthermore, only those complexes for which the constitutent metal is chromium will be investigated. Whilst there are subtle differences in the reactivity of the complexes of molybdenum and tungsten, the main differences seem to be only in the ratio of product distribution and not in the chemical nature of the products formed.

## Chapter Two

## Modes of Bonding and the Structure of Chromium-Pentacarbonyl Carbene Complexes

The bonding between the metal and the carbene ligand in such complexes is often described using the Dewar-Chatt-Duncanson model, which is the same model used to rationalize the bonding between transition metals and other p-acceptor ligands such as alkenes and cyano functionalities. In that respect, there are two synergic bonding interactions that exist; these are exemplified below in figure three

The first of these synergic bonding modes involves s-donation from the occupied A1 orbital of the carbene ligand to the formally vacant dz2 orbital on the chromium atom. This is also termed for the benefit of consistency in the chapters to come as “charge donation”.

The second synergic bonding mode involves p-back donation. Electron density from the occupied dxz orbital on the chromium metal is back-bonded through to the formally vacant p-orbital on the carbene ligand. The carbene ligand in such complexes exists in a singlet state (S1) with both electrons being spin paired in the lower energy hybrid orbital, resulting in the vacancy of the higher energy p-orbital. The metal-carbene bond is thus formally regarded as a double bond, although the extent to which this statement is valid depends on the nature of the substituents bound to the carbene ligand. It has also been proposed that the p-bond character of the metal-carbene-R′ (where R′ is generally a mesomerically electron donating substituent) fragment can be described as a Cr-C-R′ 3-centre 4-electron bond (3c,4e).

## Computational Analysis of Chromium Pentacarbonyl Carbene Complexes

There has been an appreciably amount of theoretical study into the bonding and structure of carbene complexes of this type. Early analyses were carried out using semi-empirical methodologies, Hartree-Fock (HF) and many post-HF methodologies. However, most of the modern analyses have been carried out using density functional theory (DFT). In this chapter, quantification of the extent of metal-carbene charge/back-donation, metal-carbene bond length, and electrophilicity index of the carbene ligand have been studied using a wide range of computational methodologies.

## An Analysis of the Extent of Charge-Donation and Back-Donation Between the Metal and Carbene Moiety

In the previous section of this chapter, the idea was developed that the bonding between the metal and carbene moiety in these complexes involves two synergic bonding modes or interactions. This was qualitatively explained using the Dewar-Chatt-Duncanson model. However, studies have been published which have quantified this model by determining the relative number of electrons involved in both charge-donation and back-donation using computational methodologies. Cases *et al*. have used charge decomposition analysis (CDA) calculations to carry out this quantification on a wide variety of carbene complexes with varying functionality. The complexes studied are provided in table one, whilst the results of these calculations are given in table two.

What are important to note initially are the charge-donation/back-donation rations. These are contrary to what is observed when looking at the bonding between the carbonyl ligand and the chromium metal, in which back-donation is twice as significant as charge-donation, which is what would be predicted for p-acceptor ligands stabilizing a metal in a low oxidation state. The reasons for the greater significance of charge-donation over back-donation when looking at the Cr-carbene fragment can be attributed to increased orbital overlap (by a factor of about two) and lower energy gaps (by a factor of about 3 eV) in the main orbital interaction associated with charge donation.

In terms of the trend in the extent of back-donation as a function of the electron donating ability of the R'-substituent on the carbene moiety, it is clear that when the R'-substituent is an efficient electron donor, the level of back-donation is diminished. In that respect, complex **5h** (R=Me, R'=NHMe) boasted the lowest level of back-donation, with only 0.190 electrons. This observation can be attributed to the fact that due to the efficient electron donating ability of the –NHMe substituent and the weaker bonding-electron pair donation of the –Me substituent, the formally vacant p-orbital of the carbene ligand is provided with quite a significant level of electrostatic stabilization and hence is not such an efficient electron acceptor. Complex **5c** (R=H, R′=NHMe) had a higher level of back-donation (0.218 electrons) on account of the non-existent bonding-electron pair donation of the H substituent.

In contrast, complex **5e** (R=H, R′=H) boasted the highest level of back-donation (0.284 electrons) on account of the non-existent electron donating ability of both of the H-substituents. Complex **5j** (R=Me, R′=H) had a slightly lower level of back-donation (0.267 electrons) on account of the weak bonding electron pair donating ability of the –Me substituent over the –H substituent. Interestingly it might have been anticipated that complex **5y** (R=CCH, R′=H) ought to have the highest level of back-donation on account of the non-existent electron donating ability of the H-substituent and the electron-withdrawing ability of the –CCH substituent, however, it is clear that there is some distortion of this –CCH substituent which retards its ability to effectively withdraw electron-density.

## Effects of R- and R′-Substituents on the Cr=C Bond Length

Illustrated in the previous section of this chapter was a trend in the extent to which p-back donation occurs depending on the electron-donating ability of the R′-

substituent and the donor/acceptor character of the R-substituent (alkyl, alkenyl, alkynyl, aryl).

Cases *et al.* have carried out a computational analysis using the Amsterdam Density Functional (ADF) package developed by Baerends *et al.* (vectorised by Revenek) which has allowed a determination of the effects of the substituents bound to the carbene ligand on the length of the chromium-carbene bond. Results of this analysis are shown in the table below.

It would be expected that when the R′-substituent on the carbene ligand is an efficient electron donor, the Cr=C bond length ought to be longer, due to the diminished level of p-back-donation which occurs between the chromium metal and the carbene ligand. This is certainly what is observed, with complexes **5i** (R=Me, R′=NH2) and **5s** (R=Ph, R′=NH2) boasting maximum calculated bond lengths of 2.16 A, but for each of these two complexes three individual calculations were carried out using differing levels and basis sets resulting in the computation of three different bond lengths per complex, with complex **5i** having the longest average bond length of 2.098 A, and complex **5s** boasting a slightly shorter average bond length of 2.085 A, but which was still longer than the bond lengths of any of the other complexes studied. Between these two complexes, this average result is what would be expected due to the more efficient bonding-electron pair donating ability of the –Me substituent over the –Ph substituent which is distorted from planarity and as such is not as efficient at electron donation as what might have originally been anticipated. Complex **5h** (R=Me, R′=NHMe) had an average bond length of 2.083 A. These results were somewhat surprising as the –NHMe functionality in all other computational calculations shows indication of being a more efficient p-electron donor than the –NH2 functionality, and as such, would be expected to result in longer bond lengths than the –NH2 substituted complexes, however that was not the case in this particular analysis.

The shortest Cr=C bond was found in complex **5e** (R=H, R′=H) with an average bond length of 1.915 A. This can be attributed to the non-existent bonding electron-donating ability of H substituents, resulting in an increased level of p-back-donation, which was verified in the previous section of this chapter.

## Effects of R- and R′-Substituents on the Electrophilicity of the Central Carbene Carbon

The carbene moiety in Fischer-type chromium carbene complexes possesses an electrophilic character. This property is the result of charge-donation being greater than p-back-donation, hence resulting in a (OC)5Cr – C charge separation. Subsequently, this means that the carbene moiety can undergo reaction with nucleophiles, the implications of this on the chemistry that these complexes can undergo is explored later on in this review. Below is a table of electrophilicity indexes calculated for the 25 complexes studied by Cases *et al*.

Electrophilicity indexes were calculated using an equation developed by Parr, Szentpaly, and Liu. The equation involves two components, the chemical potential and the hardness. The calculation of both of these components involves the determination of the HOMO and LUMO energies of the complexes, which has been carried out using semi *inito ab* calculations. The equations of interest are shown below;

The results obtained using this equation developed by Cases *et al*. show that complex **5h** (R=Me, R′=NHMe) had the lowest electrophilicity index (3.059). This can be explained in terms of the efficient p-electron donating ability of the –NHMe functionality as well as the weak donating ability of the –Me functionality. This latter statement is verified by comparing the electrophilicity index of complex **5h** with that of complex **5c** (R=H, R′=NHMe), which boasted a slightly higher index (3.250) on account of the non-existent electron donating ability of the H-substituent. This phenomenon of bonding electron-pair donation (R=Me, alkyl) is analogous to that of hyperconjugation in the electronic stabilization of electron deficient carbocations. Complex **5y** (R= CCH, R′=H) had the highest electrophilicity index (10.487) of all of the 25 complexes studied. This can be attributed to the electron withdrawing nature of the alkynyl substituent.

## Chapter Three

## Synthesis of Chromium-Pentacarbonyl Carbene Complexes

A wide variety of synthetic methodologies exist which result in the formation of chromium-pentacarbonyl carbene complexes of varying functionality. In this chapter, the synthesis of carbene complexes is investigated in brief.

## Synthesis of Alkyl,Alkoxy-Carbene Complexes

Direct reaction of an organolithium reagent with chromium hexacarbonyl results in the formation of a lithium alkoxide intermediate (e.g. **6**) which can be alkylated resulting in the formation of a chromium-pentacarbonyl alkoxy-carbene complex (e.g. **7**). This alkylation is an Sn2 process; hence the reaction works well for primary and secondary alkylating agents (e.g. alkyl halides) but does not work well with tertiary substituted alkylating agents on account of the increased steric hindrance. In the first reported synthesis of such a complex, the alkylation was facilitated through the use of an alkyl halide, typically an iodide or bromide. However, in more recent times, the use of trialkyloxonium tetrafluoroborate salts has become common. These reagents offer not only faster reaction rates, but also result in higher yields of product.

There are however various other ways in which such carbene complexes can be prepared. When the tetrafluoroborate salt **8** reacts with the quaternary ammonium salt **9** in dichloromethane, the product is the alkyl-alkoxy carbene complex **10** which is formed in an 84% yield.

When an organolithium reagent is allowed to react with chromium hexacarbonyl in diethyl ether, the formation of a lithium alkoxide occurs. Upon addition of methyl iodide and tetrabutylammonium bromide in water, the carbene complex **11** is formed in a 90% yield, which is even more superior than in the previous methodology. The tetrabutylammonium bromide acts as a phase transfer catalyst transporting the lithium alkoxide intermediate species towards the non-aqueous methyl iodide phase where alkylation occurs, the catalytic action of the tetrabutylammonium bromide salt results in the higher yields of the final carbene complex.

When the reducing agent Lithium is added to chromium hexacarbonyl, the product is the [Cr(CO)5]2- species **12**. This species, which is countered by two lithium cations, undergoes reaction with acetyl chloride in THF, followed through by reaction with trimethyloxonium tetrafluoroborate in water, resulting gin the formation of the carbene complex **13** but in the lowest yield reported thus far, a meager 34%.

Pentacarbonyl-(5-*exo*-methylene-2-oxacyclopentylidene)chromium carbene complexes (e.g. **16**) have been prepared in moderate to good yields through a two step reaction process. In the methdologly reported by Dotz *et al.*, chromium hexarbonyl will undergo a ligand exchange process in tetrahydrofuran under photolysis resulting in the formation of the pentacarbonyl-THF chromium carbene complex **14**. This species readily undergoes a cycloisomerization process with but-3-yn-1-ol resulting in the formation of the 2-oxacyclopentylidene skeleton **15**. a-Deprotonation is facilitated through the use of butyl lithium (1.1 equivalents) at low temperatures (-78oC), which result sin the formation of a carbanionic intermediate species to which 2.2 equivalents of [(CH3)2N=CH2]Cl is added. The reaction is carried out at –78oC, but is gradually brought up to room temperature, resulting in the formation of the *exo*-methylene containing complex **16**. Applications of such complexes are documented in later chapters (refer to chapter 5).

## Synthesis of Alkenyl,Alkoxy-Carbene Complexes

The reaction of vinyl-lithium derivatives with chromium hexacarbonyl in procedures analogous to the preparation of alkyl,alkenyl-carbene complexes is a well-utilized route to the preparation of alkenyl,alkoxy-carbene complexes.

The preparation of alkenyl-carbene complexes (e.g. **18**) can also be accomplished through an Aldol-type condensation involving an alkyl carbene complex and an enolizable aldehyde/ketone. Such reactions are best performed using an aliphatic aldehyde that is pre-complexed with a suitable Lewis acid (refer to table 5). The final elimination sequence (E1cB) is effectively facilitated using mesyl chloride (MsCl) and triethylamine, which acts as a base.

The highest yield of the b-hydroxy carbene complex **17** was achieved when R=*n*-Pr and when SnCl4 was used as the Lewis acid. The reaction required 2 equivalents of the aldehyde and the reaction was allowed to proceed for 2 hours, resulting in an 84% yield. No unreacted complex was recovered. The lowest yield of b-hydroxy carbene complex **17** was achieved when R=Me and when TiCl(OiPr)3 was used as the Lewis acid using 2 equivalents of the aldehyde and allowing the reaction to proceed for 2 hours. Under these conditions less than 6% of the product was isolated, whilst 58% of the unreacted alkyl-carbene complex was recovered.

In terms of the formation of the alkenyl-carbene complex through the E1cB elimination of the b-hydroxy carbene complex, the highest yield was observed when R=*n*-Pr and when 2.2 equivalents of NEt3 and 2.0 equivalents of MsCl were used. Under these conditions reaction for only 0.1 hours resulted in a 72% yield of the alkenyl-carbene complex. In contrast, the lowest yield was reported when R=me and when no base was used. Under these conditions, allowing reaction for 4 hours resulted in a miniscule yield of only 25%.

## Synthesis of Amino-Substituted Carbene Complexes

The synthesis of amino-substituted carbene complexes **19** is generally carried out through the reaction of an alkoxy-substituted carbene complex and an amine, primary or secondary amines give rise to products but for obvious reasons, tertiary amines do not. However, this is not the only method by which such carbene complexes can be effectively synthesized. The synthesis of amino-substituted carbene complexes is explored in this section of the chapter.

The addition of N-aryl imines to alkyne(pentacarbonyl)chromium carbene complexes resulting in the synthesis of alkenyl,amino-carbene complexes **22** has been reported by Abd-Elzaher *et al*. The reactions involve photolysis of chromium hexacarbonyl in the presence of dichloromethane resulting in the formation of the intermediate species **20** which undergoes reaction with an arylacetylene derivative resulting in the formation of a thermolabile arylacetylene complex **21**. Reaction of this intermediate with *N*-Ph benzylideneimines results in the formation of the final alkenyl, amino-carbene complex **22**.

The preparation of (*O*-acyl imidato)- and (*O*-alkyl imidato)carbene complexes **23** has been reported by Wulff *et al*. which involve the reaction of alkyl, alkoxy-carbene complexes with nitriles. It was determined through X-Ray crystallography that the C-N-C angle ranges from 153o to 174o which indicates that the nitrogen plays a significant role in the electrostatic stabilization of the carbene complex, something which had already been deduced from computational analyses discussed previously.

*N,N*-dialkylation of aminocarbene complexes under phase-transfer conditions has been reported by Zhao *et al*. and has been used in the synthesis of azetidine, pyrrolidine, hexamethyleneimine and dihydroisoindole derivatives **25**. The reactions are effectively facilitated due to the strong electron-withdrawing ability of the chromium-pentacarbonyl fragment, which means that the formation of an "amide" analogue **24** is very easily accomplished.

Reaction of the resulting antion and a a,w-diiodoalkane results in the formation of the cyclic moiety of the complexes The use of the phase-transfer catalyst dramatically increases the efficiency of the reaction by transporting the anion to the interface between the aqueous and non-aqueous diiodoalkene where reaction takes place.

## Chapter Four

### Cyclopropanation Reactions – The Synthesis of Three-Membered Rings

Perhaps the most fundamental reactions of carbenes in general is their ability to undergo [2+1] cyclopropanation reactions with alkenes. Hence, it is not surprising that soon after the discovery of such carbene complexes, E. O. Fischer and other groups set out to try and affect the cyclopropanation of alkenes. It was originally thought, due to heteroatom stabilization, that cyclopropanation reactions involving Fischer carbene complexes would only proceed to give appreciable amounts of cyclopropanated product if an excess of electron-deficient alkene or a 1,3-diene was used. Electron-rich alkenes were thought to only be able to undergo such reactions if a high CO pressure was maintained during the course of the reaction, which retards the 'olefin metathesis' process from occurring hence favoring the cyclopropanation reaction. It was also originally thought that electrically neutral alkenes could simply not undergo cyclopropanation reactions with Fischer carbene complexes, and resulted solely in the decomposition of the carbene complex. There were certainly early reports of this being the case. One of the first cyclopropanation reactions reported by Fischer *et al.* is shown below, as well as providing a mechanism by which such reactions occur.

Very clearly the reaction involves an initial oxidative addition of the alkene, resulting gin the formation of a chromacyclobutane derivative **26**, which preferentially undergoes a reductive elimination sequence resulting in the formation of the cyclopropane derivatives **27a**-**27b**. Only when the alkene is electron-rich will the olefin metathesis process be favored to any appreciable extent.
In more recent times there have been diverse examples of reports involving the cyclopropanation reactions of electron-rich/neutral alkenes, which have lead in many cases to high yields of cyclopropanated product with typically high diastereoselectivities. This is explored in greater depth in this chapter.

## Cyclopropanation of Electron-Deficient Alkenes and 1,3-Dienes

In recent times there have been many reports of cyclopropanation reactions involving electron-deficient alkenes and 1,3-dienes that proceed to give high yields of cyclopropanated product, and often under conditions which are not nearly as severe as those required when the first reports of such reactions were published.

Indeed, the only example of an intermolecular cyclopropanation reaction of a diene reacting with a pentacarbonyl-chromium carbene complex prior to 1988 was the reaction between the methoxy carbene complex **28** with Danishefsky's diene **29**. The reaction was carried out at room temperature for 5 days resulting in the formation of the cyclopropanated product **30** in a 52% yield.

Furthermore when carbene complex **31** was allowed to react with cyclohexa-1,3-diene under a CO pressure at room temperature, using an irradiation procecure, two products were identified. The cyclobutanone **32** was formed as the major product of reaction (55%), whilst the cyclopropanted product **33** was formed in an 11% yield, but which was higher than any yield reported when such reactions were attempted at room temperature without the irradiation procedure.

In 2001, Sierra *et al*. reported a series of low temperature carbene transfer reactions which were carried out under photolysis in the presence of methyl acrylate **34**. These reactions proceeded to give a mixture of diastereomeric cyclopropanes **35** and C-H inserstion products **36**.

What is interesting to note is the apparent solvent dependence on the diastereoselectivity in the final cyclopropanated products. When the reaction is carried out in the co-ordinating solvent acetonitrile, the *trans* isomer is favored (ratio of 98:2), however when the reaction is carried out in benzene there is roughly equal amounts of both isomer formed. As will be seen in further examples, acetonitrile is a particularly good solvent in the diastereoselective/enantioselective cyclopropanation of alkenes. When the reaction is carried out in toluene, the highest overall yield of products **35** and **36** was reported (98% overall), with 49% of that yield corresponding to **35**, the cyclopropanated product. The *cis:trans* stereoselectivity was 30:70, which was mid-range in comparison with reactions carried out in the other solvents.

In light of the fact that acetonitrile appears to be a good solvent in the diastereoselective cyclopropanation of alkenes, Barluenga *et al.* has reported a series of reactions involving the use of novel chiral Fischer-carbene complexes (phosphine-substituted) reacting with alkenes in the presence of acetonitrile resulting in the general of cyclopropane derivatives with exceptionally high diastereoselectivities, although such complexes are not within the scope of this review and this point is mentioned only for further reference.

In another contribution, Barluenga *et al.* reported a series of Nickel (0)-mediated cyclopropanation reactions that occur at room temperature. In this sense, carbene complex **37** reacts with acrylonitrile in the presence of [Ni(cod)2] (cod = cycloocata-1,5-diene) resulting in the synthesis of the cyclopropanated product **39** in good yields. It is believed that these reactions proceed via the reactive nickel carbene complex intermediate **38**, which is formed through a chromium – nickel transmetallation process.

However, the diastereoselectivity of such reactions is low, with a 1:1 *cis/trans* mixture being isolated, which in the case of reactions carried out using method B is somewhat surprising given that in many other reactions the use of acetonitrile results in a generally high diastereoselectivity. Never the less, the cyclopropanation reaction proceeds at low temperatures and for relatively short periods of time, resulting in excellent yields overall.

The cyclopropanation of fulvenes has been given particular attention by Barluenga *et al*. in part because of the attractive structural nature of the fulvene system, which boasts both theoretical points of interest and also because the fulvene system is an important building block towards the synthesis of polycyclic cyclopentanoids. In this contribution, pentafulvene derivatives **40a**-**40i** with varying R2 and R3 substituents have been allowed to react with pentacarbonyl chromium carbene complexes **41a**-**41c** in acetonitrile at 80oC.

The chromium alkoxy-carbene complexes and substituted fulvenes (ratio of 1:1.2 with concentrations in the range 0.01 – 0.08 mol L-1) were heated in acetonitrile for 12 hours at 80 oC. After such time, the reaction mixture was taken in hexanes/ethyl acetate (5:1) and then demetalated. This dematalation procedure involved exposure of the resulting solution to the air and sunlight for 4-8 hours.
Once this had been accomplished, the mixture was filtered through a celite pad. The solution obtained contained the homofulvene derivatives, which for further purification and isolation of the respective isomers was chromotographed using silica gel chromatography eluting with hexanes/ethyl acetate (5:1). Products were isolated in good to very good yields (63-95%) with generally high

diastereoselectivity typical of what one would expect using the co-ordinating solvent acetonitrile.

It is apparent that the cyclopropanation reaction takes place at the endocyclic C=C bond, resulting in the preferential formation of the *E*-isomer in the case of the asymmetrical fulvenes (R3=H). The reactions are stereospecific with the *endo*-cycloadducts being formed at the major products of all of the reactions reported.

## Cyclopropanation of Electrically Neutral Alkenes

Considering that it was once believed that the direct cyclopropanation of an electrically neutral alkene with a pentacarbonyl-chromium carbene complex resulted in no more than the decomposition of the carbene complex, the mere fact that in recent times examples of such cyclopropanation reactions have been reported and often resulting in good yields exemplifies the importance and versatility of such complexes in organic synthesis.

Barluenga *et al*. has reported the cyclopropanation reactions of electronically neutral alkenes with 2- and 3-chloroalkoxycarbene complexes. The respective carbene complexes were formed through a two-step process. The first sequence involved the reaction of chromium hexacarbonyl with the vinyl lithium derivative **42** resulting in the formation of a lithium alkoxide, which underwent further reaction with tetramethylammonium bromide in dichloromethane

at room temperature resulting in the formation of the carbene complex **43** (90% yield).
The second step involved the reaction of the carbene complex **43** with 2,2-dimethyl-propionyl chloride in dichloromethane at –40 oC, followed by reaction with either 2-chloroethanol (n=1) or 3-chloropropanol (n=2), at –40 to 20 oC, resulting in the formation of complexes **44** and **45** (an iodinated complex **46** was also prepared) respectively. The complexes were purified by carrying out silica gel chromatography, the complexes **44** and **45** were isolated as stable green garnet crystalline solids.
They undergo cyclopropanation reactions with electronically neutral alkenes **46a**-**46c** at elevated temperatures (100-130 oc), in tetrahydrofuran to give cyclopropanated products **47a**-**47e** in good to excellent yields (67-88%). Clearly in contrast to what had originally been believed about the reactivity of such complexes.

Illustrated too are the reactions of pentacarbonyl-chromium carbene complexes with enynes (e.g. **48**) resulting in the formation of a fused ring structure **50**, boasting both a three- and five-membered ring. The reactions proceed via initial co-ordination and subsequent insertion of the alkyne resulting in the formation of the vinyl-carbene intermediate **49**. The final product **50** is formed through an intramolecular cyclopropanation reaction.

Katz and Harvey *et al*. have reported similar tandem reaction sequences involving the reaction of the carbene complex **51** with allylpropargyl ether **52** and allylpropargylamine **53**, resulting in the synthesis of

1-(2-oxopropyl)-3-oxabicyclo[3.1.0]hexane **54** and 1-(2-ozapropyl)-3-azabicyclo[3.1.0]hexane **55** in good yields. The reactions are carried out using benzene as the solvent under reflux for 0.3 hours.

Tandem reaction processes involving the use of strained bicyclic alkenes have been reported with proceed via a [2+2+1]/[2+1] co-cycloaddition sequence. In particular, when alkynyl carbene complexes (e.g. **56a**-**56c**, 10 equivalents) react with strained bicyclic electrically neutral alkenes (e.g. **57a**-**57c**) in toluene under reflux, the product is a complicated ring system (e.g. **58a**-**58i**)which contains two units of the alkene, one molecule of the carbene complex and a CO moiety. In total, five new C-C s-bonds are formed, which include the formation of both cyclopropyl- and cyclopentenone moieties. The solely cyclopropanated product is isolated as the minor product of the reaction **59a**-**59d** (12-26%) when the alkene used boasts ring strain and has an appreciable amount of steric hindrance. The results are illustrated below in table ten.

Interestingly, when one carries out the same reaction using *E*-cyclooctene, the reaction proceeds to general the cyclopropanated product **60** (93%) as the near sole product of reaction (refluxing in toluene for 30 minutes – method A). The reason for this is attributed to the decrease in steric hindrance present in *E*-cyclooctene over the alkenes **57a**-**57c**.

# Chapter Five

## The Synthesis of Four-Membered Rings

It is believed that upon the photolysis of chromium-petancarbonyl carbene complexes that a reversible CO ligand insertion takes place, resulting gin the formation of a transient Cr-ketene complex (e.g. **61**). However, an attempt to directly detect the intermediacy of such a complex has met with no success, leaving many questions regarding the structure and properties of such complexes unanswered.

However, the reactions of chromium-pentacarbonyl carbene complexes with both imines and alkenes under photolysis have been shown to result in the formation of a plethora of four-membered ring derivatives including b-lactams, b-lactones and cyclobutanones respectively, which from a retrosynthetic analysis implies the existence of a transient ketene intermediate. These syntheses are discussed in this chapter.

## The Synthesis of Cyclobutanone Derivatives

There have been various reports of the formation of cyclobutanone derivatives through the reaction of pentacarbonyl-chromium carbene complexes and alkenes, which proceed upon photolysis of the reaction mixture.

Sierra *et al*. reported a series of reactions between the carbene complex **62** and a series of alkenes with different substitution patterns **63a**-**63f**, which resulted in good to excellent yields of the cyclobutanone products **64a**-**64f**. The reactions were found to be highly regio- and stereoselective, producing in all cases a single diastereomer with a selectivity of greater than 95%.

Unactivated alkenes required forcing conditions for the reactions to proceed. The resulting cyclobutaones decomposed on silica gel, alumina and florosil, making their purification via column chromatography somewhat difficult. The products were therefore purified using evaporative distillation where they did not decompose to readily.
The regioselectivity observed corresponds to that resulting from attack of the more nucleophilic alkene carbon on the (electrophilic) ketene carbonyl carbon. In all cases, the methyl group of the carbene was *syn* to the substituent on the alkene, whilst the methoxy group was *anti*.

Wulff *et al*. has investigated the reactions of enynes with chromium-pentacarbonyl carbene complexes resulting in the synthesis of cyclobutanone derivatives. The original motivation for this investigation was in fact to determine the reactivity of alkyne versus alkene functionalities towards chromium-pentacarbonyl carbene complexes. It was determined through the use of enyne derivatives (e.g. **66** and **68**) that the alkyne moiety is significantly more reactive towards the carbene complexes and that because the alkene and alkyne are tethered together in the starting enyne that the overall reactions lead to the generation of bicyclic compounds (e.g. **67** and **69**) in which one of the principle ring components is a cyclobutanone moiety.

The reactions proceed via initial co-ordination (to the chromium) and subsequent insertion of the alkyne resulting in the formation of an e3-vinyl carbene complex **70** which undergoes a subsequent [2+2] cyclization involving the alkene functionality and the Cr=C bond of the transient ketene species **71** formed upon further insertion of a carbonyl ligand into the Cr=C bond.

Hegedus *et al*. has also reported the synthesis of a cyclobutanone derivative through the reaction of the methoxy carbene complex **72** and the enamine containing species **73**, which proceeded to give the highly functionalised cyclobutanone derivative **74** in good yields.

## The Synthesis of Cyclobutane Derivatives

Pentacarbonyl-(5-*exo*-methylene-2-oxacyclopentylidene)-chromium carbene complexes (e.g. **75**) readily undergo [2+2] cycloaddition reactions with enol ethers **76** resulting in moderate to good yields of fused cyclobutyl-oxacyclopentylidene complexes (e.g. **77**). These reactions proceed well under thermal conditions which is especially interesting as the [2+2] cycloaddition reaction in general is usually associated with photolysis, which can be rationalized using the Woodward-Hoffman (or the Fukuii frontier orbital approach) theory, and corresponds to an energetically favourable suprafacial-suprafacial mode of orbital interaction. The pentacarbonyl-chromium fragment activates the *exo*-methylene C=C bond for thermal [2+2] cycloaddition reactions such that these complexes react readily with enol ethers at in most cases room temperature, although some reactions require heating to about 50 oC. The resulting fused-ring structures are formed as single diastereomers which suggests that either the reaction is concerted, which would be consistent with a suprafacial-antarafacial approach of the two 'ene' functionalities, or that ring closure is fast in comparison with rotation of substituents around the carbon center.

The highest yield of the cyclobutane-containing product was obtained when the carbene complex was added neat and when the enol ether corresponded to *tert*-butyl-vinyl ether. The reaction was allowed to proceed for 3 hours resulting in an 81% yield.
In stark contrast, the lowest yield was observed when 0.05 M of the carbene complex was added and when the vinyl ether corresponded to allyl-vinyl ether. The reaction took 60 hours, resulting in a 26% yield of the cyclobutane-containing derivative.

In an analogous report, the electron deficient alkynyl substituent of carbene complex **78** undergoes reaction with the six-membered vinyl ether **79** resulting in the formation of the cyclobutene derivative **80** in an 82% yield. The electron-withdrawing nature of the Cr=C fragment lowers the LUMO energy of the alkynyl functionality, whilst the electron donating ability of the oxygen heteroatom results in an increase in the HOMO energy of the vinyl ether, resulting in a lower HOMO-LUMO energy gap and hence efficient reaction resulting in high yields of the cyclobutene product at room temperature.

Reactions of alkynyl-carbene complexes and electron-rich 1,3-dienes has been shown to result in the formation of cyclobutenes in the case of carbene complex **81** and cyclohexa-1,4-dienes in the case of carbene complex **82**. The cyclobutene derivative **83** is formed through a [2+2] cycloaddition reaction involving the CC bond of the alkynyl carbene complex and the electron-rich C=C bond of the diene. The reaction proceeds to give the four-membered product in a 51% yield. In contrast, the cyclohexa-1,4-diene derivative **84** if formed through the [4+2] Diels-Alder cycloaddition reaction. Such an example shows the difference in reaction pathways that can be observed upon the alternation of the substituents bound terminally to the alkynyl-carbene complex.

## The Synthesis of B-Lactone Derivatives

The synthesis of b-lactones **87** through the reaction of propargylic alcohols (e.g. **86**) and pentacarbonyl-chromium carbene complexes (e.g. **85**) has been given particular attention by Good *et al*. and Caldwell *et al*. who have established and optimized methods for the effective synthesis of such compounds.

In particular, both groups have identified that the use of ultrasound not only provides superior yields in comparison to the yields obtained through thermolysis, but the reactions also proceed at faster rates.

Both aldehydes and ketones will undergo reaction with chromium-pentacarbonyl carbene complexes in the presence of a Lewis acid under photolysis, resulting in the synthesis of b-lactones (e.g. **87**). Whilst the intermolecular reaction does produce b-lactone derivatives, it does so in poor yields and requires longer reaction times than the analogous intramolecular reactions. The poor yield is most likely a result of the instability of b-lactone derivatives in the presence of Lewis acids, which due to the longer reaction times required mean they decompose before they can be isolated. Intramolecular reactions result in moderate to good yields of b-lactone derivatives. When **88** is allowed to react in an intramolecular fashion under a CO pressure and initiated through a photolysis procedure in tetrahydrofuran (Lewis acid-=ZnCl2), the b-lactone derivative **89** is formed in good yield (72%).

## The Synthesis of b-Lactam Derivatives

Commented on already is the fact that upon irradiation (wavelengths greater than 350 nm) pentacarbonyl-chromium carbene complexes undergo a reversible transition, which is thought to he a metal-ligand charge transfer transition, that results in the formation of a transient chromium-ketene species which exhibits the characteristic behaviour of typical 'organic' ketenes. Hence, it is not surprising that such ketene-complexes have the ability to react with imines in a formal [2+2] cycloaddition process resulting in the formation of b-lactams.

Indeed, Arrieta *et al*. has reported the reaction of carbene complex **90** with the imine derivative **91**, resulting in the formation of the b-lactam products **92a**-**92b** in good yields. When the carbene complex **90** reacted with **91** under photolysis, a racemic mixture of both the *cis*- and *trans*-diastereomers was obtained. However, under thermolysis the *cis*-diastereomer was the sole product of reaction.

Reaction of the carbene complex **93** and the imine containing derivative **94** under photolysis results in the formation of the isolable intermediate species **95**, which his used in additional reaction sequences resulting in the formation of the antiobiotic compound **96** given the name 1-carbacephalothin.

## Chapter Six

## The Synthesis of Five-Membered Rings

A wide variety of functionalised five-membered ring products can be prepared through the use of chromium-pentacarbonyl carbene complexes, these include in addition to carbocyclic molecules, a plethora of heterocyclic molecules containing oxygen and nitrogen. These syntheses are discussed in this chapter.

### The Synthesis of Cyclopentene Derivatives

There are many methods by which cyclopentene derivatives can be prepared through the use of chromium-pentacarbonyl carbene complexes. Many of these reactions result in not only high yields of the cyclopentene derivative, but also boast both high regio- and diastereoselectivities.

Perhaps one of the most difficult reactions to envisage forming a cyclopentene derivative is the reaction of *p*-

tolyllithium with the carbene complex **97**. Instead of the expected 1,4-addition, or even the 1,2-addition resulting in the formation of a ketene species, two cyclopentene products are formed. The major product of reaction **98**, is formed in a 40% yileld whilst the second regioisomer **99** is formed in a 5% yield, but which is still formed in larger amounts than the expected 1,4-addition product **100** (1%). This was the only reaction of this kind studied by Fisher *et al.* which resulted in a cyclopentene derivative being formed as the major product of reaction. Very clearly the intermediate species that is formed through initial 1,3-attack by the p-tolyllithium is attacked again by the alkynyl carbene complex.

In a more conventional approach, Wienand *et al.* has reported the preparation of the cyclopentene derivatives **103** through the reaction of the alkenyl carbene complexes **101** with methyl acrylate **102**. Interestingly, the cyclopentene is only formed in appreciable amounts when the aryl moiety of the alkenyl carbene complex is a pyrrole derivative (e.g. **101a**) and when the Acc substituent of the alkene corresponds to –CO2Me. However, the yield is still relatively low (40%). The formation of the cyclopentene derivative sit thought to be the result of the rearrangement of the originally formed cyclopropane derivative **104** which are the major products of all of the other reactions when the aryl and Acc moieties are not the ones specified above.

In 1995, Hoffman *et al.* reported the synthesis of the cyclopentene derivative **108** through the reaction of the alkenyl carbene complex **105** and the donor/acceptor substituted 1,3-diene **106**. The reaction is believed to involve the formation of a chromacyclohexene intermediate species (e.g. **107**), which undergoes a reductive elimination process resulting in the formation of the final cyclopentene derivative **108** in good yields. The reaction has also been termed an inverse electron demand Diels-Alder cycloaddition reaction, a term which certainly fits the observed reaction pathway.

Along a similar line, Barluenga *et al*. reported the first example of [3+2] or [4+1] cycloaddition reactions of alkoxy-carbene complexes (e.g. **109**), resulting in the formation of cyclopentene derivatives **111a**-**111b** in good yields.

It is evident from this study that the transfer reaction of the carbene complex as a three-carbon synthon (e.g. [3+2] reaction), which seems to be more general than that in which it acts as a one-carbon synthon, takes place with total regio- and diastereoselectivity.

A,b-unsaturated hydrazones(e.g. **112**) have been shown to undergo reaction with a,b-unsaturated alkenyl carbene complexes (e.g. **113**) giving rise to cyclopentene **114** and pyrrole **115** derivatives, with the former being isolated in 45-55% yields and the later in 25-28% yields, both after separation by column chromatography. It is believed that the aminopyrroles arise from [4+1] cycloaddition reactions involving the hydrazone acting as a hetero-1,3-diene with the Cr=C bond of the carbene complex acting as a 'dienophile', whilst the cyclopentene is formed through a [3+2] cycloaddition reaction involving the alkenyl-carbene complex acting as the

1,3-diene and the N=C bond acting as the dienophile. Both reactions proceed via so-called 'metalla-Diels-Alder cycloaddition reactions'.

The resulting cyclopentene derivatives can be converted into the corresponding cyclopentanone derivatives **114b-114c** through treatment with acid, although the product formed depends on the concentration of the acid as well as the solvent in which the reaction is carried out in.

## The Synthesis of Cyclopentadiene Derivatives

Upon heating a b-amino-substituted a,b-unsaturated carbene complex **116** with a terminal alkyne **117** in a donor solvent such as acetonitrile or pyridine at temperatures ranging from 55 to 80 oC, a 1,5-disubstituted 5-(dialkylamino)-3-ethoxycyclopentadiene **118** is formed as the major product of the reaction, with the 2,5-disubstituted regioisomer often being formed in minor amounts. None of the reactions produced any Dotz benzannulation product, this can be attributed to the effect of both the electron donating substituents bound to the carbene ligand and the donor solvent which acts as a ligand in the intermediate complexes, both effects combined resulting in the inability for a CO ligand to undergo insertion into the chromium-carbene bond, a process that is required for the Dotz benzannulation reaction to take place.

Sierra *et al*. has reported the self-condensation-cycloisomerization reactions of alkoxy,alkenyl-carbene complexes which result in the generation of cyclopentadiene containing products **119**. This reaction makes use of the exceptional heterogeneous reducing reagent potassium graphite (C8K) laminate, which can be prepared through the reaction of metallic potassium and graphite at 150-160 oC under argon for a short period of time.

Potassium graphite as a reducing agent has been widely used in other areas of organic and inorganic synthesis, but its application in the synthesis of chromium carbene complexes is very recent, with only two applications being reported thus far. The first application was reported by Hegedus *et al*, in the synthesis of amino-carbene complexes, in which it was used in the oxidation of chromium hexacarbonyl to the corresponding chromium pentacarbonyl anion. The use reported here has been a significant development as it provides a very efficient methodology by which highly functionalised cyclopenta-1,3-dienes **119** can be prepared in very few reaction steps. The postulated mechanism by which such reactions take place is shown below.

Initial one electron reduction of the alkynyl-carbene complex using the electron generated through the oxidation of potassium graphite results in the formation of chromium-carbene readical anion species **120**, for which two of such species readily undergo a tail-to-tail dimerization resulting in the dianionic species **121**. This species subsequently reacts with acid resulting in the formation of a dialkenylcarbene complex **122**. Neighbouring group participation by one of the double bonds results in the formation of the five-membered cyclopenta-1,3-diene structural motif **123**. The loss of chromium pentacarbonyl and a subsequent 1,5-hydride shift results in the formation of the final product **119**.

## The Synthesis of Cyclopentenone Derivatives

Cyclopropyl-substituted pentacarbonyl chromium carbene complexes undergo a photochemically induced rearrangement procedure resulting in the formation of cyclopentenone derivatives. In particular, when the carbene complex **124** is irradiated, the cyclopentenone **126** is formed in good yield (68%). The reaction is thought to proceed via a [(p2s + p2s) + s2s] rearrangement, which involves the formation of a transient ketene species **125**, a paradigmatic mode of reactivity of carbene complexes of this type which is to be explored in later chapters.

In a similar fashion, Herndon *et al*. reported the synthesis of 2-alkoxy-2-cyclopentenone derivatives through the reaction of substituted cyclopropyl containing carbene complexes **127** either under thermolysis or photolysis. Whilst in the majority of cases, the cyclopentenone derivative **128** was formed as the sole product of reaction, a different regioisomer **129** was isolated when R1=alkenyl and R2=H in good yields.

Alkynes will react with (2-dialkylaminoalkenyl)-carbene complexes resulting in the formation of cyclopentenone derivatives with an amino substituted b-carbon atom **131**. It appears evident that such reactions work well if the alkyne employed is non-terminal, and if the reaction is carried out in tetrahydrofuran. In that respect, de Meijere *et al.* have reported the reaction of (2-dibenzylaminoalkenyl)-carbenechromium **130** with a series of non-terminal alkynes.

Relatively unstable 4-aminochromahexatrienes **132** will undergo an intramolecular reaction resulting in the formation of a cyclopentadiene derivative **133**, which can be converted to a 3-dialkylaminocyclopentenone **134** through an aqueous work-up. The yields of the cyclopentenone derivative are relatively low however (35-37%).

Cyclopropyl(alkoxy)carbenechromium carbene complexes **135** will undergo reaction with alkynes resulting in the formation of a cyclopentadienone intermediate **136** which in the presence of Cr0/H20 will result in the formation of the sable cyclopentenone derivatives **137**/**138**.

The highest yields of cyclopentenone **137** were reported when both R-groups were phenyl substitutents, but with a small amount of cyclopentenone **138** being formed (4%). Entry 3 in which RL=Ph, RS=me boasted the second best yield of product **137**, but with an even higher amount of product **138** being formed (12%). All other alkynes gave lower yields of product **137**, but under no circumstances resulted in the formation of any of the **138** regioisomer.

An intramolecular form of this reaction has also been reported. When the carbene complex **139** is heated in an aqueous dioxan solution, the product is the cyclopentenone derivative **140**. The yields are relatively high and there is exceptional diastereoselectivity in many cases.

Ring expansion reactions are widely utilized in conventional organic synthesis; common examples include the pinnacol rearrangement and the Tiffeneau-Demjanov rearrangement to name but a few, which result in the formation of carbonyl containing products. Herndon *et al.* has reported the ring expansion reactions of carbene complexes exocyclic to carbon-1 of a cyclic alcohol **141**, which are easily generated through coupling of alkynols with carbene complexes. The result is the synthesis of a carbonyl-containing molecule, in the illustrated case a ketone **142**.

## Synthesis of Heterocyclic Five-Membered Rings

A variety of oxygen and nitrogen-containing five-membered heterocyclic molecules have been prepared through reactions involving pentacarbonyl chromium carbene complexes.

The synthesis of five-membered lactones has been accomplished, and follows on from the synthesis of four-membered b-lactams, which have already been mentioned. In this respect, Good *et al.* has reported the synthesis of the five-membered lactam species **143** in modest yields, utilizing both a thermolysis procedure and an ultrasound procedure. The ultrasound methodology provides slightly better yields and in half the time that it takes for the thermally induced reaction to take place.

Campos *et al*. has reported the preparation of both triazolines **144** and oxazolines **145** through the reaction of imine-carbene complexes **146** and either azo compounds or carbonyls (ketones, aldehydes) **147/148**. In the case of the generation of triazolines **144** a significant proportion of 1,3-diazabuta-1,3-diene **149** is formed, but in lower levels than the anticipated triazoline. The formation of the diene derivative is believed to proceed through a metathesis reaction between the Cr=C bond of the carbene complex, and the N=N bond in the azo compound. In order to understand this metathesis process, the imine-carbene complex **146** was irradiated by itself and was found to give a metathesis product **151** which had obviously been formed through reaction between the Cr=C bond of one carbene complex and the N=C bond of another carbene complex. It is believed that the reaction proceeds via a metallocycle spcies **150**, which readily undergoes decomposition by way of a reductive elimination process giving rise to the observed metathesis product.
When a carbonyl was used, instead of an azo compound, none of the metathesis product was observed and the oxazoline **145** was the sole product of the reaction.

The use of nitrilimines **152** in 1,3-dipolar cycloaddition reactions is quite well established. Their synthesis is normally achieved *in situ* from hydrazonoyl chlorides **153** and are trapped with dipolarophiles resulting in the generation of D2-pyrazolines **155** as a mixture of regioisomers unless specific conditions favouring the formation of one particular regioisomer are invoked. These species are of interest for at least three main reasons. The first of these is that such compound exhibit anti-inflammatory character, the second is that they boast at least two significant practical applications as optical brightners and fluorescent switches. The first application is that they are frequently used as starting materials for the synthesis of fictionalized acyclic and cyclic compounds.

(+/-)-Menthol derived alkenyl carbene complexes (e.g. **156**) undergo reaction with nitrilimines resulting in the formation of the D2-pyrazoline **157** derivatives in good yields. However, these compounds are unstable and purification from their oxidation products is difficult. They are therefore converted to esters through the addition of pyridine-*N*-oxide (PNO) resulting in the formation of the esters in moderate to good yields. Better yields of the D2-pyrazoline derivatives were obtained using a “one-pot” methodology, which does not involve any intermediate isolation sequences during which decomposition could occur and hence the higher observed yields.

Chan and Wulff have reported the reaction of trimethylsilyldiazomethane **159** and alkynyl carbene complexes **158** resulting in the formation of pyrazolyl(methoxy)carbene complexes **160** in good yields (76%) with superior regioselectivity (300:1). The reactions proceed at room temperature in hexane, requiring only 2 hours to go to completion.

The synthesis of 2,3-dihydroisozazolyl(methoxy)carbene chromium complexes **161** has been reported. The synthesis involves the reaction between an alkynyl carbene complex and trimethylsilyldiazomethane in hexane at 25oC for 2 hours.

Schmidt *et al.* and Dotz *et al.* have reported the synthesis of substituted oxolenes **162** and furans **163** by metal-assisted cyclization of alkynols using labile five- and six-membered oxacyclic pentacarbonyl chromium carbene complexes. The first reported synthesis of an oxacyclic carbene complex was in 1974 by Casey *et al.*

The synthesis of b-substited pyroglutamic acid derivatives (e.g. **165**) has been reported by Barluenga *et al.* which involves the initial formation of a cyclic *trans*-disubstituted amino carbene complex **164** and subsequent oxidation of the carbene fragment to the corresponding carbonyl **165**, a process which can be facilitated through the addition of dimethylsulfoxide. The carbene complex is formed through a Michael-type 1,4-addition of the lithium derivative to the a,b-unsaturated carbene complex **163**, which undergoes subsequent cyclization resulting in the formation of the *trans*-disubstituted aminocarbene complex. The yields of the b-substituted pyroglutamic acid derivatives **165** range from good to exceptional (62-95%).

## Chapter Seven

## The Synthesis of Six-Membered Rings

Six-membered rings are a fundamental component of natural products, be they carbocyclic or heterocyclic ring entities. The application of chromium-pentacarbonyl carbene complexes in the synthesis of six-membered rings is perhaps the most widely probed area of their use in organic synthesis. These applications are investigated in this chapter.

### The Synthesis of Phenol and Naphthol Derivatives

Early work by Dotz *et al*. revealed that upon that reaction of an alkenyl/aryl-substituted chromium-pentacarbonyl carbene complex with an alkyne, in an appropriate solvent and at standard conditions, either a phenol or a naphthol derivative could be generated. This reaction has now conveniently been termed the "Dotz benzannulation" reaction and is widely used in the synthesis of natural products with highly substituted aromatic ring systems. The likely mechanism for a generic Dotz benzannulaion reaction is illustrated below.

Initial co-ordination of the alkyne to the chromium is followed by the insertion of the alkyne resulting in the formation of the e3-vinyl carbene complex **166**. If R=alkoxy or some other substitutent which is not such an efficient p-electron donor (relative to say, the amino-substituents which can be in general considered superior), the reversible insertion of a CO ligand occurs which is believed to come about through a metal-ligand charge transfer (MLCT) transition, resulting in the formation of the transient ketene **167**. If the R-substituent is an efficient p-electron donor, then this insertion is suppressed and metallacyclohezene is formed as an intermediate, which undergoes a reductive elimination process resulting in the formation of the five-membered product.

The resulting ketene **167** readily undergoes a thermally induced 6-electron electrocyclic ring closure resulting in the formation of the a,b-unsaturated carbonyl containing intermediate **168**. This entity undergoes tautomerism resulting in the formation of the aromatic ring system **169**, but with the chromium tricarbonyl moiety still tethered. This moiety is lost upon exposure of the reaction mixture to air, resulting in the final product **170**.

Natural products that have been synthesized employing the Dotz benzannulation reaction as a key step in the total synthetic sequence include shikonin/alkannin, vitamins E and K1, as well as antibiotics such as nanaomycin, deoxyfrenolicin, daunomycinone and angelicin.

The history of naphthoquinone natural products such as shikonin and alkannin have been known for many centuries, however it was until only recently that the structures with correct absolute stereochemistry were determined. Both skikonin and alkannin are enantiomers with shikonin having *(R)*-stereochemistry and alkannin having *(S)*-stereochemistry, and both have been prepared using the Dotz benzannulation reaction. A retrosynthetic analysis for the synthesis is shown below.

The alkyne **171** and carbene complex **172** react together under varying conditions (temperature/reaction time/ solvent) through a Dotz benzannulation reaction resulting in modest to very good yields of species **173**. The results of this study are shown below.

The highest yield reported (76%) was achieved when 20 equivalents of the alkyne **171** were used, and when the reaction was carried out in dichloromethane. The lowest yield was reported when the reaction was carried out using 1.2 equivalents of the alkyne, in tetrahydrofuran. Under these conditions only an 18% yield was obtained, which required long reaction times. It is evident that the reactions proceed best when carried out in non-polar solvents such as dichloroethane, and are somewhat retarded when carried out in more polar solvents such as tetrahydrofuran. This is attributed to the diminished ability of a CO ligand to undergo insertion resulting in the necessary transient ketene species when a donor solvent is used, which tends to bind to the intermediate species and suppress this insertion process from taking place. Computational analyses have also verified the hindrance of donor solvents in allowing the formation of the required transient ketene, pushing the reaction towards the generation of the chromacyclohexene, which undergoes reductive elimination resulting in the formation of the five-membered derivatives.

Daunomycinone (R=OH) **174** and 11-deoxydaunomycinone (R=H) **175** have been prepared using the Dotz benzannulation reaction. These derivatives have exhibited promising antileukemic activity and powerful anti-tumor activity against many other forms of cancer. In that respect, two methods have been reported which have lead to the synthesis of these derivatives. In the first methodology, carbene complex **176** has been allowed to react with the alkyne **177** resulting in the precursor species **178**. The second methodology involves the reaction of carbene complex **179** with the alkyne **180**, which results in the synthesis of the precursor species **181**. The second route is often favored because the conversion of **181** to the final product is in many easy easier than the conversion of **178** to the final product.

Angelicin **182** and derivatives occur in a number of plants belonging to the *Umbelliferae* family. They have showed much promise as anticancer agents. In particular, they have been shown to bind covalently to DNA in bacteria, yeast and other cultured mammalian cells. These derivatives have also been prepared using the Dotz benzannulation reaction. In that respect, carbene complex **183** has been allowed to react with the alkyne as shown in scheme 60, resulting in the formation of a precursor species **184** that can then be converted to the desired final product in only two additional reaction steps.

Nanaomycin **188** is an antibiotic having the 5-hydroxy-1,4-naphthoquinone structure. It has been prepared through the initial formation of a precursor species **187**, which is formed through an intramolecular Dotz benzannulation reaction involving carbene complex **186**.

Indolocarbazole derivatives (e.g. **189** and **190**) have an interesting and important history as natural products used in medicines and bioactive materials. Their history began in 1977 when the molecule *staurosponine* was isolated from *Streptomyces staurosporeus*. The work was initiated whilst Omura and co-workers were searching for new microbial alkaloids, which exist in actinomyceles. There are currently several indolocarbazole alkaloids that are in clinical trials for their potential use in cancer therapy. The synthesis of such compounds involves an intramolecular benzannulation type sequence, in which insertion of a carbonyl ligand results in the formation of a transient ketene, in a process analogous to the Dotz benzannulation reaction.

## The Synthesis of Cyclohexene Derivatives

The use of alkenyl carbene complexes as dienophiles in Diels-Alder cycloaddition reactions is a well-established area and has provided positive synthetic results. The facile reactivity of carbene complexes of this type can be attributed to the powerful electrowithdrawing ability of the (OC)5Cr=C fragment.

## References

[1] E. O. Fischer, A. Maasbol, *Angew. Chem. Int. Ed.,* **1964**, *76*, 645

[2] E. O. Fischer, A. Maasbol, *Angew. Chem. Int. Ed. Engl.,* **1964**, *3*, 580
[3] K. H. Dotz, *Angew. Chem.,* **1984**, *96*, 573
[4] M. A. Sierra, *Chem. Rev.,* **2000**, *100*, 3591
[5] R. Aumann, H. Nienaber, *Adv. Organomet. Chem.,* **1997**, *41*, 163
[6] A. de Meijere, H. Schirmer, M. Duetsch, *Angew. Chem.,* **2000**, *112*, 4124
[7] J. Barluenga, F. J. Fananas, *Tetrahedron.* **2000**, *56*, 4597
[8] D. F. Harvey, D. M. Sigano, *Chem. Rev.,* **1996**, *96,* 271
[9] L. S. Hegedus, *Pure Appl. Chem.,* **1990**, *62*, 691
[10] E. O. Fischer, *Angew. Chem.,* **1974**, *86*, 651
[11] K. H. Dotz, I. Pruskil, J. Muhlemier, *Chem. Ber.,* **1982**, *115*, 1278
[12] K. H. Dotz, W. Kuhn, *Angew. Chem.,* **1983**, *95*, 750
[13] M. F. Semmelhack, J. J. Bozell, L. Kelter, T. Sato, E. J. Speirs, W. Wulff, A. Zask, *Tetrahedron*, **1985**, *41*, 5813
[14] C. F. Bernasconi, M. W. Stronach, *J. Am. Chem. Soc.,* **1993**, *115*, 1341
[15] C. F. Bernasconi, S. Bhattacharya, *Organometallics,* **2003**, *22*, 426
[16] C. F. Bernasconi, S. Bhattacharya, *Organometallics*, **2003**, *22,* 1310
[17] J. Barluenga, J. Florez, F. J. Fananas, *J. Orgmet. Chem.*, **2001**, *5(17)*, 624
[18] T. R. Cundari, M. S. Gordon, *Organometallics*, **1992**, *11*, 55
[19] T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.,* **1992**, *114*, 539
[20] R. R. Schrock, *Acc. Chem. Res.,* **1979**, *12*, 72
[21] T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.,* **1991**, *113*, 5231
[22] R. R. Schrock, *J. Am. Chem. Soc.,* **1974**, *96*, 6796

[23] A. Miyashita, *Kagaku Zohan (Kyoto)*, **1995**, *124*, 101
[24] R. R. Schrock, H. H. Fox, B. L. Goodall, *Synthesis of Molybdenum and Tungsten Complexes*, **1992**, *US 5142073 A 19920825 CAN 117:259162 AN 1992:659162*
[25] M. D. Cooke, E. O. Fischer, *J. Organomet. Chem.*, **1973**, *56*, 279
[26] J. Barluenga, K. Muniz, A. Ballesteros, S. Martinez, M. Tomas, *ARKIVOC*, **2002**, *5*, 111
[27] H. –W. Fruhauf, *Chem. Rev.*, **1997**, *97*, 523
[28] J. Barluenga, M. Tomas, *J. Am. Chem. Soc.*, **2001**, *123*, 11113
[29] B. Schmidt, P. Kocienski, G. Reid, *Tetrahedron*, **1996**, *52*, 1617
[30] H. –G. Schmalz, *Angew. Chem.*, **1994**, *106*, 311
[31] M. J. S. Dewar, *Bul. Soc. Chim. Fr.*, **1951**, *18*, C79
[32] J. Chatt, L. A. Duncanson, *J. Am. Chem. Soc.*, **1953**, 2829
[33] S. F. Vyboishchikov, G. Frenking, *Chem. Eur. J.*, **1998**, *4*, 98
[34] J. Poater, M. Cases, X. Fradera, M. Duran, M. Sola, *J. Chem. Phys.*, **2003**, *294*, 129
[35] C. –C. Wang, Y. Wang, H. –J. Liu, K. –J. Lin, L. –K. Chou, K. –S. Chan, *J. Phys. Chem. A.*, **1997**, *101*, 8887
[36] S. F. Vyboishchikov, G. Frenking, *Chem. Eur. J.*, **1998**, *4(8)*, 1428
[37] K. H. Dotz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert, *Transition Metal Carbene Complexes*, **1983**, VCH, Weiheim
[38] T. F. Block, R. F. Fenske, *J. Am. Chem. Soc.*, **1977**, *99*, 4321
[39] R. J. Goddard, R. Hoffmann, E. D. Jemmis, *J. Am. Chem. Soc.*, **1980**, *120*, 7667
[40] T. F. Block, R. F. Fenske, *J. Am. Chem. Soc.*, **1977**, *99*, 4321
[41] T. F. Block, R. F. Fenske, C. P. Casey, *J. Am. Chem. Soc.*, **1976**, *98*, 441

[42] F. Voltatron, O. Einstein, *J. Am. Chem. Soc.,* **1986**, *108*, 2173
[43] J. Ushio, H. Nakatsuji, T. Yonezawa, *J. Am. Chem. Soc.,* **1984**, *106*, 5892
[44] H. Nakatsuji, J. Ushio, S. Han, T. Yonezawa, *J. Am. Chem. Soc.,* **1983**, *105*, 426
[45] T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.,* **1992**, *114*, 539
[46] T. R. Cundari, M. S. Gordon, *J. Am. Chem. Soc.,* **1991**, *113*, 5231
[47] D. S. Marynick, C. M. Kirkpatrick, *J. Am. Chem. Soc.,* **1985**, *107*, 1993
[48] H. Jacobsen, T. Ziegler, *Inorg. Chem.,* **1996**, *35*, 775
[49] T. R. Cundari, M. S. Gordon, *Organometallics*, **1992**, *11*, 55
[50] A. Marquez, J. Fernandez, *J. Am. Chem. Soc.,* **1992**, *114*, 2903
[51] R. W. W. Bader, *Atoms in molecules : A Quantum Theory,* **1990**, *Clarendon Press, Oxford*
[52] E. A. Carter, W. A. Goddard, *J. Am. Chem. Soc.,* **1986**, *108*, 4746
[53] T. E. Taylor, M. B. Hall, *J. Am. Chem. Soc.,* **1984**, *106*, 1576
[54] S. F. Vyboischikov, G. Frenking, *Chem. Eur. J.,* **1998**, *4*, 1428
[55] H. Jacobsen, T. Ziegler, *Organometallics*, **1995**, *14*, 224
[56] G. Frenking, *J. Organomet. Chem.,* **2001**, *9*, 635
[57] G. Frenking, U. Pidun, *J. Chem. Soc., Dalton Trans.,* **1997**, 1653
[58] H. Jacobsen, G. Schreckenbach, T. Ziegler, *J. Phys. Chem.,* **1994**, *98*, 11406
[59] A. W. Ehlers, S. Dapprich, S. F. Vyboishchikov, G. Frenking, *Organometallics*, **1996**, *15*, 105
[60] S. Dapprich, G. Frenking, *J. Phys. Chem.,* **1995**, *99*, 9352

[61] M. Torrent, M. Duran, M. Sola, *Organometallics*, **1998**, *17*, 1492
[62] M. Cases, G. Frenking, M. Duran, M. Sola, *Organometallics*, **2002**, *21*, 4182
[63] S. Dapprich, G. Frenking, CDA 2.1, Marburg, **1994**, Available for download (anonymous FTP server); ftp.chemie.uni-marburg.de (/pub/cda)