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Cycloaddition Reactions of Group 6 Fischer Carbene Complexes

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Abstract Group 6 heteroatom-stabilised carbene complexes (Fischer carbene complexes) offer many interesting possibilities to build rings (carbocycles and heterocycles) not readily accessible through conventional methods. In this chapter, a summary of cycloaddition reactions involving group 6 Fischer carbene complexes is presented. Firstly, two-component coupling reactions where a substrate reacts with the carbene complex to afford three- to nine-membered carbo- or heterocycles are considered. Next, cyclisation processes where more than two components are involved in the formation of the final ring are summarised. Finally, a few examples of tandem cycloaddition reactions are presented in order to highlight the amazing possibilities that Fischer carbene complexes offer for the efficient synthesis of complex molecules.

Keywords Fischer carbene complexes · Cycloaddition reactions · Carbocycles · Heterocycles

Abbreviations

Ac	Acetyl
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	Benzyl
cod	1,5-Cyclooctadiene
Cp	Cyclopentadienyl
de	Diastereoisomeric excess
DMF	*N*,*N*-Dimethylformamide
ee	Enantiomeric excess
Fc	Ferrocenyl
2-Fu	2-Furyl
LDA	Lithium diisopropylamide
MCPBA	Metachloroperbenzoic acid
PMDTA	*N*,*N*,*N*′,*N*′,*N*″*P*-Pentamethyldiethylenetriamine
RT	Room temperature
TBDMS, *TBS*	*Tert*-butyldimethylsilyl
Tf	Trifluoromethanesulphonyl
TFA	Trifluoromethanesulphonic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl

1 Introduction

Fischer carbene complexes have proved to be very efficient and extraordinarily versatile starting materials for carrying out a wide range of cycloaddition reactions, which provide a great array of carbocyclic and heterocyclic ring systems with a high degree of selectivity in most cases. The need to employ stoichiometric amounts of a group 6 transition metal is, perhaps, the major drawback of these synthetically useful molecules and this, most likely, has been hampering their general use in organic synthesis. Nevertheless, efforts to perform the chemistry of Fischer carbene complexes using catalytic amounts of the metal are under way and some limited success has been achieved.

In this chapter, an important part of the chemistry of group 6 Fischer carbene complexes will be discussed. Particularly, those processes in which cyclic compounds are formed will be described in detail [1]. The chapter is organised by looking firstly at the number of reacting components taking part in the cycloaddition process and then at the size of the ring being formed [2]. The characteristic reactions of either heteroatom-stabilised (X=OR, NR_2) or non-heteroatom-stabilised (X=alkyl, aryl) alkyl- (**1**), alkenyl- (**2**), aryl- (**3**) and alkynylcarbene (**4**) complexes of a group 6 metal (Cr, Mo, W) are presented in this work (Fig. 1).

The type of cycloaddition reaction is identified by the topological notation which will be used in a formal sense to describe the number of atoms provided

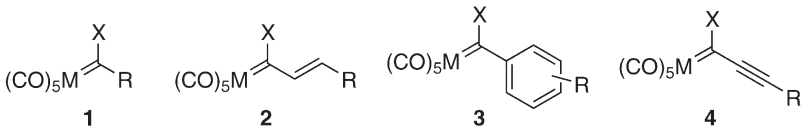


Fig. 1 Heteroatom-stabilised (X=OR, NR_2) and non-heteroatom-stabilised (X=alkyl, aryl) alkyl- (**1**), alkenyl- (**2**), aryl- (**3**) and alkynylcarbene (**4**) complexes of group 6 metals

by each fragment to the final cycloadduct, regardless of the mechanism and the number of steps involved [3]. The subscripts C=carbene complex and S=substrate refer to the corresponding reagent. The Dötz benzannulation reaction ([3_C+2_S+1_{CO}], CO=carbonyl ligand), the photochemical reactions of carbene complexes with organic substrates such as imines, alkenes or azo compounds ([2_S+1_C+1_{CO}]) besides the photochemical benzannulation reactions ([5_C+1_{CO}]), and the cycloaddition reactions involving β-donor-substituted alkenylcarbene complexes will not be included in this chapter as they are covered elsewhere in this book.

2
Two-Component Cycloaddition Reactions

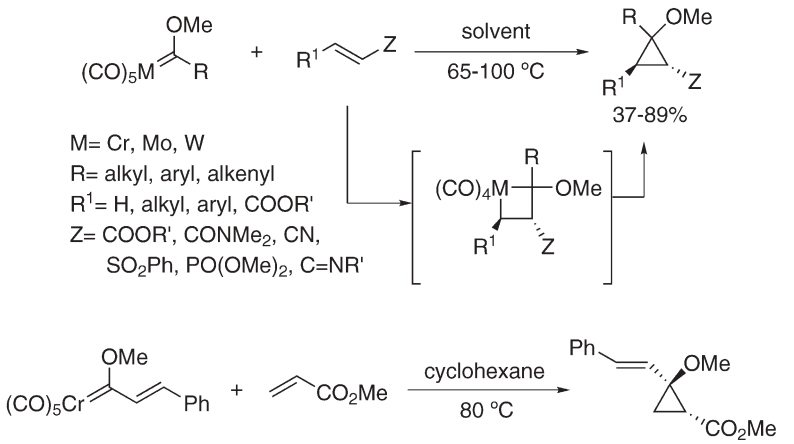
2.1
[2_S+1_C] Cycloaddition Reactions: Cyclopropanation of Alkenes and Dienes with Fischer Carbene Complexes

The cyclopropanation reaction of an unsaturated substrate is one of the most important strategies to access three-membered ring derivatives. The use of Fischer carbene complexes to perform this kind of cyclisation has become an important tool in organic synthesis [4]. In the next few sections the most significant features of this chemistry are briefly described.

2.1.1
Cyclopropanation of Alkenes

The ability of Fischer carbene complexes to transfer their carbene ligand to an electron-deficient olefin was discovered by Fischer and Dötz in 1970 [5]. Further studies have demonstrated the generality of this thermal process, which occurs between (alkyl)-, (aryl)-, and (alkenyl)(alkoxy)carbene complexes and different electron-withdrawing substituted alkenes [6] (Scheme 1). For certain substrates, a common side reaction in these processes is the insertion of the carbene ligand into an olefinic C–H bond [6, 7]. In addition, it has been ob-

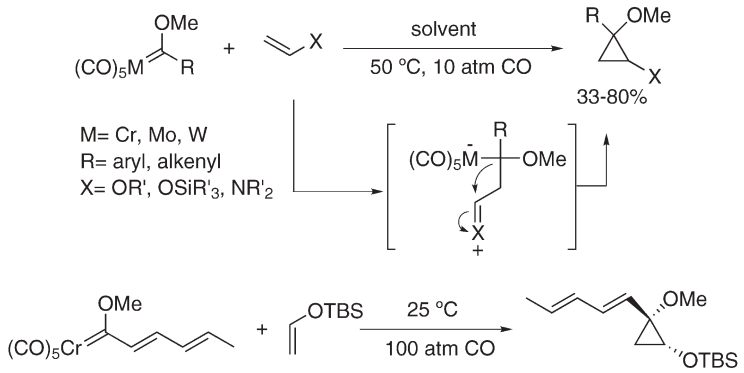
served that steric hindrance caused by either the number or the size of the substituents of the alkene is a limitation of the cyclopropanation reaction [6c]. The diastereoselectivities of these carbene transfer reactions are generally low, leading to the corresponding cyclopropanes as nearly equimolecular mixtures of *cis* and *trans* isomers/epimers at the carbon arising from the carbene carbon atom. Nevertheless, better diastereoselectivities were attained when the cyclopropanation reactions involve a conjugated system either in the carbene ligand or in the alkene [8] (Scheme 1). The mechanism to explain the cyclopropanation of electron-deficient olefins with Fischer carbene complexes was initially proposed by Casey and Cesa [9], and involves dissociation of a CO ligand, coordination of the alkene, generation of a 16-electron metalacyclobutane intermediate, and finally reductive elimination of the metal fragment (Scheme 1).



Scheme 1

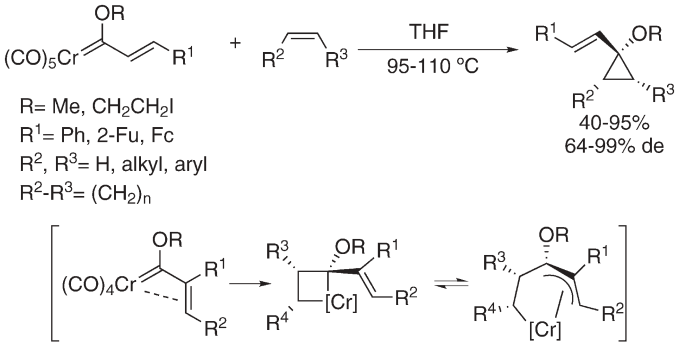
Alkenes substituted with electron-donating groups can also be cyclopropanated under thermal conditions in an intermolecular fashion with alkoxycarbene complexes [10] (Scheme 2). In most cases this reaction must be carried out under high pressure of carbon monoxide in order to avoid the formation of the corresponding olefin metathesis products [11]. These [2_S+1_C] cycloaddition reactions are assumed to involve nucleophilic addition of the electron-rich alkene to the electrophilic carbene carbon atom to produce a zwitterionic intermediate which further undergoes ring closing [12]. Moreover, the diastereoselectivity of this reaction, generally low, is clearly improved by the use of alkenylcarbene complexes [10a] (Scheme 2).

Although the intramolecular cyclopropanation of simple alkenes easily occurs in those cases where a five- or six-membered ring is formed in addition to the three-membered ring [13], the intermolecular version of this process was described by Barluenga et al. in 1997 [14c]. Thus, this reaction has shown a high



Scheme 2

degree of diastereoselectivity with different substituted alkoxy(alkenyl)- and alkoxy(2-heteroaryl)carbene complexes of chromium and terminal, acyclic and cyclic 1,2-disubstituted simple olefins. In addition, a good functional group tolerance at the allylic position of the olefin is observed [14] (Scheme 3). A mechanism similar to that described for the electron-poor olefins and which involves the initial formation of a chelated tetracarbonyl complex intermediate is proposed to account for the experimental results. The cyclopropane stereochemistry can be explained on the basis of steric interactions between the alkenyl substituent of the carbene ligand and the olefin alkyl chain which will favour a relative *trans* disposition of these groups [14b,c] (Scheme 3). The use of 2-iodoethoxy-substituted alkenylcarbene complexes allows the easy preparation of cyclopropanol derivatives by removing the 2-iodoethyl moiety of the corresponding cyclopropane derivative by treatment with *t*BuLi at low temperature [14a].

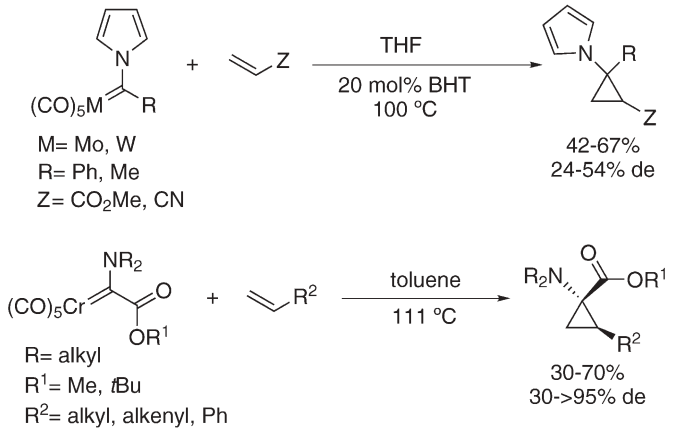


Scheme 3 [Cr]= $Cr(CO)_4$

The first examples of alkene cyclopropanation reactions with alkynylcarbene complexes were reported by Barluenga et al. in 2002 [15]. These intermolecular

processes involve the treatment of singular simple olefins, such as fulvenes [15a] and strained olefins [15b], with methoxy(alkynyl)carbene complexes.

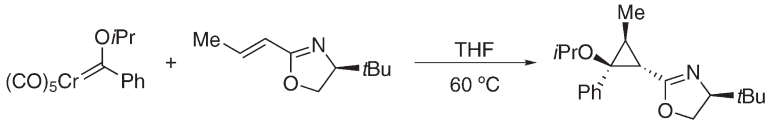
The cyclopropanation reaction with aminocarbene complexes has been much less studied than the corresponding reaction with alkoxy-derived carbene complexes. Indeed, these reagents have shown scarce ability to effectively transfer their carbene ligands to an alkene and, in general, electron-deficient olefins react with aminocarbene complexes to form open-chain products resulting from a formal C_{sp2}-H insertion [6c, 16]. Only one example involving the reaction of pyrrolo-derived carbene complexes and electron-deficient olefins leading to cyclopropane derivatives has been reported [17] (Scheme 4). In this context, very recently an example involving the intermolecular cyclopropanation of a simple alkene with an aminocarbene complex has been described [18] (Scheme 4). Moreover, two examples of intramolecular cyclopropanation of simple alkenes with chromium- [13b] and tungstencarbene complexes [13d] are known.



Scheme 4

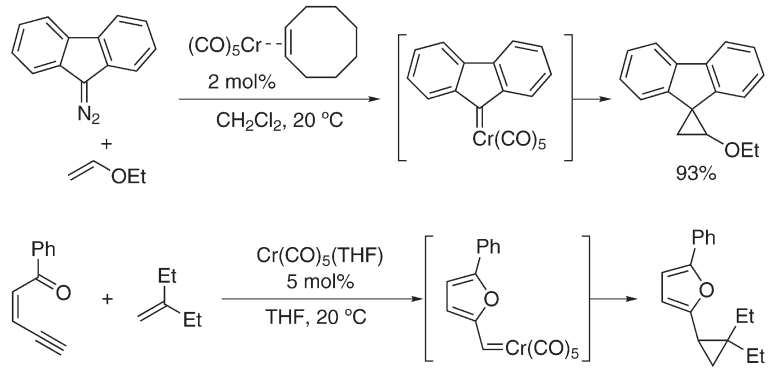
Non-heteroatom-stabilised Fischer carbene complexes also react with alkenes to give mixtures of olefin metathesis products and cyclopropane derivatives which are frequently the minor reaction products [19]. Furthermore, non-heteroatom-stabilised vinylcarbene complexes, generated in situ by reaction of an alkoxy- or aminocarbene complex with an alkyne, are able to react with different types of alkenes in an intramolecular or intermolecular process to produce bicyclic compounds containing a cyclopropane ring [20].

Asymmetric versions of the cyclopropanation reaction of electron-deficient olefins using chirally modified Fischer carbene complexes, prepared by exchange of CO ligands with chiral bisphosphites [21a] or phosphines [21b], have been tested. However, the asymmetric inductions are rather modest [21a] or not quantified (only the observation that the cyclopropane is optically active is reported) [21b]. Much better facial selectivities are reached in the cyclopropanation of enantiopure alkenyl oxazolines with aryl- or alkyl-substituted alkoxycarbene complexes of chromium [22] (Scheme 5).



Scheme 5

Catalytic cyclopropanation of alkenes has been reported by the use of diazoalkanes and electron-rich olefins in the presence of catalytic amounts of pentacarbonyl(η^2-*cis*-cyclooctene)chromium [23a,b] (Scheme 6) and by treatment of conjugated ene-yne ketone derivatives with different alkyl- and donor-substituted alkenes in the presence of a catalytic amount of pentacarbonylchromium tetrahydrofuran complex [23c]. These [2_S+1_C] cycloaddition reactions catalysed by a Cr(0) complex proceed at room temperature and involve the formation of a non-heteroatom-stabilised carbene complex as intermediate.



Scheme 6

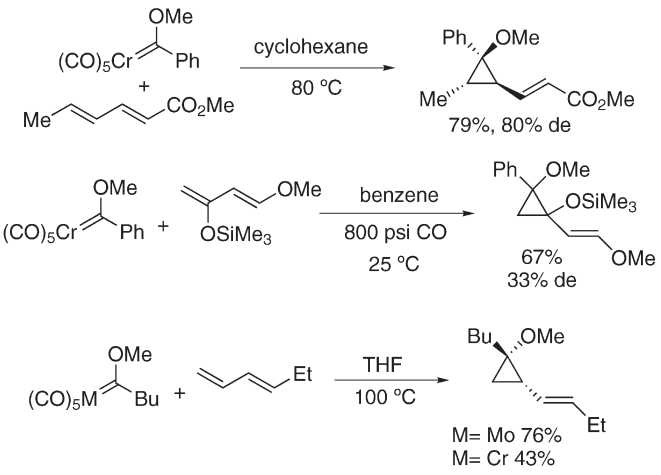
2.1.2 Cyclopropanation of 1,3-Dienes

The reactions of Fischer carbene complexes with 1,3-dienes (carbodienes or heterodienes) lead to the formation of cyclic products with different ring sizes depending upon both the nature of the reaction partners and the reaction conditions. Between these synthetically useful transformations are found [2_C+2_S], [3_C+2_S], [4_S+1_C], [3_S+3_C], [4_S+2_C], [4_S+3_C] and [2_S+1_C+1_{CO}] cycloaddition reactions which will be summarised further on, in addition to the [2_S+1_C] cycloaddition processes here described.

Electron-deficient 1,3-dienes are known to react when heated with methoxy(aryl)- or methoxy(alkyl)carbene complexes to afford vinylcyclopropane derivatives with high regioselectivity and diastereoselectivity [8a, 24]. Cyclopropanation of the double bond not bearing the acceptor functional group and

formation of the diastereoisomer with the methoxy group *cis*-positioned with respect to the olefinic moiety are both largely favoured. One example is shown in Scheme 7. Even trisubstituted 1,3-dienes undergo this [2_S+1_C] cycloaddition reaction [24a].

Electron-rich 1,3-dienes react smoothly with Fischer carbene complexes, but these reactions have been reported to produce cyclopropanes only in very isolated examples [25]. Methoxy(phenyl)carbene complex reacts with Danishefsky's dienes to produce, with low diastereoselectivity, the vinylcyclopropane resulting from the regioselective transfer of the carbene ligand to the more electron-rich double bond of the diene [25b] (Scheme 7). The reaction must be carried out under pressure of carbon monoxide to minimise the formation of side products. Methoxy(alkenyl)carbene complexes of chromium also react with this type of 1,3-diene, affording initially divinylcyclopropanes that in most cases undergo Cope rearrangement in the reaction medium to give seven-membered rings, as will be described in a following section. The cyclopropanation reaction of 4-substituted 2-(*tert*-butyldimethylsiloxy)-1,3-butadiene with acetoxy(methyl)- and acetoxy(alkenyl)carbene complexes of chromium has also been reported [26].

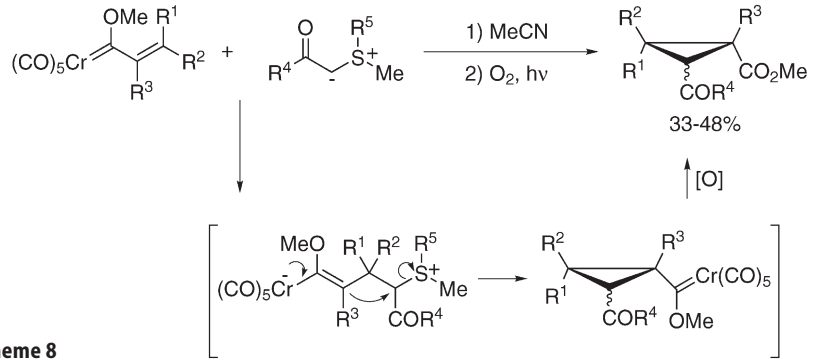


Scheme 7

Simple 1,3-dienes also undergo a thermal monocyclopropanation reaction with methoxy(alkyl)- and methoxy(aryl)carbene complexes of molybdenum and chromium [27]. The most complete study was carried out by Harvey and Lund and they showed that this process occurs with high levels of both regio- and diastereoselectivity. The chemical yield is significantly higher with molybdenum complexes [27a] (Scheme 7). Tri- and tetrasubstituted 1,3-dienes and 3-methylenecyclohexene (diene locked in an *s-trans* conformation) fail to react [28]. The monocyclopropanation of electronically neutral 1,3-dienes with non-heteroatom-stabilised carbene complexes has also been described [29].

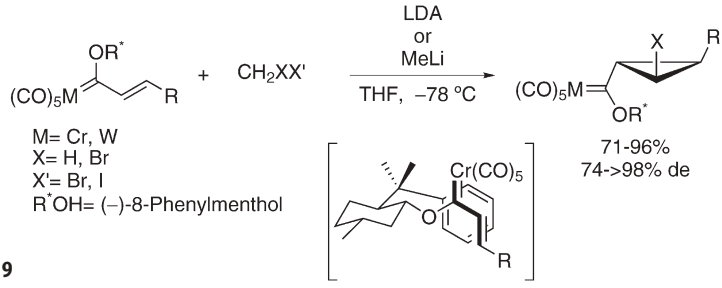
2.2
[2_C+1_S] Cycloaddition Reactions: Synthesis of Cyclopropylcarbene Complexes

Stabilised sulphur ylides react with alkenylcarbene complexes to form a mixture of different products depending on the reaction conditions. However, at –40 °C the reaction results in the formation of almost equimolecular amounts of vinyl ethers and diastereomeric cyclopropane derivatives. These cyclopropane products are derived from a formal [2_C+1_S] cycloaddition reaction and the mechanism that explains its formation implies an initial 1,4-addition to form a zwitterionic intermediate followed by cyclisation. Oxidation of the formed complex renders the final products [30] (Scheme 8).



Scheme 8

Alkenylcarbene complexes react with in situ-generated iodomethyllithium or dibromomethyllithium, at low temperature, to produce cyclopropylcarbene complexes in a formal [2_C+1_S] cycloaddition reaction. This reaction is highly diastereoselective and the use of chiral alkenylcarbene complexes derived from (–)-8-phenylmenthol has allowed the enantioselective synthesis of highly interesting 1,2-disubstituted and 1,2,3-trisubstituted cyclopropane derivatives [31] (Scheme 9). As in the precedent example, this reaction is supposed to proceed through an initial 1,4-addition of the corresponding halomethyllithium derivative to the alkenylcarbene complex, followed by a spontaneous γ-elimination of lithium halide to produce the final cyclopropylcarbene complexes.

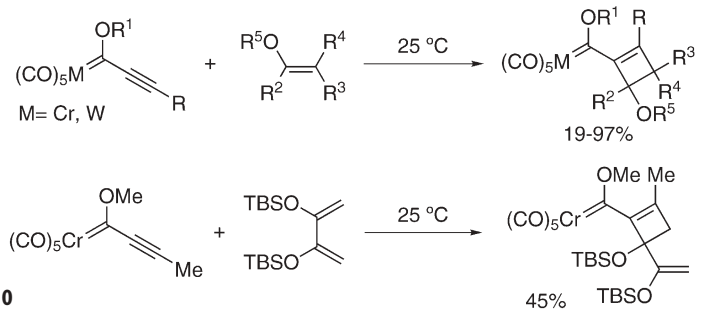


Scheme 9

The asymmetric induction that has been observed in this reaction can be explained in terms of the model shown in Scheme 9. In the most stable conformation the appropriately positioned phenyl group shields selectively the *Re*,*Re* face of the chromadiene by π,π-orbital overlap forcing the nucleophile to attack preferentially on the opposite side.

2.3 $[2_C+2_S]$ Cycloaddition Reactions: Synthesis of Cyclobutenylcarbene Complexes

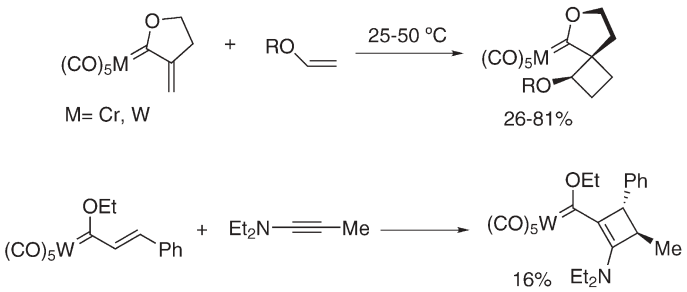
The [2+2] cycloaddition reaction is the most versatile method to access four-membered rings [32]. This process may proceed under thermal, photochemical or metal-catalysed conditions. However, the thermally induced reaction can only be applied to a limited extent, especially in the reaction of ester-functionalised acetylene derivatives with enol ethers [33]. Nonetheless, if Fischer alkynylcarbene complexes are used as ester analogues, such [2+2] cycloaddition reaction gives the corresponding cyclobutene derivatives under milder experimental conditions according to the overall reaction shown in Scheme 10 [34]. The first example of this kind of reaction was observed by Wulff and Faron during their investigations on the Diels–Alder reaction of 2,3-bis(*tert*-butyldimethylsilyloxy)-1,3-butadiene with alkynylcarbene complexes of chromium [35]. After this initial discovery several examples of [2+2] cycloaddition reactions involving enol ethers, silyl enol ethers, vinyl acetates and ketene acetals were published [36].



Scheme 10

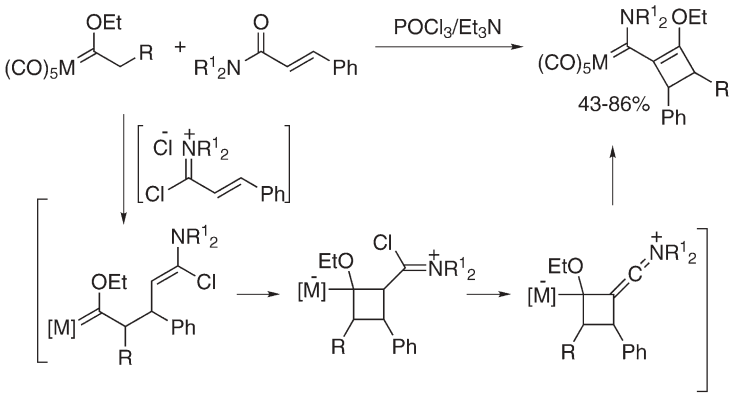
Apart from these oxygen-substituted electron-rich olefins, it has been reported that nitrogen-substituted olefins such as lactims and alkenyl imidates react with alkynylcarbene complexes through domino reactions, in which a [2+2] process is involved, to give cyclobutene-containing biscarbene complex derivatives [37]. While the [2+2] cycloaddition reaction of alkynylcarbene complexes with electron-rich olefins has been widely studied, the analogous reaction using alkenylcarbene complexes remains almost unexplored and only two examples have been reported so far. Thus, α-*exo*-methylene-2-oxacyclopentylidene complexes of chromium and tungsten undergo [2+2] cycloaddition processes with enol ethers under mild thermal conditions to give spiro-

cyclobutanes in good yields and as single diastereoisomers [38] (Scheme 11). The other example of an alkenylcarbene complex involved in a [2+2] cycloaddition implies the reaction of an ynamine and a tungsten alkenylcarbene complex leading to a new cyclobutenylcarbene complex as a side product and in very low yield [39] (Scheme 11).



Scheme 11

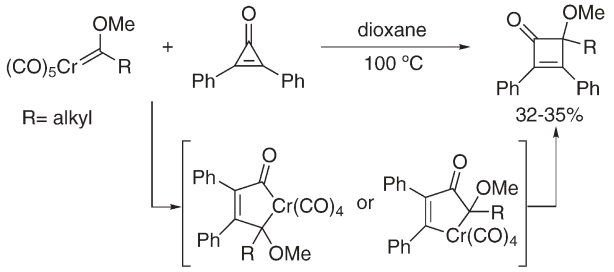
An unusual example of a formal [2+2] cycloaddition process is that described by Aumann et al. who referred to the reaction of alkyl-substituted carbene complexes with *α,β*-unsaturated *N,N*-disubstituted acid amides in the presence of $POCl_3/Et_3N$ [40]. This reaction is initiated by the transformation of the acid amides into the more reactive iminium chlorides. A 1,4-addition of the conjugated base of the carbene complex to the iminium chloride generates an open-chain carbene complex derivative, which undergoes a cyclisation process to afford a cyclobutene complex derivative. This intermediate evolves by HCl elimination followed by a [1,3]-migration of the metal fragment to furnish the final aminocarbene derivatives (Scheme 12). Interestingly, in those cases where R^1=H, the reaction follows a different pathway affording a mixture of open-chain, formal $[3_S+2_C]$ and formal $[3_S+2_S+1_C]$ products in low yield [40].



Scheme 12 [M]= $M(CO)_5$, M= Cr, W

2.4
[3_S+1_C] Cycloaddition Reactions

The [3_S+1_C] cycloaddition reaction with Fischer carbene complexes is a very unusual reaction pathway. In fact, only one example has been reported. This process involves the insertion of alkyl-derived chromium carbene complexes into the carbon–carbon σ-bond of diphenylcyclopropenone to generate cyclobutenone derivatives [41] (Scheme 13). The mechanism of this transformation involves a CO dissociation followed by oxidative addition into the cyclopropenone carbon–carbon σ-bond, affording a metalacyclopentenone derivative which undergoes reductive elimination to produce the final cyclobutenone derivatives.

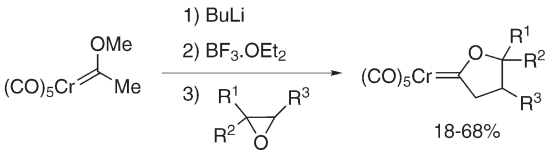


Scheme 13

2.5
[3_S+2_C] Cycloaddition Reactions

The 1,3-dipolar cycloadditions are a powerful kind of reaction for the preparation of functionalised five-membered heterocycles [42]. In the field of Fischer carbene complexes, the α,β-unsaturated derivatives have been scarcely used in cycloadditions with 1,3-dipoles in contrast with other types of cycloadditions [43]. These complexes have low energy LUMOs, due to the electron-acceptor character of the pentacarbonyl metal fragment, and hence, they react with electron-rich dipoles with high energy HOMOs.

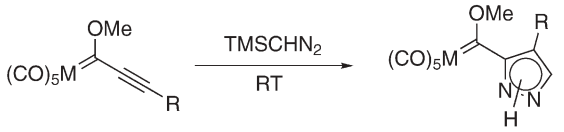
Although most of the examples of [3_S+2_C] cycloaddition reactions with carbene complexes are referred to as 1,3-dipolar processes, we should include in this section another kind of "non-dipolar" transformation dealing with the reaction of pentacarbonyl(methoxymethylcarbene)chromium with a base followed by treatment with an epoxide in the presence of boron trifluoride. This reaction gives cyclic carbene complexes in a process that can be considered a [3_S+2_C] cycloaddition [44] (Scheme 14).



Scheme 14

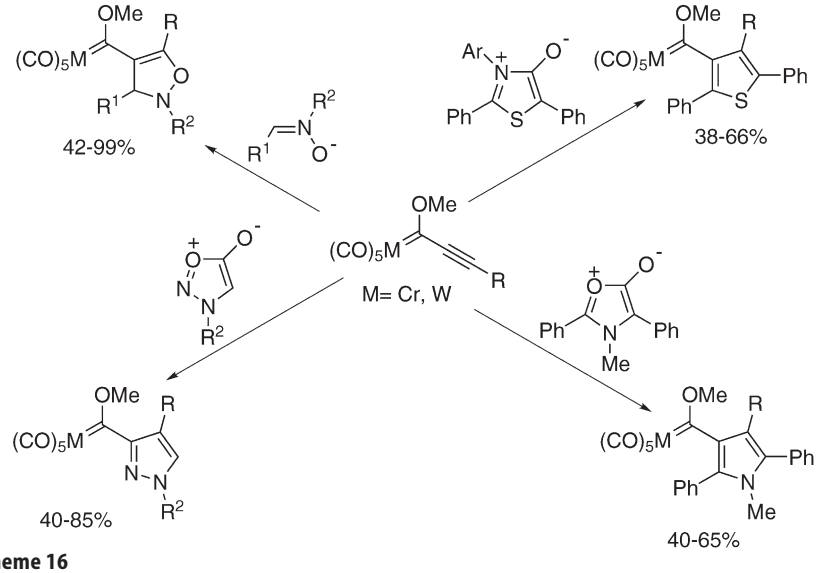
2.5.1
Alkynylcarbene Complexes in 1,3-Dipolar Cycloadditions

The first $[3_S+2_C]$ cycloaddition reaction using a Fischer carbene complex was accomplished by Fischer et al. in 1973 when they reported the reaction of the pentacarbonyl(ethoxy)(phenylethynyl)carbene complex of tungsten and diazomethane to give a pyrazole derivative [45]. But it was 13 years later when Chan and Wulff demonstrated that in fact this was the first example of a 1,3-dipolar cycloaddition reaction [46, 47a]. The introduction of a bulky trimethylsilyl group on the diazomethane in order to prevent carbene-carbon olefination leads to the corresponding pyrazole carbene complexes in better yields (Scheme 15).



Scheme 15 M= Cr, W 57-87%

(Alkoxy)alkynylcarbene complexes have been shown to react with nitrones to give dihydroisoxazole derivatives [47]. Masked 1,3-dipoles such as 1,3-thiazolium-4-olates also react with alkynylcarbene complexes to yield thiophene derivatives. The initial cycloadducts formed in this reaction are not isolated and they evolve by elimination of isocyanate to give the final products [48]. The analogous reaction with munchnones or sydnones as synthetic equivalents of

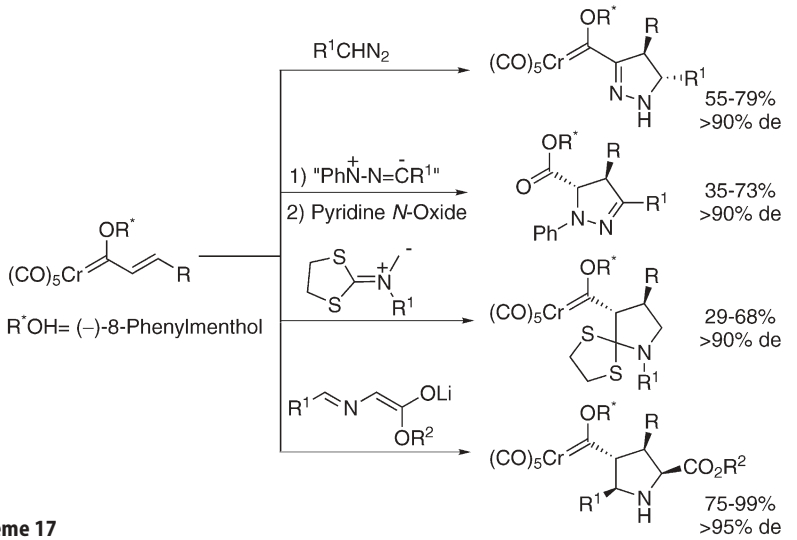


Scheme 16

azomethine ylides and imines, respectively, leads to pyrrole or pyrazole carbene complexes. In these cases, the final products are those derived from carbon dioxide extrusion and are obtained as single regioisomers [49] (Scheme 16).

2.5.2 Alkenylcarbene Complexes in 1,3-Dipolar Cycloadditions

Diazo compounds react with alkenylcarbene complexes to yield the corresponding [3+2] cycloadduct as a single regioisomer but as a mixture of diastereoisomers [50]. However, chiral α,β-unsaturated carbene complexes derived from (–)-8-phenylmenthol react with different diazo compounds to give the corresponding pyrazoline derivatives as single diastereoisomers [51]. In the same way, the cycloaddition reaction of these chiral carbene complexes has been successfully performed with other 1,3-dipoles. Thus, the reaction with nitrilimines leads, after oxidation of the pentacarbonylchromium fragment, to Δ^2-pyrazoline derivatives as single diastereoisomers [52]. Moreover, the reaction with azomethine ylides also produces the $[3_S+2_C]$ adducts as single regioisomers in a highly diastereoselective fashion. Interestingly, this latter reaction has been used as the key step in the total synthesis of the pharmaceutically useful compound (+)-rolipran [53]. Another proof of the potential of chiral α,β-unsaturated carbene complexes derived from (–)-8-phenylmenthol can be found in the formal $[3_S+2_C]$ cycloaddition reaction of these complexes and *N*-alkylidene glycine ester anions. This reaction is thought to proceed through an initial 1,4-addition of the enolate to the α,β-unsaturated carbene followed by a 5-*endo-trig* ring closure. The cycloadducts obtained in this reaction are precursors of interesting enantiomerically highly enriched proline derivatives [54] (Scheme 17).



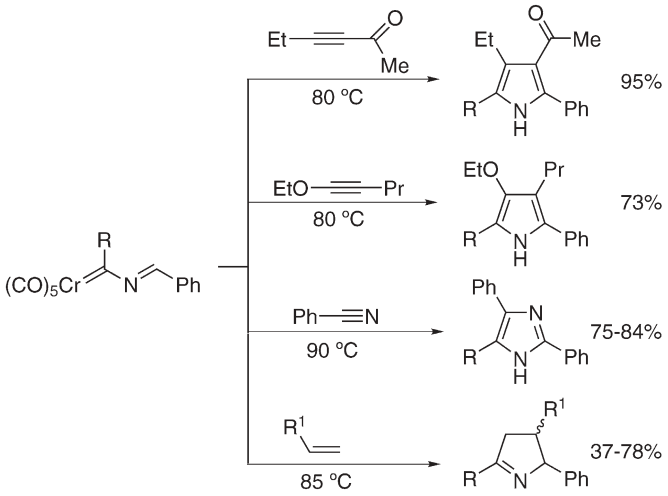
Scheme 17

2.6 [3_C+2_S] Cycloaddition Reactions

Fischer carbene complexes are valuable C3 building blocks for the formal [3_C+2_S] carbo- and heterocyclisation reactions [55]. Thus, not only the traditional α,β-unsaturated but also aryl and iminocarbene complexes have been used to get a great variety of compounds derived from the [3_C+2_S] reaction with different C2 counterparts.

2.6.1 Iminocarbene Complexes as C3 Building Blocks

Iminocarbene complexes of chromium and tungsten are useful isolable synthetic equivalents to nitrile ylides having the advantage that the range of 1,3-dipolarophiles is not limited to electron-acceptor substrates and can be extended to electronically neutral as well as to electron-rich systems [56] (Scheme 18).



Scheme 18

The regioselectivity observed in these reactions can be correlated with the resonance structure shown in Fig. 2. The reaction with electron-rich or electron-poor alkynes leads to intermediates which are the expected on the basis of polarity matching. In Fig. 2 is represented the reaction with an ynone leading to a metalacycle intermediate (formal [4_C+2_S] cycloadduct) which produces the final products after a reductive elimination and subsequent isomerisation. Also, these reactions can proceed under photochemical conditions. Thus, Campos, Rodríguez et al. reported the cycloaddition reactions of iminocarbene complexes and alkynes [57, 58], alkenes [57] and heteroatom-containing double bonds to give 2*H*-pyrrole, 1-pyrroline and triazoline derivatives, respectively [59].

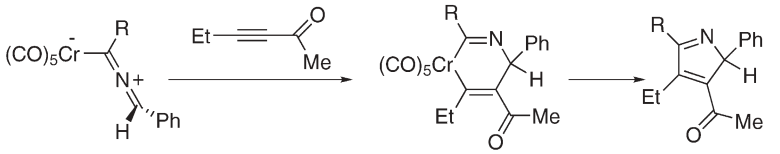
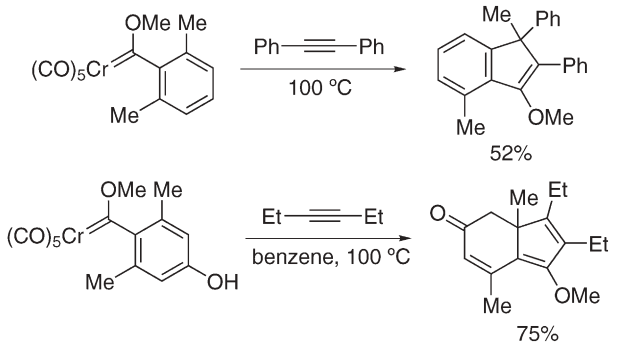


Fig. 2 Reaction of an iminocarbene complex of chromium with an ynone

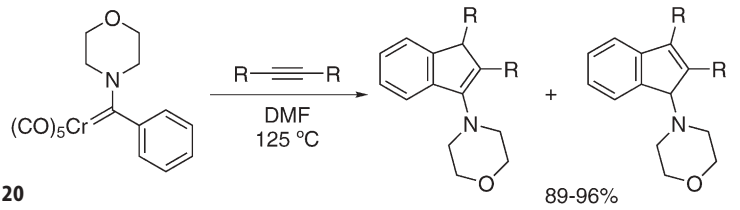
2.6.2 Arylcarbene Complexes as C3 Building Blocks

The reaction of alkoxyarylcarbene complexes with alkynes mainly affords Dötz benzannulated [3_C+2_S+1_{CO}] cycloadducts. However, uncommon reaction pathways of some alkoxyarylcarbene complexes in their reaction with alkynes leading to indene derivatives in a formal [3_C+2_S] cycloaddition process have been reported. For example, the reaction of methoxy(2,6-dimethylphenyl)chromium carbene complex with 1,2-diphenylacetylene at 100 °C gives rise to an unusual indene derivative where a sigmatropic 1,5-methyl shift is observed [60]. Moreover, a related (4-hydroxy-2,6-dimethylphenyl)carbene complex reacts in benzene at 100 °C with 3-hexyne to produce an indene derivative. However, the expected Dötz cycloadduct is obtained when the solvent is changed to acetonitrile [61] (Scheme 19). Also, Dötz et al. have shown that the introduction of an isocyanide ligand into the coordination sphere of the metal induces the preferential formation of indene derivatives [62].



Scheme 19

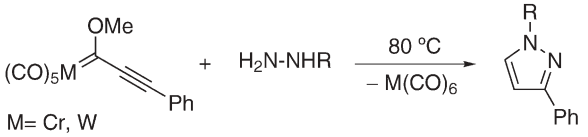
Interestingly, amino(aryl)carbene complexes react with alkynes to give exclusively [3_C+2_S] cycloaddition derivatives in high yields. This behaviour is totally different from the analogous alkoxy(aryl)carbene complexes as these preferentially lead to Dötz cycloadducts. Thus, Yamashita et al. found that morpholinophenylcarbene complex reacts with symmetrical alkynes to produce, after hydrolysis, the corresponding indanone derivatives [63] (Scheme 20). The dialkylaminofuranylcarbene complexes [64] and amidoarylcarbene complex derivatives [65] react in a similar way.



Scheme 20

2.6.3 Alkynylcarbene Complexes as C3 Building Blocks

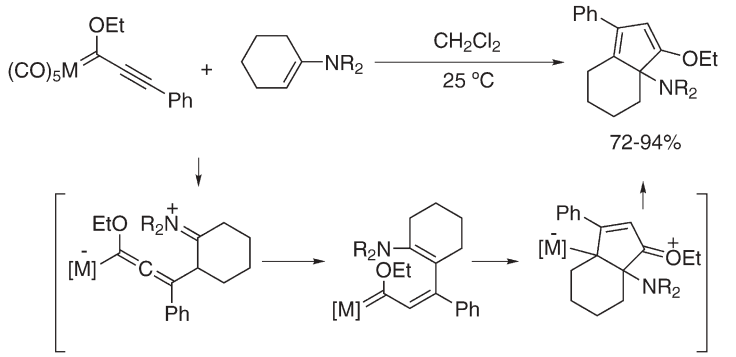
α,β-Unsaturated carbene complexes have two electrophilic positions, so they may react with nucleophiles by the carbene carbon in a 1,2-addition fashion or by the β-carbon in a Michael-type or 1,4-addition way. Thus, compounds such as hydrazines, which possess two nucleophilic centres, react with alkynyl carbene complexes to formally produce the cycloaddition products coming from a double 1,2- and 1,4-addition process [66]. When the reaction is performed using the electron-deficient acetylhydrazine or phenylhydrazine, the intermediate cyclic carbene complex is not isolated and the reaction produces the corresponding pyrazole derivatives in high yields (Scheme 21).



Scheme 21

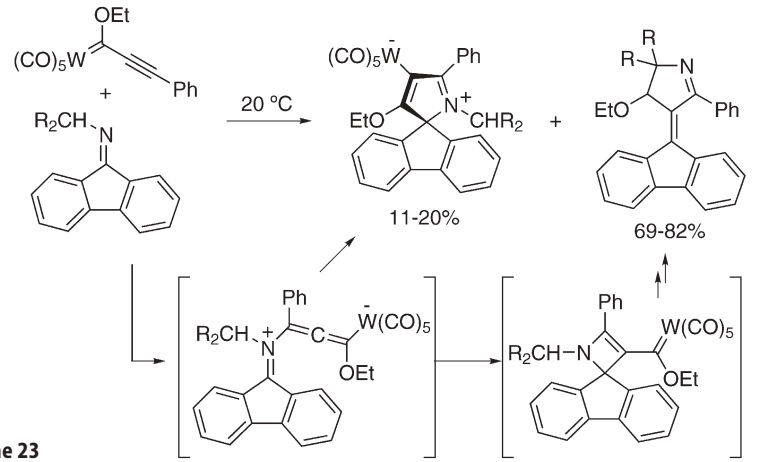
Fused cyclopentadiene derivatives are easily obtained by the reaction of alkynylcarbene complexes and cyclic enamines of five-, six- or seven-membered rings derived from secondary amines [67]. The overall $[3_C+2_S]$ cycloaddition process is highly regioselective and proceeds under very mild reaction conditions. The reaction pathway is initiated by Michael-type addition of the nucleophilic tertiary cycloalkenylamine to the electrophilic alkynylcarbene complex resulting in the formation of a zwitterionic allene-type intermediate. This undergoes intramolecular hydrogen transfer to give a 1-metalatriene which cyclises to a cyclopentadiene complex yielding the final products after decomplexation and isomerisation (Scheme 22).

Non-enolizable imines such as 9-fluorene imines react with alkynylcarbene complexes to afford mixtures of mesoionic pyrrolium carbonyltungstates and dihydropyrrole derivatives [68] (Scheme 23). Although both compounds can be considered as $[3_C+2_S]$ cycloadducts, formation of each of them follows a very different pathway. However, the first intermediate of the reaction is common for both compounds and supposes the conjugated addition of the imine to the alkynylcarbene complex to form a zwitterionic intermediate. A cyclisation



Scheme 22 [M]= $M(CO)_5$, M= Cr, W

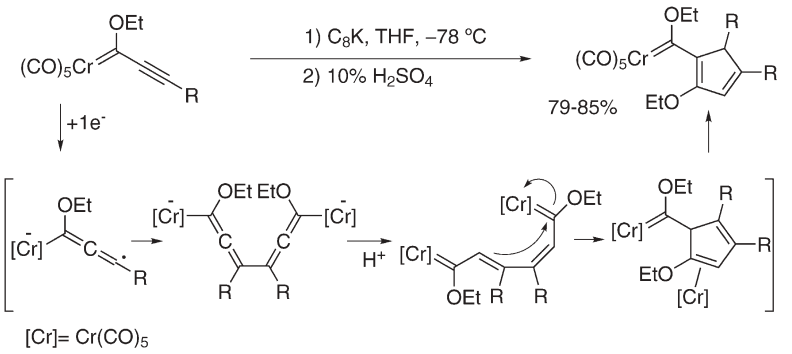
favoured by a [1,2]-migration of the metallic fragment leads to the mesoionic pyrrolium carbonyltungstates. On the other hand, formation of the dihydropyrrole derivatives follows a more complicated reaction sequence involving the formation of a four-membered ring intermediate followed by a metathesis step and rearrangement (Scheme 23).



Scheme 23

A particular case of a $[3_C+2_S]$ cycloaddition is that described by Sierra et al. related to the tail-to-tail dimerisation of alkynylcarbenes by reaction of these complexes with C_8K (potassium graphite) at low temperature and further acid hydrolysis [69] (Scheme 24). In fact, this process should be considered as a $[3_C+2_C]$ cycloaddition as two molecules of the carbene complex are involved in the reaction. Remarkable features of this reaction are: (i) the formation of radical anion complexes by one-electron transfer from the potassium to the carbene complex, (ii) the tail-to-tail dimerisation to form a biscarbene anion intermediate and finally (iii) the protonation with a strong acid to produce the

final product. Also, alkynylcarbene complexes react with alkenyl *N*-H imidates to give 2*H*-pyrrole complexes in a process which formally represents a [3_C+2_S] cycloaddition reaction. However, these compounds are obtained as minor products of the reaction and in very low yield (6–8%) [70].



Scheme 24

2.6.4 Alkenylcarbene Complexes as C3 Building Blocks

The utility of alkenylcarbene complexes as C3 building blocks in the [3_C+2_S] cycloaddition reaction has been demonstrated by the wide variety of five-membered hetero- and carbocycles obtained when these complexes are treated with several C2 building block reagents. This impressive chemistry will be briefly discussed in the next few sections.

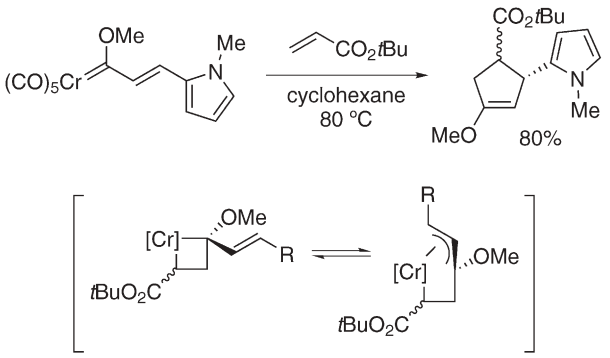
2.6.4.1 Reaction with Alkynes

In the same way as arylcarbene complexes, alkenylcarbene complexes typically react with alkynes to provide [3_C+2_S+1_{CO}] Dötz cycloadducts (see Chap. "Chromium-Templated Benzannulation Reactions", p. 123 in this book). However, some isolated examples involving the formation of five-membered rings through [3_C+2_S] cycloaddition processes have been reported [71]. In this context, de Meijere et al. found that β-donor-substituted alkenylcarbene complexes react with alkynes to give cyclopentene derivatives [71a]. This topic is also discussed in detail in Chap. "The Multifaceted Chemistry of Variously Substituted α,β-Unsaturated Fischer Metalcarbenes", p. 21 of this book.

2.6.4.2 Reaction with Electron-Poor Alkenes

The reaction of alkenylcarbene complexes and electron-poor alkenes normally leads to mixtures of the expected [2_S+1_C] vinylcyclopropane derivatives (see

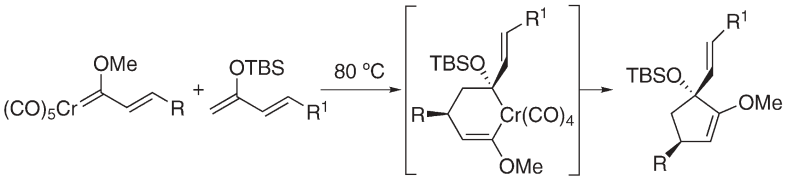
Sect. 2.1.1) and [3_C+2_S] cyclopentene derivatives. The product distribution can be controlled by choosing the appropriate reaction conditions [72]. Moreover, the cyclopentene derivatives are the exclusive products from the coupling of β-pyrrolyl-substituted carbene complexes [72b,c] (Scheme 25). The crucial intermediate chromacyclobutane is formed in an initial step by a [2+2] cycloaddition. This chromacyclobutane rearranges to give the η^3-complex when non-coordinating solvents are used. Finally, a reductive elimination leads to the formal [3_C+2_S] cyclopentene derivatives.



Scheme 25 [Cr]= $Cr(CO)_4$

2.6.4.3 Reaction with Electron-Rich Siloxy-Substituted 1,3-Dienes

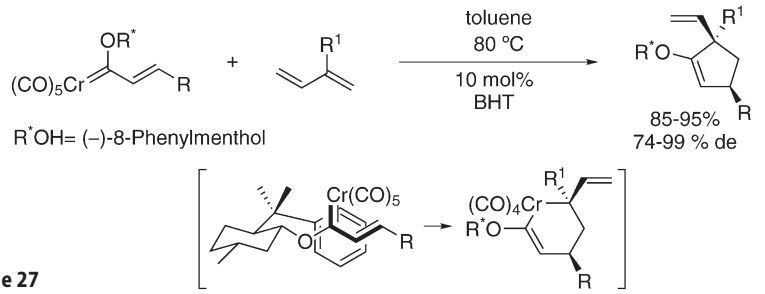
Coupling of alkenylcarbene complexes and siloxy-substituted 1,3-dienes affords vinylcyclopentene derivatives through a formal [3_C+2_S] cycloaddition process. This unusual reaction is explained by an initial [4_C+2_S] cycloaddition of the electron-poor chromadiene system as the 4π component and the terminal double bond of the siloxydiene as the dienophile. The chromacyclohexene intermediate evolves by a reductive elimination of the metal fragment to generate the [3_C+2_S] cyclopentene derivatives [73] (Scheme 26).



Scheme 26 16-72%

2.6.4.4
Reaction with Electronically Neutral 1,3-Dienes

While studying the intermolecular cyclopropanation of simple alkenes with alkenylcarbene complexes, Barluenga et al. observed that the reaction between these complexes and electronically neutral 1,3-dienes results in the formation of mixtures of $[3_C+2_S]$ and $[4_S+1_C]$ cycloadducts [74a]. The reaction seems to be highly dependent on the solvent [74b] and temperature of the reaction, and selective formation of the $[3_C+2_S]$ cyclopentene derivative can be achieved by performing the reaction in toluene at 80 °C. Moreover, high asymmetric induction is observed when chiral alkenylcarbene complexes derived from (–)-8-phenylmenthol are used (Scheme 27). The mechanism proposed for this reaction follows a pathway analogous to that described before for the reaction of siloxy-substituted 1,3-dienes. Thus, the alkenylcarbene complex acts as a 1-chroma-1,3-diene in a Diels–Alder-type cycloaddition reaction to give a chromacyclohexene, which generates the final products after reductive elimination of the metal fragment. Interestingly, the observed diastereofacial selection cannot be explained by the model previously proposed (see Scheme 9), in which the phenyl group of the chiral auxiliary shields the *Re*,*Re* face of the alkenyl moiety allowing the substrates to approach from the *Si*,*Si* face. In this case, the necessary *s-cis* conformation of the chromadiene makes the dienophile react from the *Si-Re* face of the chromadiene (Scheme 27).

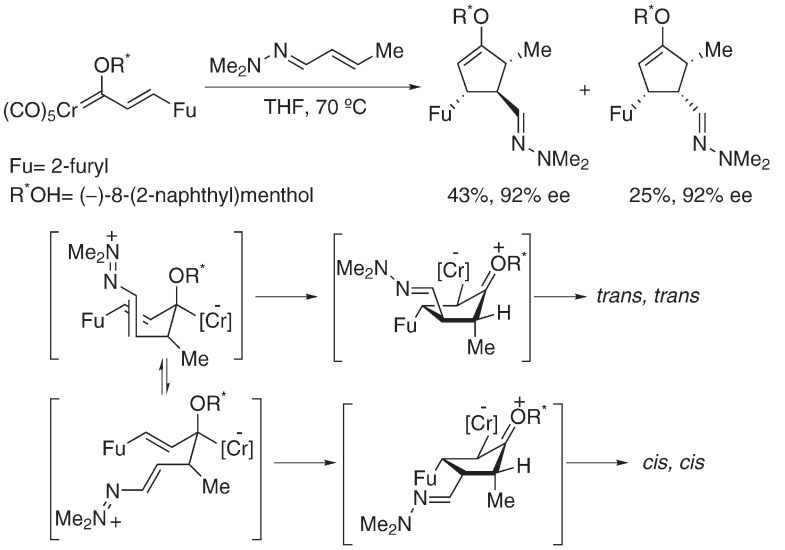


Scheme 27

2.6.4.5
Reaction with 1-Amino-1-Aza-1,3-Dienes

Fischer alkenylcarbene complexes undergo cyclopentannulation to alkenyl *N*,*N*-dimethylhydrazones (1-amino-1-azadienes) to furnish $[3_C+2_S]$ substituted cyclopentenes in a regio- and diastereoselective way along with minor amounts of $[4_S+1_C]$ pyrrole derivatives. Enantiopure carbene complexes derived from (–)-8-(2-naphthyl)menthol afford mixtures of *trans*,*trans*-cyclopentenes and *cis*,*cis*-cyclopentenes with excellent face selectivity [75]. The mechanism proposed for the formation of these cyclopentene derivatives is outlined in Scheme 28. The process is initiated by nucleophilic 1,2-attack of the C_β carbon

of the hydrazone on the less hindered face of the Cr=C double bond to generate a zwitterionic intermediate which may undergo a [1,2]-$Cr(CO)_5$ shift-promoted ring closure. Formation of one or the other diastereoisomer of the final product depends on the orientation of the azadiene moiety during this cyclisation step. Finally, hydrogen transfer to chromium followed by reductive elimination leads to the final *trans*,*trans*- or *cis*,*cis*-cyclopentenes.

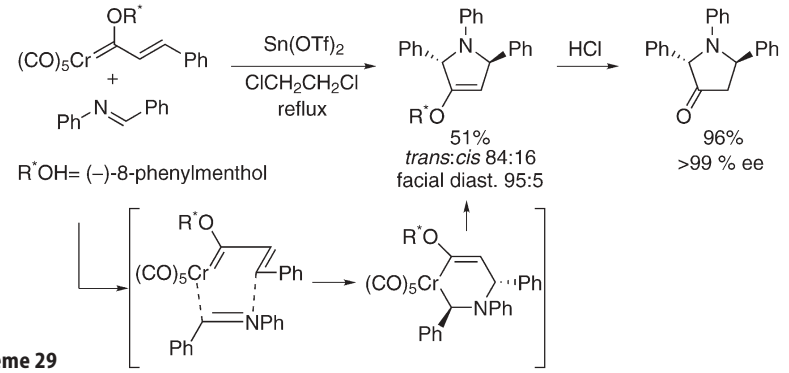


Scheme 28 [Cr]= $(CO)_5Cr$

2.6.4.6 Reaction with Imines

The reaction of alkenylcarbene complexes and imines in the presence of a Lewis acid generates pyrroline derivatives as a result of a $[3_C+2_S]$ cyclisation process [76]. This reaction has been extended to an asymmetric version by the use of chiral alkenylcarbene complexes derived from several chiral alcohols. However, the best results are found when (–)-8-phenylmenthol-derived complexes are used and catalytic amounts of $Sn(OTf)_2$ are added to the reaction. In these conditions high levels of *trans*/*cis* selectivity are achieved and the hydrolysis of the major *trans* diastereoisomers allows the preparation of optically pure 2,5-disubstituted-3-pyrrolidinone derivatives (Scheme 29).

The diastereofacial selectivity of this asymmetric $[3_C+2_S]$ process is explained following a model similar to that described in Sect. 2.6.4.4 for the reaction of chiral alkenylcarbene complexes and 1,3-dienes. Thus, the proposed mechanism that explains the stereochemistry observed assumes a [4+2] cycloaddition reaction between the chromadiene system and the C=N double bond of the imine. The necessary *s-cis* conformation of the complex makes the imine

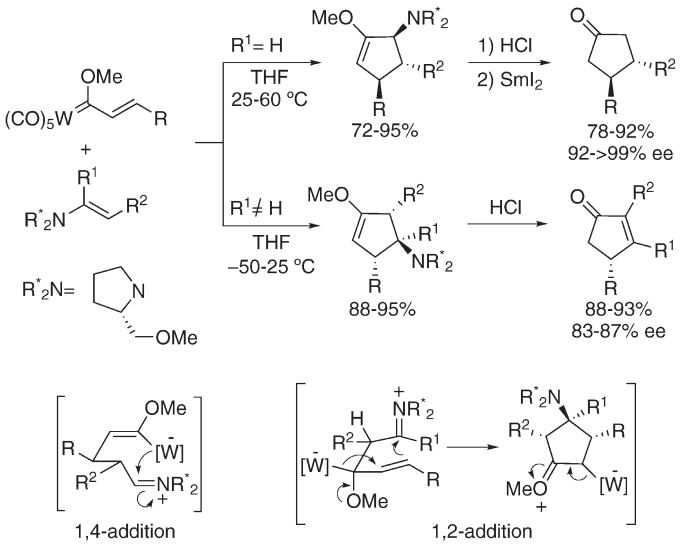


Scheme 29

approach from the less hindered *Si*,*Re* face of the complex to give a chromacyclohexene which, after reductive elimination, leads to the observed major 2*S*,5*R* isomer of the final product (Scheme 29).

2.6.4.7 Reaction with Enamines

Diastereoselective and enantioselective [3_C+2_S] carbocyclisations have been recently developed by Barluenga et al. by the reaction of tungsten alkenylcarbene complexes and enamines derived from chiral amines. Interestingly, the regiochemistry of the final products is different for enamines derived from aldehydes and those derived from ketones. The use of chiral non-racemic enamines allows the asymmetric synthesis of substituted cyclopentenone derivatives [77] (Scheme 30).

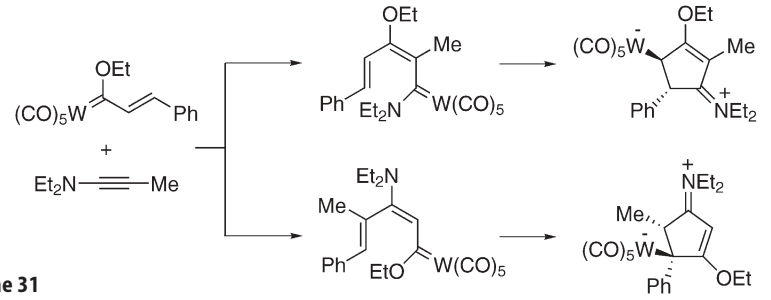


Scheme 30

The mechanism for aldehyde-derived enamines involves a Michael-type 1,4-addition of the enamine to the alkenylcarbene complex to generate a zwitterionic intermediate which evolves to the final product by cyclisation. On the other hand, ketone-derived enamines react through an initial 1,2-addition to the carbene carbon to generate a different zwitterionic intermediate. Then, a [1,2]-$W(CO)_5$ shift-promoted ring closure produces a new intermediate which, after elimination of the metal moiety, furnishes the corresponding cyclopentene derivatives (Scheme 30).

2.6.4.8 Reaction with Ynamines

The insertion reaction between alkenylcarbene complexes and electron-rich alkynes such as 1-alkynylamines (ynamines) leads to mixtures of two regioisomeric cyclopentyl derivatives [78]. Thus, if the insertion occurs on the carbon–metal bond a new aminocarbene complex is produced which evolves to a cyclopentenylmetal derivative. On the other hand, if the insertion reaction occurs on the carbon=carbon double bond of the alkenyl complex, the reaction gives a 1-metala-4-amino-1,3,5-triene complex which finally generates a different regioisomer of the cyclopentenylmetal derivative (Scheme 31).



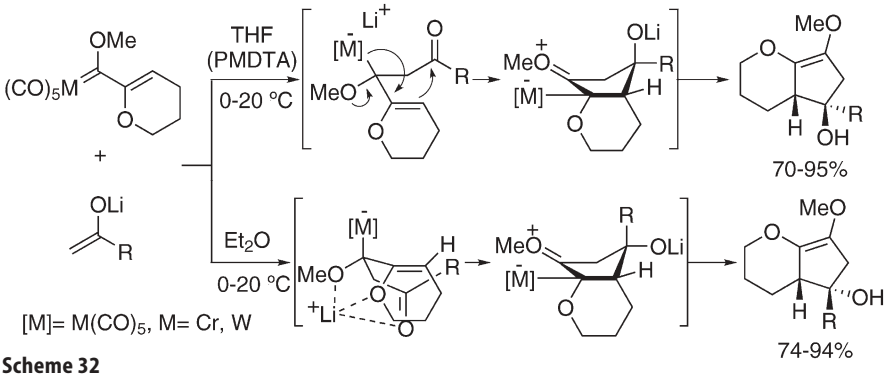
Scheme 31

2.6.4.9 Reaction with Methyl Ketone Lithium Enolates

An interesting strategy for the diastereoselective synthesis of five-membered carbocycles was achieved by the reaction of alkenylcarbene complexes and lithium enolates derived from simple methyl ketones [79]. The use of more or less coordinating solvents (THF or Et_2O) or the presence of cosolvents such as PMDTA allows the selective synthesis of one or the other diastereoisomer of the final cyclopentene derivative (Scheme 32).

The α-substitution in the alkenylcarbene complex seems to be crucial to direct the reaction to the five-membered rings. The mechanism proposed for this transformation supposes an initial 1,2-addition of the enolate to the carbene carbon atom to generate a zwitterionic intermediate. Cyclisation promoted by

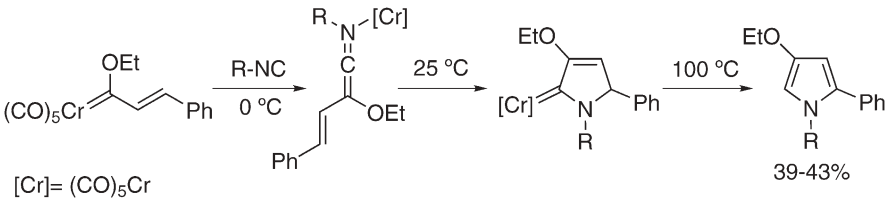
[1,2]-$(CO)_5M$ migration followed by loss of the metal fragment and decoordination leads to the final cyclopentene derivatives. Formation of one or the other diastereoisomer depending on the solvent used for this reaction seems to be closely related to coordinative effects of the lithium ions to the oxygen atoms of these intermediates, favouring the orientation of the carbonyl group in a particular conformation (Scheme 32).



Scheme 32

2.6.4.10 Reaction with Isonitriles

Isonitriles react with alkenylcarbene complexes to form initially at 0 °C a 3-ethoxy-3-styrylketeneimine complex, which on warming to room temperature leads to the formation of a cyclic 3-ethoxy-2,5-dihydro-2-pyrrolylidene complex. Finally, on heating to 100 °C a pyrrole derivative is produced [80] (Scheme 33).

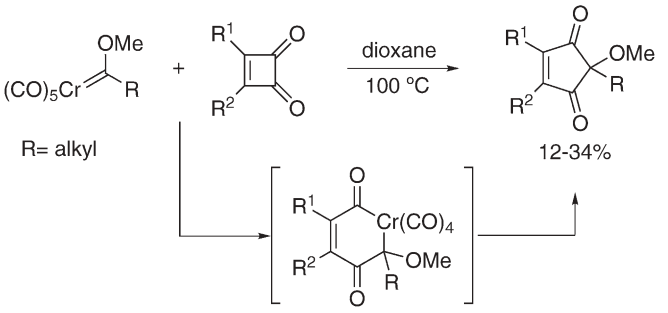


Scheme 33

2.7 [4_S+1_C] Cycloaddition Reactions

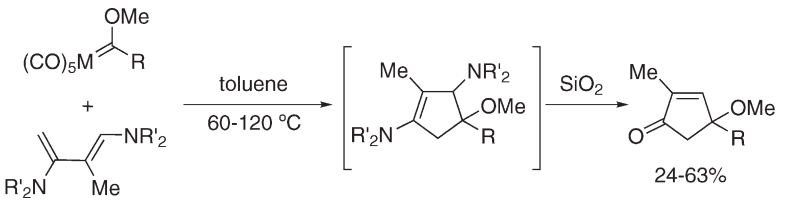
The participation of carbene/carbenoid metal complexes in [4_S+1_C] cycloaddition reactions is very infrequent [81]. In fact, only a few examples involving Fischer carbene complexes have been reported in recent years [82]. A remark-

able [4_S+1_C] cycloaddition process was reported by Herndon et al. when they reacted alkyl-derived chromium carbene complexes and cyclobutenediones to obtain furanone derivatives [83] (Scheme 34). The mechanism of this reaction involves the oxidative addition of the carbene to the acyl–acyl carbon–carbon σ-bond to finally produce a chromacyclohexenedione derivative which, after reductive elimination, generates the final products.



Scheme 34

The reaction of 1,3-diamino-1,3-dienes with aryl or α,β-disubstituted alkenylcarbene complexes leads to the formation of formal [4_S+1_C] cyclopentenones [25a] (Scheme 35). In the case of alkenylcarbene complexes, the substitution of the double bond of the complex in both α- and β-carbons seems to play a fundamental role as reactions performed in the same conditions but using alkenylcarbene complexes with other substitution patterns leads to compounds of a different nature ([4+3], [4+2] and [2+1] cycloadducts).

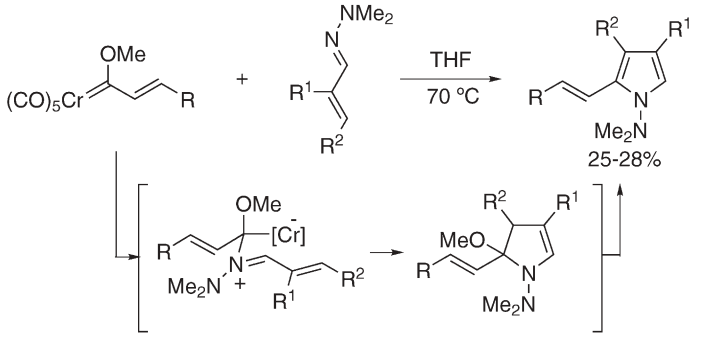


M= Cr, Mo
R= Ph, 1-cyclopentenyl, 1-cyclohexenyl
R'$_2$NH= morpholine

Scheme 35

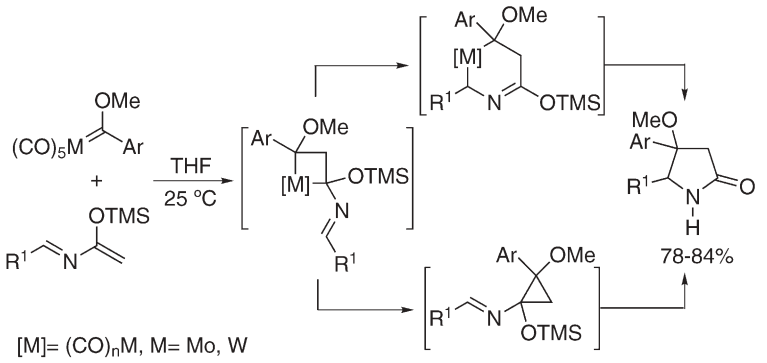
The reaction of *N*,*N*-dimethylhydrazones (1-amino-1-azadienes) and alkenylcarbene complexes mainly produces [3_C+2_S] cyclopentene derivatives (see Sect. 2.6.4.5). However, a minor product in this reaction is a pyrrole derivative which can be considered as derived from a [4_S+1_C] cycloaddition process [75]. In this case, the reaction is initiated by the nucleophilic 1,2-addition of the nitrogen lone pair to the metal–carbon double bond followed by cyclisation and

elimination of the corresponding alcohol (Scheme 36). If we compare this mechanism to that proposed for the formation of the major [3_C+2_S] product we may realise that formation of one or the other compound depends on the initial nucleophilic 1,2-addition (nitrogen or C_β attack) (compare to mechanism in Scheme 28, Sect. 2.6.4.5).



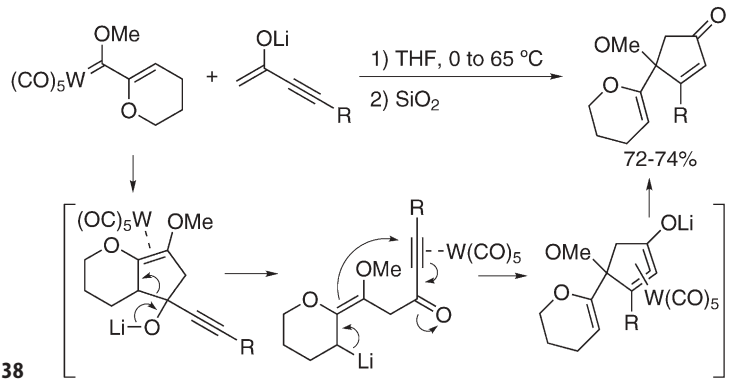
Scheme 36 [Cr]= $(CO)_5Cr$

Also, 2-aza-1,3-dienes react with arylcarbene complexes to undergo a formal [4_S+1_C] cycloaddition reaction to furnish pyrrolidinone derivatives in good yield [84a,b]. The formation of these cycloadducts is explained by initial [2+2] cycloaddition of the metal carbene to the electron-rich C=C double bond of the azadiene to form an intermediate metalacyclobutane. Transformation of this species into the final adducts can follow two pathways: (i) [1,3]-metal migration to form a 1-metala-3-azacyclohexene followed by reductive elimination and (ii) reductive metal elimination followed by three- to five-membered ring expansion of the resulting *N*-cyclopropylimine intermediate [84a] (Scheme 37). In a similar way, 1-aza-1,3-dienes react with arylcarbene complexes to furnish pyrrole derivatives through a formal [4_S+1_C] cycloaddition process, probably by a tandem cyclopropanation and ring enlargement [8a, 84c].



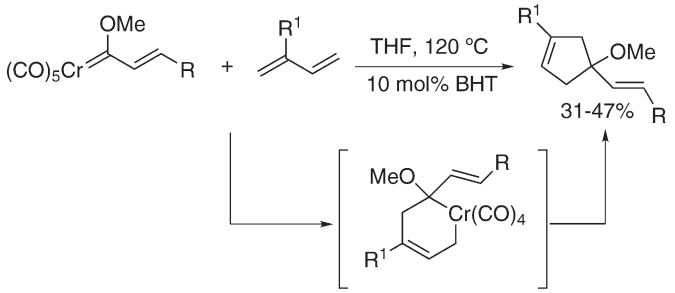
Scheme 37

Another example of a $[4_S+1_C]$ cycloaddition process is found in the reaction of alkenylcarbene complexes and lithium enolates derived from alkynyl methyl ketones. In Sect. 2.6.4.9 it was described how, in general, lithium enolates react with alkenylcarbene complexes to produce $[3_C+2_S]$ cycloadducts. However, when the reaction is performed using lithium enolates derived from alkynyl methyl ketones and the temperature is raised to 65 °C, a new formal $[4_S+1_C]$ cyclopentenone derivative is formed [79] (Scheme 38). The mechanism proposed for this transformation supposes the formation of the $[3_C+2_S]$ cycloadducts as depicted in Scheme 32 (see Sect. 2.6.4.9). This intermediate evolves through a retro-aldol-type reaction followed by an intramolecular Michael addition of the allyllithium to the ynone moiety to give the final cyclopentenone derivatives after hydrolysis. The role of the pentacarbonyltungsten fragment seems to be crucial for the outcome of this reaction, as experiments carried out with isolated intermediates in the absence of tungsten complexes do not afford the $[4_S+1_C]$ cycloadducts (Scheme 38).



Scheme 38

$[4_S+1_C]$ Cycloadducts have also been obtained in the reaction of alkenylcarbene complexes with electronically neutral 1,3-dienes by appropriate choice of the reaction conditions (see for comparison Sect. 2.6.4.4). Thus, performing the reaction in THF at 120 °C in a sealed flask the formal $[4_S+1_C]$ cyclopentene derivative is generated in moderate yield [74a, 85] (Scheme 39). The key step



Scheme 39

in the proposed mechanism for this transformation involves a metala-Diels–Alder reaction in which the Cr=C acts as dienophile to produce a chromacyclohexene derivative intermediate which, after reductive elimination, leads to the final [4_S+1_C] cyclopentene derivatives.

At this point the catalytic process developed by Dötz et al. using diazoalkanes and electron-rich dienes in the presence of catalytic amounts of pentacarbonyl(η^2-*cis*-cyclooctene)chromium should be mentioned. This reaction leads to cyclopentene derivatives in a process which can be considered as a formal [4_S+1_C] cycloaddition reaction. A Fischer-type non-heteroatom-stabilised chromium carbene complex has been observed as an intermediate in this reaction [23a].

2.8 [3_C+3_S] Cycloaddition Reactions

Despite the fact that transition metal complexes have found wide application in the synthesis of carbo- and heterocycles, [3+3] cyclisation reactions mediated or assisted by transition metals remain almost unexplored [3, 86]. However, a few examples involving Fischer carbene complexes have been reported. In all cases, this complex is α,β-unsaturated in order to act as a C3-synthon and it reacts with different types of substrates acting as C3-synthons as well.

All around this chapter, we have seen that α,β-unsaturated Fischer carbene complexes may act as efficient C3-synthons. As has been previously mentioned, these complexes contain two electrophilic positions, the carbene carbon and the β-carbon (Fig. 3), so they can react via these two positions with molecules which include two nucleophilic positions in their structure. On the other hand, alkenyl- and alkynylcarbene complexes are capable of undergoing [1,2]-migration of the metalpentacarbonyl allowing an electrophilic-to-nucleophilic polarity change of the carbene ligand β-carbon (Fig. 3). These two modes of reaction along with other processes initiated by [2+2] cycloaddition reactions have been applied to [3+3] cyclisation processes and will be briefly discussed in the next few sections.

2.8.1 Reaction of α,β-Unsaturated Fischer Carbene Complexes with 1,3-Dinucleophiles

Alkynylcarbene complexes react with β-dicarbonyl compounds and catalytic amounts of a base to generate formal [3+3] pyranylidene derivatives [87]. The

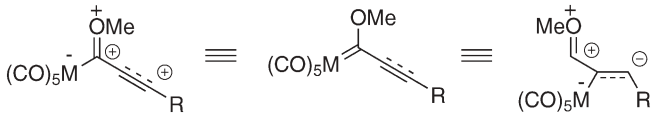
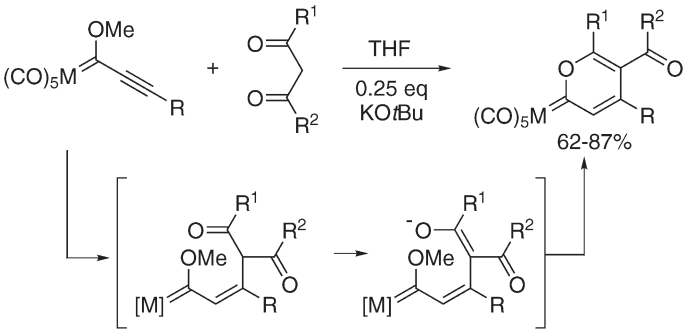


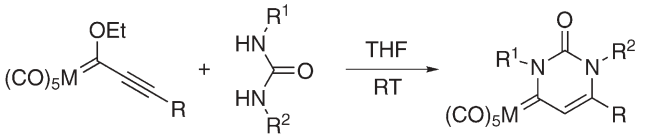
Fig. 3 The 1,2-migration of the metalpentacarbonyl of alkenyl- and alkynylcarbene complexes

reaction is initiated by the addition of the enolate to the β-position leading to an intermediate which evolves through an intramolecular exchange of the alkoxy group (Scheme 40).



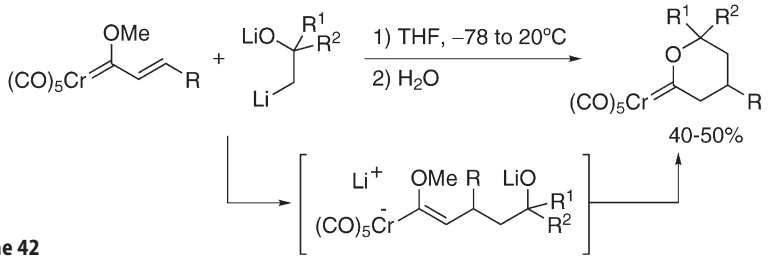
Scheme 40 [M]= $(CO)_5M$, M= Cr, W

In a similar way, 1,3-dinitrogen systems such as diamines, amidines, guanidines, aminothiazoles, aminopyridines, ureas and thioureas react with alkynylcarbene complexes generating the corresponding heterocycles. Of particular interest is the reaction with ureas, as the process can be applied to the easy synthesis of pyrimidine derivatives [88] (Scheme 41).



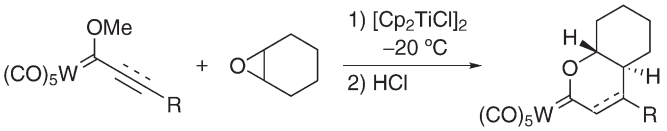
Scheme 41 M= Cr, W

β-Oxygen-functionalised sp^3 organolithium compounds react with alkenylcarbene complexes to generate the corresponding cyclic carbene complexes [89] (Scheme 42). This sequence involves initial Michael addition of the β-alkoxide organolithium reagent to give an anionic adduct which subsequently undergoes a spontaneous intramolecular alkoxide exchange.



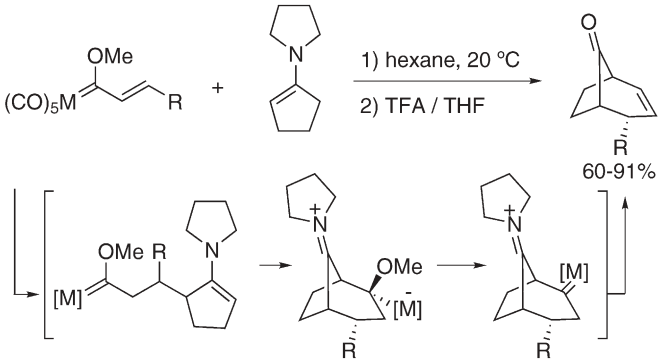
Scheme 42

In a reaction closely related to the latter, pyranylidene derivatives are obtained by the intermolecular radical coupling of alkynyl- or alkenylcarbene complexes and epoxides. Good diastereoselectivities are observed when cyclic epoxides are used. Moreover, the best results are reached by the generation of the alkyl radical using titanocene monochloride dimer [90] (Scheme 43).

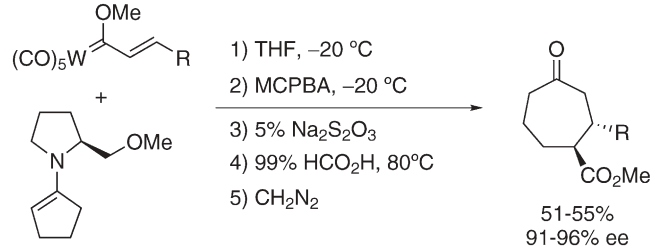


Scheme 43 36-74%

The potential of Fischer carbene complexes in the construction of complex structures from simple starting materials is nicely reflected in the next example. Thus, the reaction of alkenylcarbene complexes of chromium and tungsten with cyclopentanone and cyclohexanone enamines allows the diastereo- and enantioselective synthesis of functionalised bicyclo[3.2.1]octane and bicyclo[3.3.1]nonane derivatives [12] (Scheme 44). The mechanism of this transformation is initiated by a 1,4-addition of the C_{β}-enamine to the alkenylcarbene complex. Further 1,2-addition of the $C_{\beta'}$ of the newly formed enamine to the carbene carbon leads to a metalate intermediate which can



Scheme 44 [M]= $M(CO)_5$, M= Cr, W

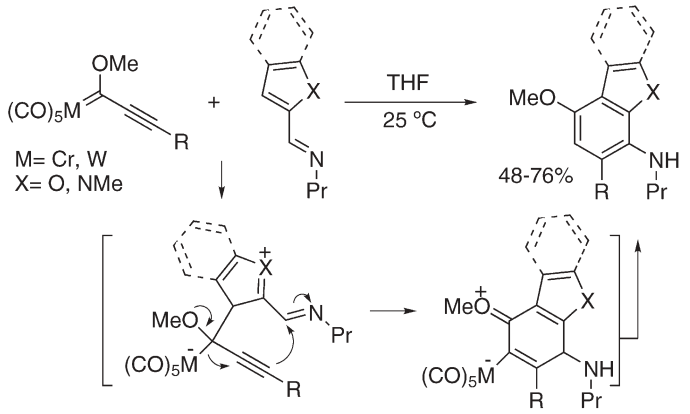


Scheme 45 51-55%
91-96% ee

be isolated. This metalate may suffer an acid-induced elimination of methanol to form a non-heteroatom-stabilised carbene species, which then undergoes β-hydrogen elimination and reductive elimination to yield the final products after hydrolysis of the imonium function. Applying this α,β,β'-annulation reaction it is possible to access enantioenriched 3,4-disubstituted cycloheptanones in a one-pot process from chiral cyclopentanone enamines (Scheme 45).

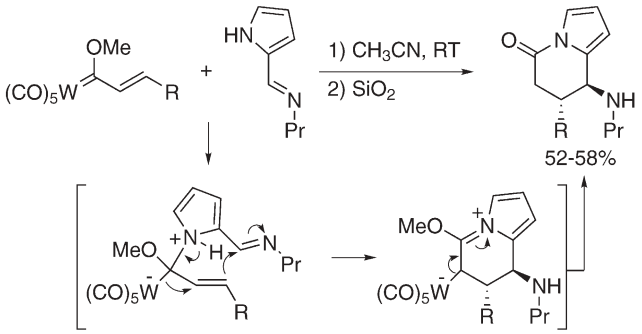
2.8.2 [1,2]-Metalpentacarbonyl-Promoted [3+3] Cycloaddition Reactions

Alkynylcarbene complexes react with imines derived from furan-, benzofuran-, *N*-substituted pyrrole- and *N*-substituted indole-2-carboxaldehydes to give the corresponding formal [3+3] cyclic derivative [91] (Scheme 46). This carbocyclisation process can be explained by assuming a [1,2]-migration of the pentacarbonylmetal fragment as the key step. Thus, an initial 1,2-addition of the C3 carbon of the ring generates a zwitterionic intermediate. Further [1,2]-$M(CO)_5$ shift promotes cyclisation and finally, hydrogen transfer and reductive elimination of the metal furnishes the final products.



Scheme 46

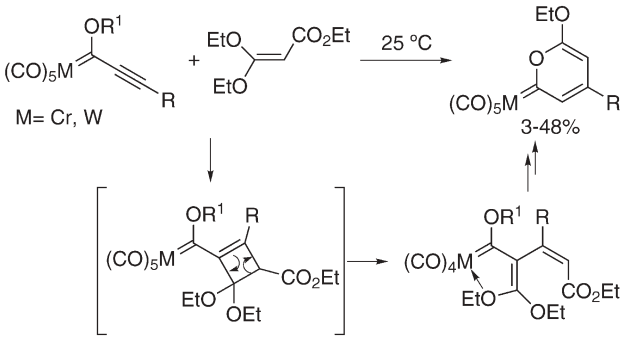
Interestingly, the analogous reaction performed with alkenylcarbene complexes and pyrrole-2-carboxaldehyde imine leads to other kinds of formal [3+3] cycloadducts. These compounds are obtained as single regio- and diastereoisomers [91] (Scheme 47). This heterocyclisation resembles the precedent [3+3] carbocyclisation of alkynylcarbene complexes, except that the unsubstituted ring nitrogen is now involved rather than the ring C3 atom. In this case, the sequence is initiated by a 1,2-addition of the N–H of the pyrrole to the carbene carbon affording a zwitterionic intermediate. Further cyclisation induced by [1,2]-$M(CO)_5$ shift followed by hydrogen transfer and reductive elimination of the metal leads to the final cycloadducts (Scheme 47).



Scheme 47

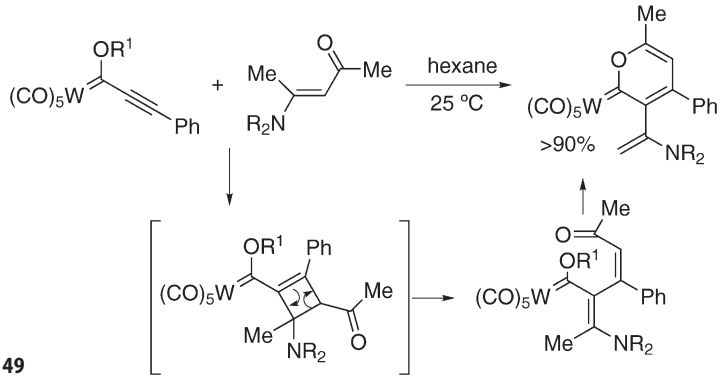
2.8.3
[3+3] Cycloaddition Reactions Initiated by a [2+2] Process

The reaction of ethyl 2,2-diethoxyacrylate with alkynylalkoxycarbene complexes affords 6-ethoxy-2*H*-2-pyranylidene metal complexes [92] (Scheme 48). The mechanism that explains this process is initiated by a [2+2] cycloaddition reaction (see Sect. 2.3), followed by a cyclobutene ring opening to generate a tetracarbonylcarbene complex. This complex can be isolated and on standing for one day at room temperature renders the final 6-ethoxy-2*H*-pyranylidene pentacarbonyl complex. This last transformation requires the formal transfer of one carbonyl group and one proton from the diethoxy methylene moiety to the metal and to the C3 2*H*-pyranylidene ring, respectively, with concomitant cyclisation. Further studies on this unusual transformation have been extensively performed by Moretó et al. [93].



Scheme 48

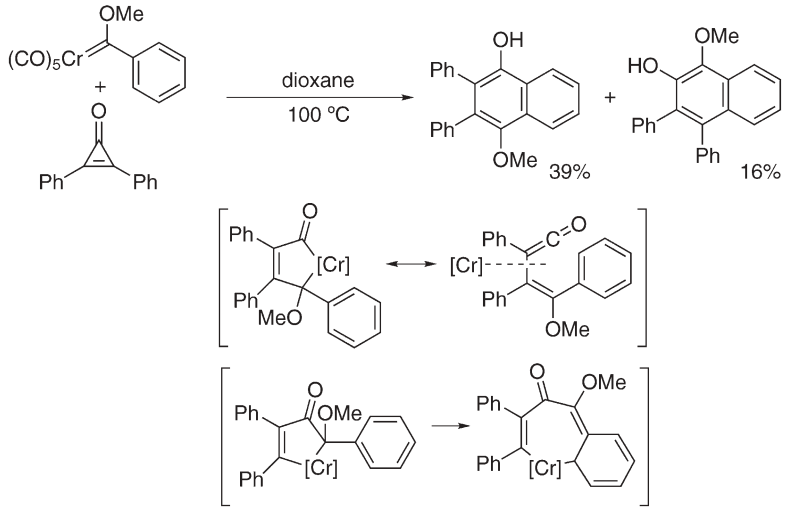
In a similar process, tertiary enaminones react with alkynylcarbene complexes to give the corresponding pyranylidene complexes following a reaction pathway analogous to that described above. First, a [2+2] cycloaddition reaction between the alkynyl moiety of the carbene complex and the C=C double bond of the enamine generates a cyclobutene intermediate, which evolves by a conrotatory cyclobutene ring opening followed by a cyclisation process [94] (Scheme 49).



Scheme 49

2.8.4
[3+3] Benzannulation Processes

Highly strained cyclic compounds such as cyclopropenone derivatives react with alkyl-derived chromium complexes to afford [3_S+1_C] cycloadducts (see Sect. 2.4). However, the use of alkenyl- or arylcarbene complexes leads to a mixture of two regioisomers of a benzannulation product which can be considered as derived from a [3+3] cycloaddition reaction [41] (Scheme 50). The reaction is initiated by the insertion of the metalcarbene into the cyclopropenone carbon–carbon σ-bond to generate two possible metalacyclopentenone derivatives. The first one evolves through a 1,3-shift of the metallic moiety to give a metalacycloheptadienone derivative which, after reductive elimination, leads to one of the regioisomers observed in the reaction. The other regioisomer can



Scheme 50 [Cr]= $Cr(CO)_n$

arise from the other metalacyclopentenone formed in the first step of the reaction. A resonance form of this compound is the vinyl ketene complex which, after electrocyclisation and isomerisation, produces the major regioisomer observed in the reaction.

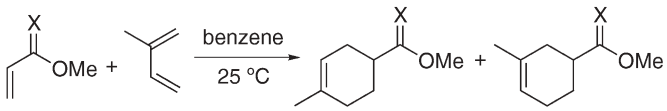
2.9 [4_S+2_C] Cycloaddition Reactions

The Diels–Alder reaction of activated olefins is considered as one of the most useful and predictable reactions in organic synthesis. The electron-acceptor character of the pentacarbonylmetal fragment makes α,β-unsaturated carbene complexes ideal substrates for the [4_S+2_C] cycloaddition reaction with dienes.

2.9.1 Alkenylcarbene Complexes as C2 Building Blocks

2.9.1.1 Alkoxy Alkenylcarbene Complexes

It has been established that alkoxy alkenylcarbene complexes participate as dienophiles in Diels–Alder reactions not only with higher rates but also with better regio- and stereoselectivities than the corresponding esters [95]. This is clearly illustrated in Scheme 51 for the reactions of an unsubstituted vinyl complex with isoprene. This complex reacts to completion at 25 °C in 3 h whereas the cycloaddition reaction of methyl acrylate with isoprene requires 7 months at the same temperature. The rate enhancement observed for this complex is comparable to that for the corresponding aluminium chloride-catalysed reactions of methyl acrylate and isoprene (Scheme 51).

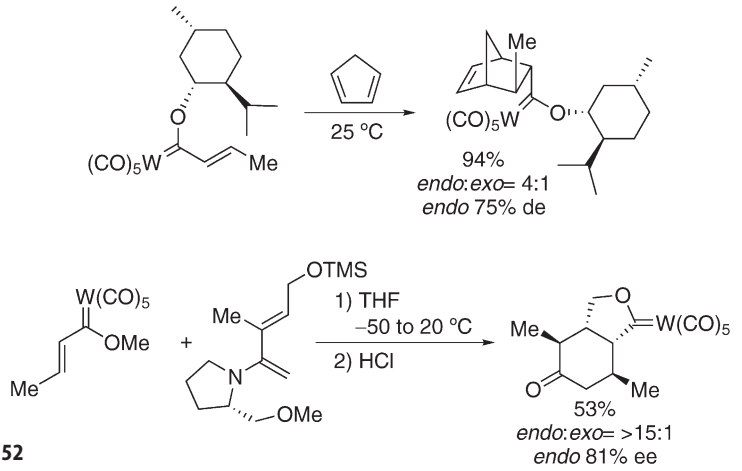


X= $Cr(CO)_5$	3h	92:8, 70%
X=O	7 months	70:30, 54%
X= O ($AlCl_3$)	3 h	95:5, 50%

Scheme 51

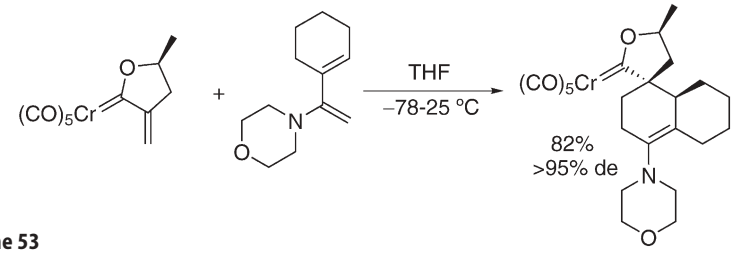
The Diels–Alder reaction of simple alkoxy alkenylcarbene complexes leads to mixtures of *endo* and *exo* cycloadducts, with the *endo* isomer generally being the major one [96, 97]. Asymmetric examples of *endo* Diels–Alder reactions have also been reported by the use of chiral auxiliaries both on the carbene complex and the diene. Thus, the reaction of cyclopentadiene with chiral alkenylcarbene complexes derived from (–)-menthol proceeds to afford a 4:1

endo:*exo* mixture. The diastereomeric excess found for the *endo* isomer is 75% [97] (Scheme 52). On the other hand, chiral 2-amino-1,3-dienes derived from (*S*)-methoxymethylpyrrolidine react with alkoxy alkenylcarbene complexes of tungsten providing the corresponding *endo* cycloadducts as the major products and with high enantioselectivities in most cases [98] (Scheme 52).



Scheme 52

However, *exo*-selective Diels–Alder reactions are found when α,β-unsaturated exocyclic carbene complexes are used as dienophiles. The fixed *s*-*cis* conformation of the vinylcarbene moiety of the complex seems to be responsible for the *exo* selectivity observed in this reaction. Moreover, the reaction of optically active carbene complexes with 2-morpholino-1,3-butadienes allows the asymmetric synthesis of spiro compounds [99] (Scheme 53).

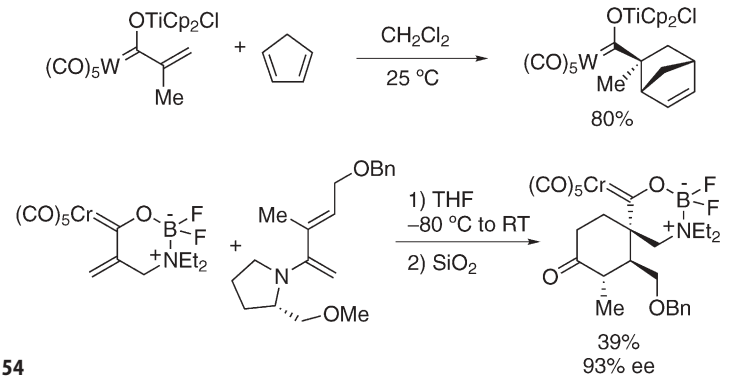


Scheme 53

2.9.1.2 Metaloxy Alkenylcarbene Complexes

Titanoxy alkenylcarbene complexes have been used as dienophiles in their reaction with cyclopentadiene to give predominantly the *exo* cycloadduct in high yield. The unexpected formation of the *exo* isomer is attributed to the

steric environment of the dienophile in opposition to the stereoelectronic factors usually identified with *endo* selectivity [100] (Scheme 54).



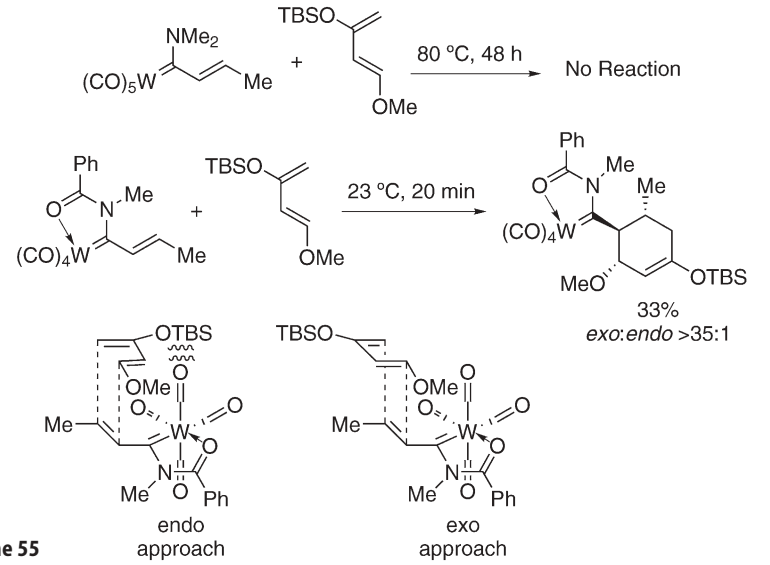
Scheme 54

Barluenga et al. have described novel vinylcarbene complexes containing a cyclic BF_2 chelated structure which temporarily fixes the *s-cis* conformation of the exocyclic C=C and Cr=C double bonds. These boroxycarbene complexes behave as dienophiles with 2-amino-1,3-butadienes in a remarkably regio- and *exo*-selective way. Moreover, high degrees of enantioselectivity are reached by the use of chiral 2-aminodienes derived from (*S*)-methoxymethylpyrrolidine [101] (Scheme 54).

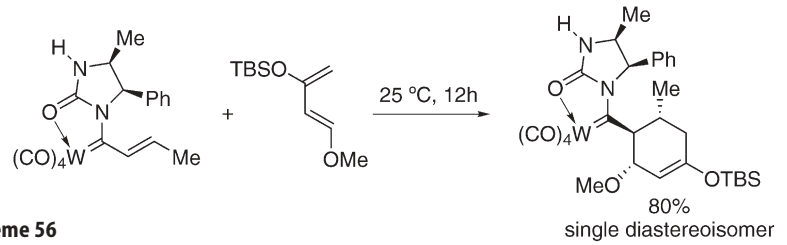
2.9.1.3 Amino Alkenylcarbene Complexes

The reactivity of α,β-unsaturated aminocarbene complexes in Diels–Alder processes is much lower than that of the corresponding alkoxycarbene complexes. Despite this low reactivity it has been possible to determine the high *exo* selectivity of processes involving the reaction of aminocarbene complexes and acyclic dienes. An important improvement on the reactivity of aminocarbene complexes was achieved by derivatisation of the nitrogen with an electron-withdrawing *N*-benzoyl group. The best results were found for tetracarbonyl complexes in which the benzoyl carbonyl oxygen is chelated to the metal. The high degree of *exo* selectivity also observed in these cases was explained as a consequence of the severe close contacts between the apical CO ligands and the diene in the *endo* but not the *exo* transition state [97, 102] (Scheme 55).

An asymmetric version of this reaction was achieved by the use of complexes derived from chiral imidazolidinones. For example, the reaction of Danishefsky's diene with these chiral complexes occurs with both high *exo*:*endo* selectivity and high facial selectivity at the dienophile [103] (Scheme 56).



Scheme 55



Scheme 56

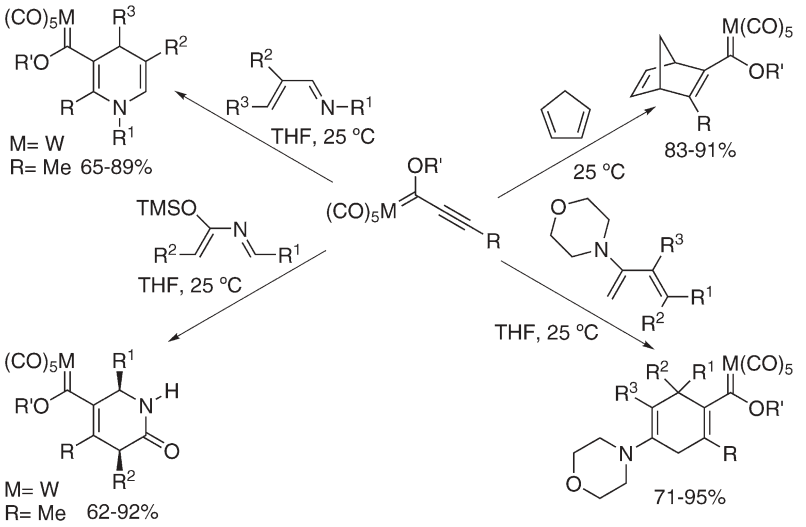
2.9.2 Alkynylcarbene Complexes as C2 Building Blocks

2.9.2.1 Alkoxy Alkynylcarbene Complexes

Alkoxy alkynylcarbene complexes undergo Diels–Alder reactions with neutral and electron-rich dienes [36f, 104] and also with 1-aza- and 2-aza-1,3-butadiene derivatives [84a, 105] (Scheme 57).

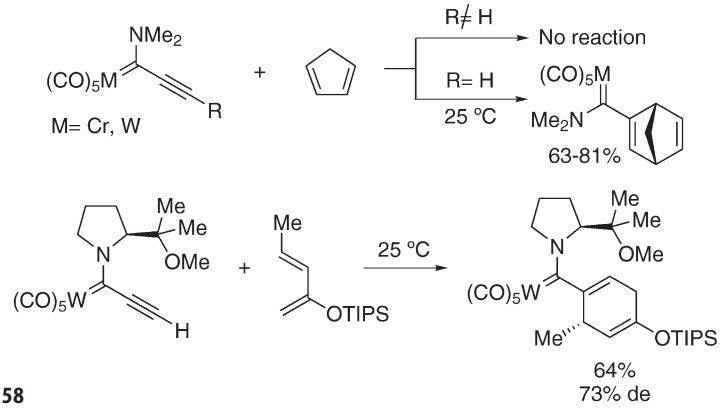
2.9.2.2 Amino Alkynylcarbene Complexes

Following the same tendency as alkenylcarbene complexes, the substitution of the alkoxy group for an amino group in alkynylcarbene derivatives greatly decreases the rate of Diels–Alder reactions [102, 104b]. In fact, substituted



Scheme 57

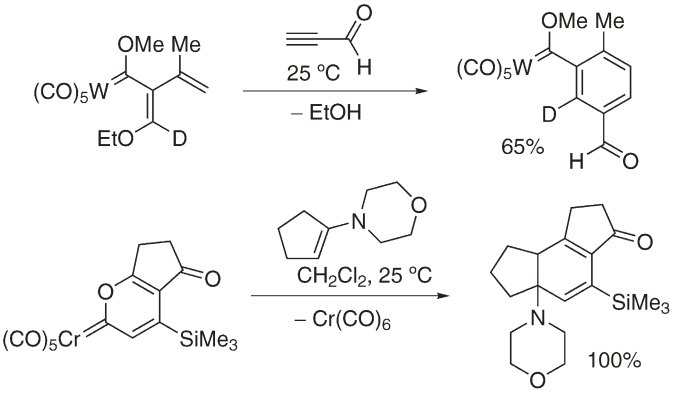
acetylenic aminocarbene complexes failed to react in intermolecular processes. Only unsubstituted amino alkynylcarbene complexes react with cyclopentadiene to produce the corresponding [4_S+2_C] cycloadduct [106]. Significant asymmetric induction can be achieved by the use of alkynylcarbene complexes derived from chiral pyrrolidines. However, this reaction seems to be highly dependent on the substituents of the diene, and the highest diastereoselectivities are found in the reaction with 2-triisopropylsiloxy-1,3-pentadiene whilst modest selectivities are reached with cyclopentadiene and α-triisopropylsiloxyvinyl cyclohexene [107] (Scheme 58).



Scheme 58

2.10
[4_C+2_S] Cycloaddition Reactions

Intermolecular [4_C+2_S] cycloaddition reactions where the diene moiety is contained in the carbene complex are less frequent than the [4_S+2_C] cycloadditions summarised in the previous section. However, 2-butadienylcarbene complexes, generated by a [2+2]/cyclobutene ring opening sequence, undergo Diels–Alder reactions with typical dienophiles [34, 35] (Scheme 59). Also, Wulff et al. have described the application of pyranylidene complexes, obtained by a [3+3] cycloaddition reaction (see Sect. 2.8.1), in the inverse-electron-demand Diels–Alder reaction with enol ethers and enamines [87a]. Later, this strategy was applied to the synthesis of steroid-like ring skeletons [87b] (Scheme 59).



Scheme 59

2.11
Intramolecular [4+2] Cycloaddition Reactions

For clarity, the reactions contained in this section can be divided into three categories according to the structure of the carbene complexes (Fig. 4): (i) those in which the dienophile and the diene are tethered through the heteroatom and the carbene carbon of the complex (type 1), (ii) those in which the dienophile and the diene are part of the same carbon chain (type 2), and finally (iii) those where the diene and the dienophile belong to different ligands within the complex (type 3).

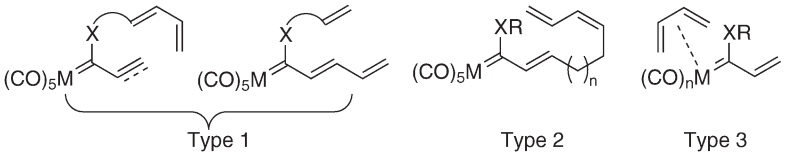
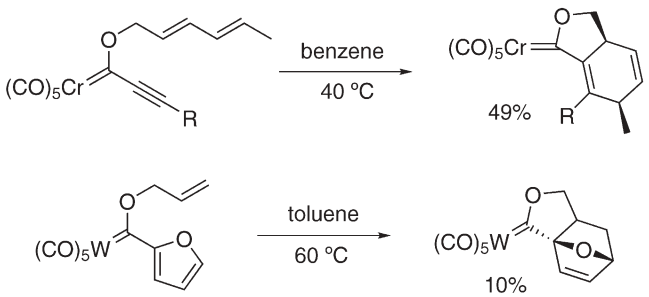


Fig. 4 Categories of intramolecular [4+2] cycloaddition reactions (for details see text)

2.11.1
Type 1 Intramolecular [4+2] Cycloadditions

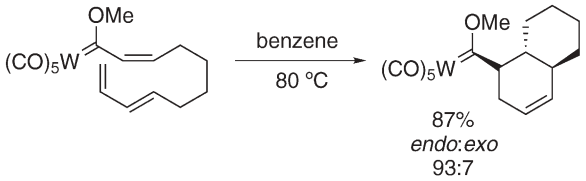
Carbene complexes containing either the dienophile or the diene functionality bonded directly to the carbene carbon undergo intramolecular [4+2] cycloadditions under mild conditions [108] (Scheme 60).



Scheme 60

2.11.2
Type 2 Intramolecular [4+2] Cycloadditions

Carbene complexes which have an all-carbon tether between the diene and the dienophile react via intramolecular Diels–Alder reaction to give the corresponding bicyclic compound. The stereoselectivities of these reactions are comparable to those observed for the Lewis acid-catalysed reactions of the corresponding methyl esters and much higher than those of the thermal reactions of the methyl esters which are completely unselective. Moreover, the *cis*-substituted complexes undergo *endo*-selective reactions where the corresponding reaction of the ester fails [109] (Scheme 61).

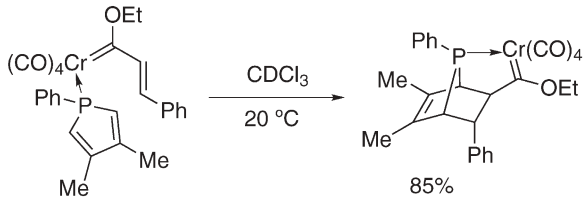


Scheme 61

2.11.3
Type 3 Intramolecular [4+2] Cycloadditions

Mathey et al. have described a quite unusual intramolecular [4+2] cycloaddition process. In this reaction the diene and the dienophile are part of two different ligands within the same complex. Thus, *cis*-(vinyl ethoxycarbene)(1-phenyl-3,4-dimethylphosphole)tetracarbonylchromium complex reacts at

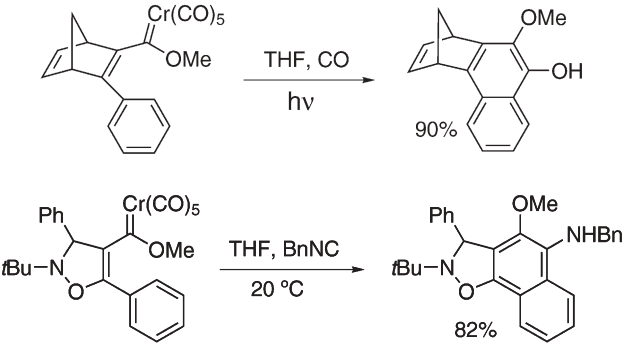
room temperature to afford the corresponding intramolecular Diels–Alder cycloadduct [110] (Scheme 62).



Scheme 62

2.12 [5_C+1_S] Cycloaddition Reactions

Several examples of [5_C+1_S] cycloaddition reactions have been described involving in all cases a 1,3,5-metalahexatriene carbene complex as the C5-synthon and a CO or an isocyanide as the C1-synthon. Thus, Merlic et al. described the photochemically driven benzannulation of dienylcarbene complexes to produce *ortho* alkoxyphenol derivatives when the reaction is performed under an atmosphere of CO, or *ortho* alkoxyanilines when the reaction is thermally performed in the presence of an isonitrile [111] (Scheme 63). In related works, Barluenga et al. carried out analogous reactions under thermal conditions [36a, c, 47a]. Interestingly, the dienylcarbene complexes are obtained in a first step by a [2+2] or a [3_S+2_C] process (see Sects. 2.3 and 2.5.1). Further reaction of these complexes with CO or an isonitrile leads to highly functionalised aromatic compounds (Scheme 63).

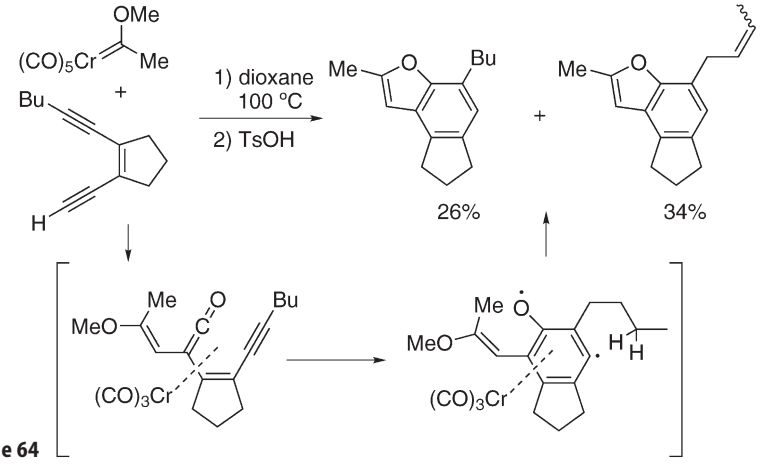


Scheme 63

Mathey et al. have described an unusual [5_C+1_S] process involving the reaction of a transient terminal phosphinidene complex [PhP=$W(CO)_5$] with a butadienyl carbene complex yielding a 1-phenyl-1,2-dihydrophosphine P-$W(CO)_5$ complex [112].

2.13
[5_S+1_{CO}] Cycloaddition Reactions

The coupling of carbene complexes with conjugated enediynes provides benzannulated compounds which incorporate five atoms of the endiyne and a CO ligand from the carbene complex [113] (Scheme 64). The formation of these products has been explained as follows: firstly, selective coupling of the less hindered alkyne moiety of the endiyne to the carbene complex gives rise, after further insertion of a CO ligand, to an enyne-ketene intermediate; then a Moore cyclisation affords a chromium-complexed diradical species which produces the final product by hydrogen abstraction (from the solvent or by intramolecular hydrogen atom transfer) followed by formation of the furan ring upon acid treatment.



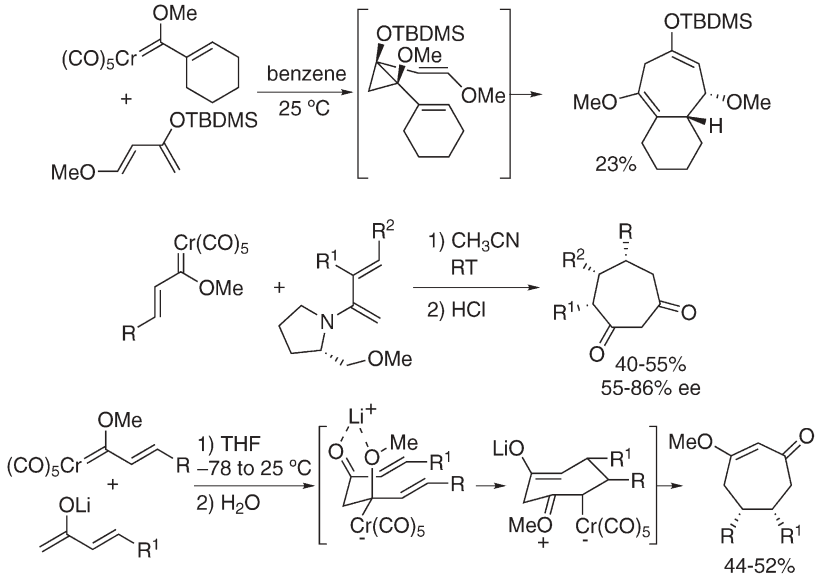
Scheme 64

2.14
[4_S+3_C] Cycloaddition Reactions

2.14.1
Alkenylcarbene Complexes as C3 Building Blocks

Electronically rich 1,3-butadienes such as Danishefsky's diene react with chromium alkenylcarbene complexes affording seven-membered rings in a formal [4_S+3_C] cycloaddition process [73a, 95a]. It is important to remark on the role played by the metal in this reaction as the analogous tungsten carbene complexes lead to [4_S+2_C] cycloadducts (see Sect. 2.9.1.1). Formation of the seven-membered ring is explained by an initial cyclopropanation of the most electron-rich double bond of the diene followed by a Cope rearrangement of the formed divinylcyclopropane (Scheme 65). Amino-substituted 1,3-butadienes also react with chromium alkenylcarbene complexes to produce the corre-

sponding seven-membered rings [25a, 114]. Applying this strategy, Barluenga et al. developed an asymmetric synthesis of substituted cyclohepta-1,3-diones using chiral 2-amino-1,3-butadienes derived from (*S*)-2-methoxymethylpyrrolidine [114] (Scheme 65).



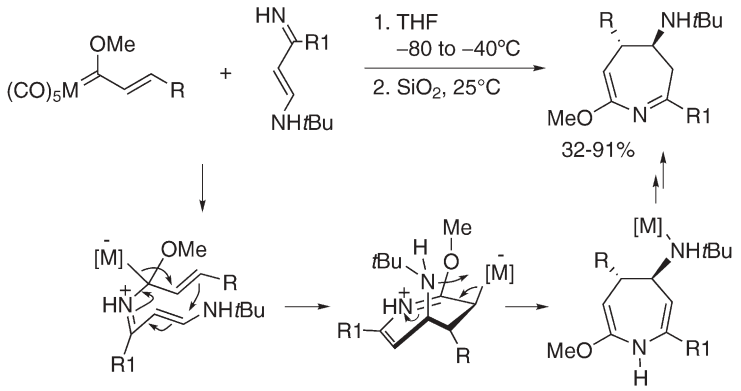
Scheme 65

Seven-membered carbocycles are also available from the reaction of alkenylcarbene complexes of chromium and lithium enolates derived from methyl vinyl ketones [79b] (Scheme 65). In this case, the reaction is initiated by the 1,2-addition of the enolate to the carbene complex. Cyclisation induced by a [1,2]-migration of the pentacarbonylchromium group and subsequent elimination of the metal fragment followed by hydrolysis leads to the final cycloheptenone derivatives (Scheme 65).

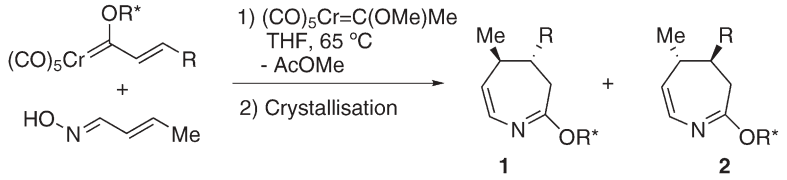
$[4_S+3_C]$ Heterocyclisations have been successfully effected starting from 4-amino-1-azadiene derivatives. The cycloaddition of reactive 4-amino-1-aza-1,3-butadienes towards alkenylcarbene complexes goes to completion in THF at a temperature as low as –40 °C to produce substituted 4,5-dihydro-3*H*-azepines in 52–91% yield [115] (Scheme 66). Monitoring the reaction by NMR allowed various intermediates to be determined and the reaction course outlined in Scheme 66 to be established. This mechanism features the following points in the chemistry of Fischer carbene complexes: (i) the reaction is initiated at –78 °C by nucleophilic 1,2-addition and (ii) the key step cyclisation is triggered by a [1,2]-$W(CO)_5$ shift.

A chiral version of this [4+3] heterocyclisation was achieved using chiral, non-racemic carbene complexes derived from menthol and oximes as depicted

in Scheme 67 [115]. This reaction requires the use of one equivalent of another simple carbene complex in order to remove the oxygen of the oxime functionality at some point during the reaction process. Significantly, the major diastereoisomer crystallises readily from methanol, allowing the isolation of the azepine in enantiomerically pure form.



Scheme 66 [M] = $(CO)_5M$, M= Cr, W



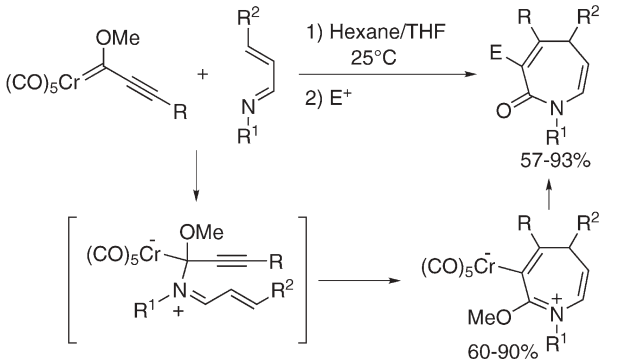
	HOR*	R	Yield	1 + 2 Ratio	Isolated Product	Isolated Yield (d.e.)
a	(-)-Menthol	Ph	87	70:30	**1a**	50% (>97%)
b	(-)-Menthol	2-Furyl	90	72:28	**1b**	48% (>97%)
c	(+)-Menthol	Ph	80	30:70	**2c**	46% (>97%)

Scheme 67

2.14.2 Alkynylcarbene Complexes as C3 Building Blocks

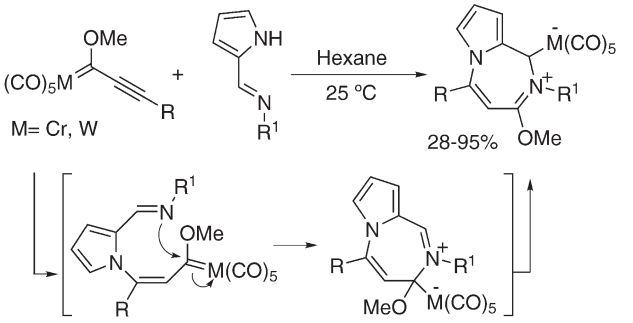
Tungsten alkynyl Fischer carbene complexes are excellent dienophile partners in the classical Diels–Alder reaction with 1-azadienes (see Sect. 2.9.2.1). On the contrary, the chromium-derived complexes exhibit a different behaviour and they react through a $[4_S+3_C]$ heterocyclisation reaction to furnish azepine derivatives [116] (Scheme 68). The reaction is initiated by a 1,2-addition of the nitrogen lone pair to the carbene carbon followed by a [1,2]-$Cr(CO)_5$ shift-pro-

moted cyclisation which generates a metalated zwitterionic intermediate. Interestingly, this intermediate crystallises and its structure could be determined unambiguously by X-ray analysis.



Scheme 68 $E^+ = H_2O, D_2O, I_2$

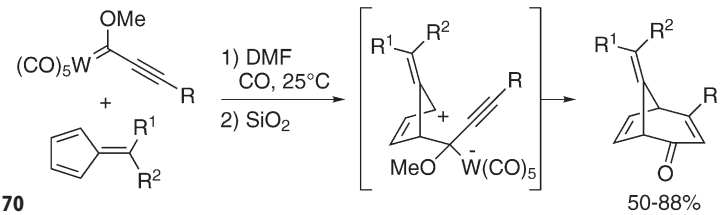
In a related process, alkynylcarbene complexes react with imines derived from *N*-unsubstituted pyrrole-2-carboxaldehyde to furnish zwitterionic pyrrolodiazepine derivatives through a formal [4_S+3_C] heterocyclisation reaction [91]. Although the imines involved in these reactions resemble the 1-azadienes described in the last paragraph, the mechanism of the process is different. Also, it has been shown how the corresponding *N*-substituted pyrrole derivatives led to [3+3] cycloadducts (see Sect. 2.8.2). In this case the reaction is initiated by an NH Michael-type addition to the carbene complex followed by an intramolecular 1,2-addition of the imine nitrogen to generate a zwitterionic intermediate. Finally, a [1,3]-migration of the metal fragment leads to the final products (Scheme 69).



Scheme 69

The cyclopropanation of fulvenes has been effected with alkynylcarbene complexes (see Sect. 2.1.1). However, this reaction is inhibited in the presence of CO and under these conditions a formal [4_S+3_C] cycloadduct is formed [15a]

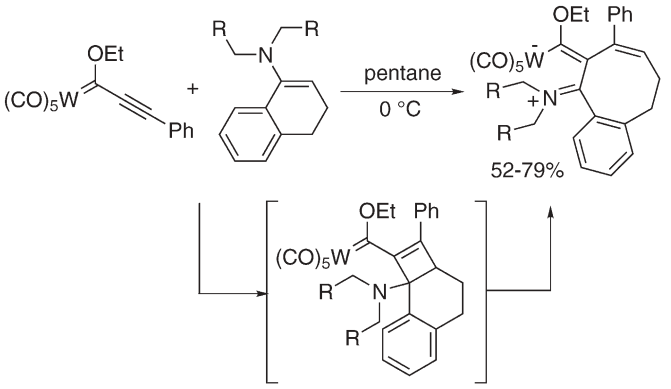
(Scheme 70). The formation of these products likely involves two key steps: (i) 1,2-addition of fulvene to the carbene carbon and (ii) regioselective cyclisation promoted by [1,2]-$W(CO)_5$ shift.



Scheme 70

2.15 [6_S+2_C] Cycloaddition Reactions

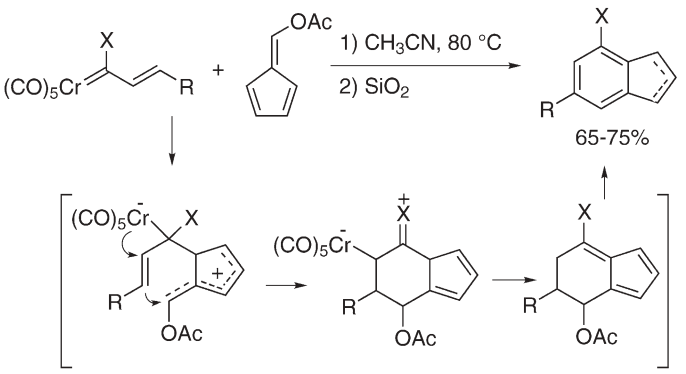
Aumann et al. have observed an unusual formal [6_S+2_C] cycloaddition reaction when they performed the reaction between an alkynylcarbene complex and 1-aminobenzocyclohexenes. The solvent used in this reaction exerts a crucial influence on the reaction course and products of different nature are obtained depending on the solvent chosen. However, in pentane this process leads to cyclooctadienylcarbene complexes in a reaction which can be formally seen as a [6_S+2_C] cycloaddition [117] (Scheme 71). The formation of these compounds is explained by an initial [2+2] cycloaddition reaction which leads to a cyclobutenylcarbene derivative which, under the reaction conditions, undergoes a cyclobutene ring opening to furnish the final products.



Scheme 71

2.16
[6_S+3_C] Cycloaddition Reactions

The unconventional structure of fulvenes with a unique C=C bond conjugation leads to unusual cycloaddition reactions with other unsaturated systems. For example, alkenylcarbene complexes react with fulvenes leading to indanone or indene derivatives which can be considered as derived from a [6_S+3_C] cycloaddition process [118] (Scheme 72). The reaction pathway is well explained by an initial 1,2-addition of the fulvene to the carbene carbon followed by [1,2]-$Cr(CO)_5$-promoted cyclisation.



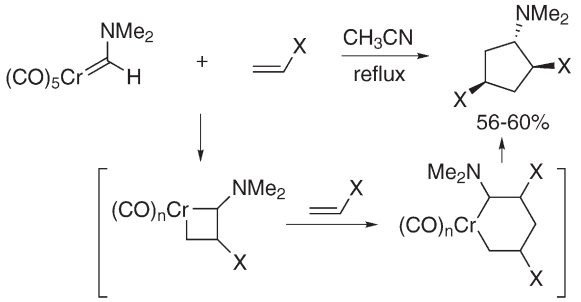
Scheme 72 X= OMe, OCH_2CH_2I, $N(CH_2)_4$, NMe_2

3
Three-Component Cycloaddition Reactions

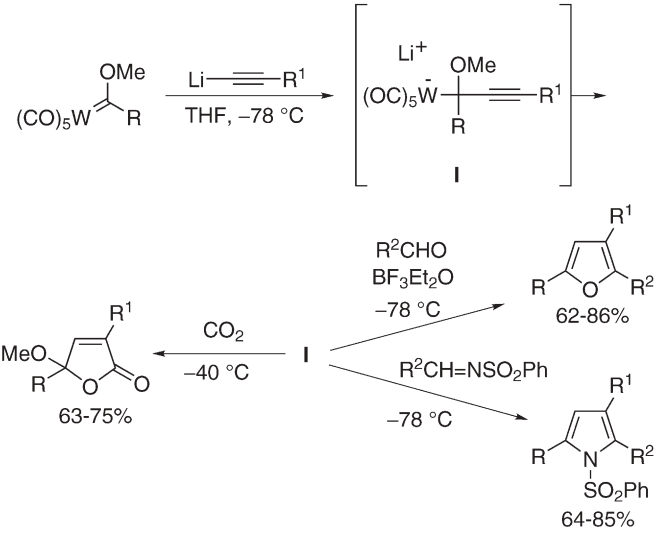
3.1
[2_S+$2_{S'}$+1_C] Cycloaddition Reactions

The reaction of methyl acrylate and acrylonitrile with pentacarbonyl[(*N*,*N*-dimethylamino)methylene]chromium generates trisubstituted cyclopentanes through a formal [2_S+2_S+1_C] cycloaddition reaction, where two molecules of the olefin and one molecule of the carbene complex have been incorporated into the structure of the cyclopentane [17b] (Scheme 73). The mechanism of this reaction implies a double insertion of two molecules of the olefin into the carbene complex followed by a reductive elimination.

Iwasawa et al. also developed a new reaction involving a three-component coupling process which affords five-membered heterocycles. This [2_S+$2_{S'}$+1_C] cycloaddition reaction supposes the consecutive addition of an alkynyllithium derivative to a Fischer carbene complex followed by the addition of a third component which can be an aldehyde, an imine, an isocyanate, or CO_2 [119] (Scheme 74).

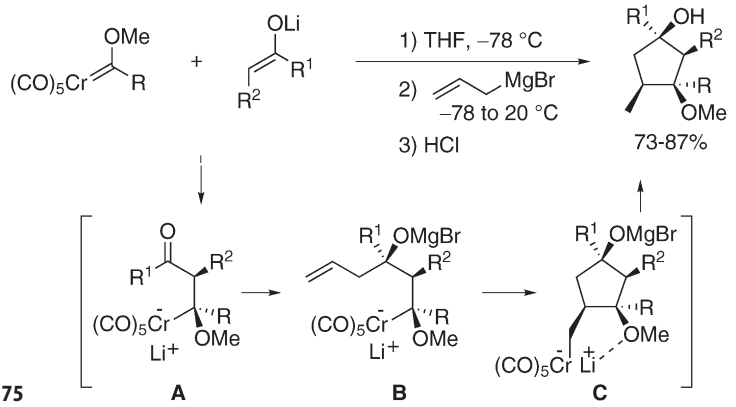


Scheme 73 X= CO_2Me, CN



Scheme 74

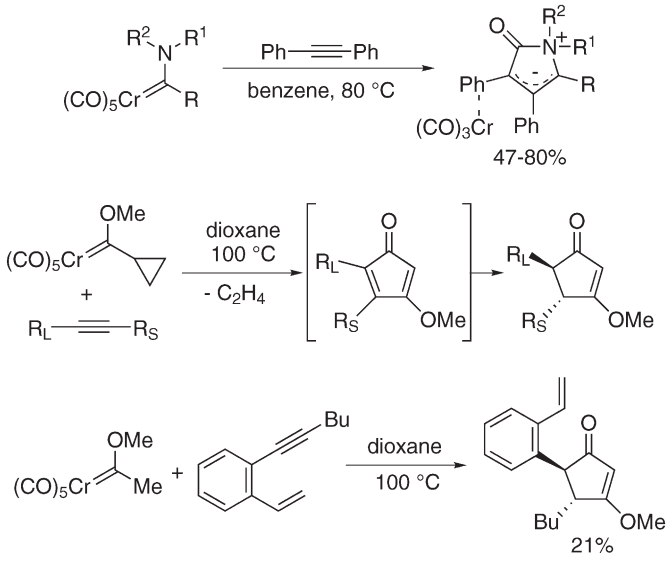
Highly substituted cyclopentanols are diastereoselectively obtained by the successive reaction of chromium carbene complexes with *β*-substituted lithium enolates and then with allylmagnesium bromide [120]. The ring skeleton of the cyclopentanols combines the carbene ligand, the enolate framework and two carbons of the allyl unit. The mechanism that accounts for the formation of this [2_S+$2_{S'}$+1_C] cycloadduct involves initial 1,2-addition of the lithium enolate to the carbene complex which generates a lithium 1-methoxy-3-oxoalkyl pentacarbonylchromate intermediate. Subsequent addition of the organomagnesium reagent to the corresponding ketone functional group produces a 5-hexenylchromate intermediate which undergoes an intramolecular carbometalation reaction to give, after hydrolysis, the final cyclopentanol derivatives (Scheme 75).



Scheme 75

3.2
[2_C+2_S+1_{CO}] Cycloaddition Reactions

The reactions of aminocarbene complexes with alkynes were widely investigated by Rudler et al. Thus, the reaction of these complexes and diphenylacetylene in refluxing benzene leads to formal [2_C+2_S+1_{CO}] cycloaddition products. The reaction implies the consecutive insertion of the alkyne into the carbene complex followed by insertion of a carbonyl ligand and finally production of ylide derivatives [121] (Scheme 76). These ylide complexes undergo, upon moderate heating, rearrangement as a result of a nitrogen-to-carbon migration of an alkyl group. Oxidation of the ylide complexes with dimethyldioxirane leads to new lactame complexes.

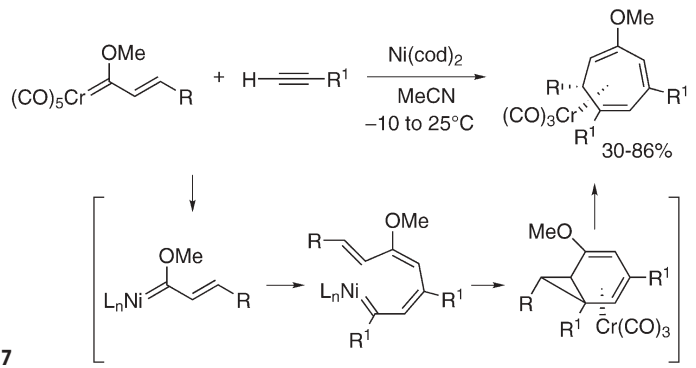


Scheme 76

Other examples of [2_C+2_S+1_{CO}] cycloaddition reactions have been described by Herndon et al. by the use of chromium cyclopropyl(methoxy)carbenes. These complexes react with alkynes releasing ethene and forming cyclopentadienone derivatives, which evolve to cyclopentenone derivatives in the presence of chromium(0) and water [122] (Scheme 76). This reaction has been extended to intramolecular processes and also to the synthesis of some natural products [123]. These authors have also described another process involving a formal [2_C+2_S+1_{CO}] cycloaddition reaction. Thus, the reaction of methyl and cyclopropylcarbene complexes with phenylacetylene derivatives does not afford the expected benzannulated products, and several regioisomers of cyclopentenone derivatives are the only products isolated [124] (Scheme 76).

3.3
[3_C+2_S+2_S] Cycloaddition Reactions

The reaction of alkenylcarbene complexes and alkynes in the presence of Ni(0) leads to cycloheptatriene derivatives in a process which can be considered as a [3_C+2_S+2_S] cycloaddition reaction [125]. As shown in Scheme 77, two molecules of the alkyne and one molecule of the carbene complex are involved in the formation of the cycloheptatriene. This reaction is supposed to proceed through the initial formation of a nickel alkenylcarbene complex. A subsequent double regioselective alkyne insertion produces a new nickel carbene complex, which evolves by an intramolecular cyclopropanation reaction to form a norcaradiene intermediate. These species easily isomerise to the observed cycloheptatriene derivatives (Scheme 77).

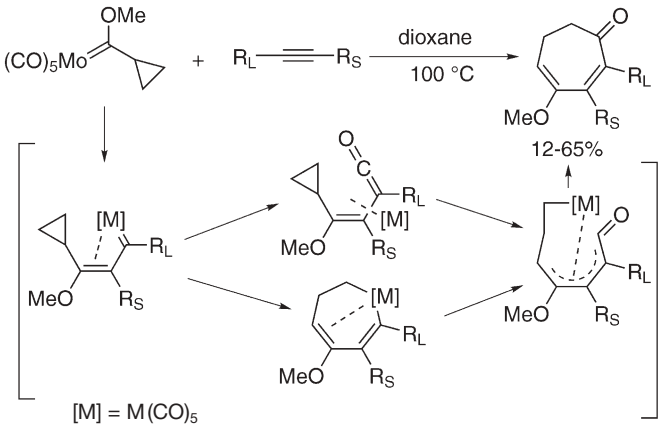


Scheme 77

3.4
[4_C+2_S+1_{CO}] Cycloaddition Reactions

Chromium cyclopropylcarbene complexes react with alkynes to provide cyclopentenone derivatives in a formal [2_C+2_S+1_{CO}] cycloaddition process (see Sect. 3.2). However, tungsten and molybdenum cyclopropylcarbene complexes

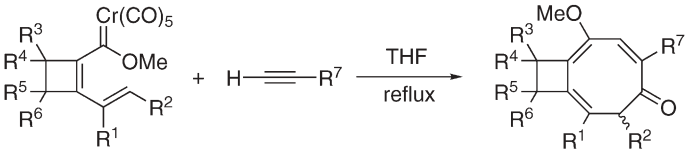
react with alkynes to afford cycloheptadienone derivatives in a sequence which can be considered as a [4_C+2_S+1_{CO}] cycloaddition reaction [126] (Scheme 78). Interestingly, this reaction can be directed to one or another diastereoisomer simply by changing the metal (W or Mo) of the starting carbene complex. The mechanism of this reaction starts with the insertion of the alkyne into the carbene complex to generate a new non-heteroatom-stabilised carbene. From here, two possible pathways can be envisaged, which differ in their timing of CO insertion vs. cyclopropane ring opening steps. The first option resembles the mechanism of the Dötz reaction, and thus the insertion of CO leads to a vinylketene derivative which then evolves by oxidative addition into a cyclopropane C–C bond followed by reductive elimination. The second option implies an initial ring opening of the cyclopropyl group to generate a new complex, which then inserts CO to generate the same intermediate as before and finally produces the cycloheptenone derivatives by reductive elimination (Scheme 78).



Scheme 78

3.5 [5_C+2_S+1_{CO}] Cycloaddition Reactions

Cyclobutene-containing dienylcarbene complexes react with alkynes to form cyclooctatrienone derivatives [127]. The reaction proceeds in a regioselective fashion leading to a mixture of diastereoisomers due to the newly created stereogenic centre (Scheme 79). This process can be viewed as a variation of the



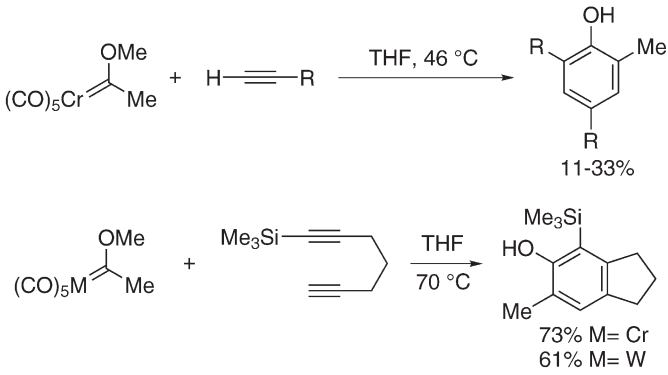
Scheme 79

Dötz reaction, since both an alkyne and CO are inserted. However, the additional double bond present in the starting complex participates in the subsequent electrocyclic ring closure, giving rise to eight-membered carbocycles.

4
Four-Component Cycloaddition Reactions

4.1
[2_S+$2_{S'}$+1_C+1_{CO}] Cycloaddition Reactions

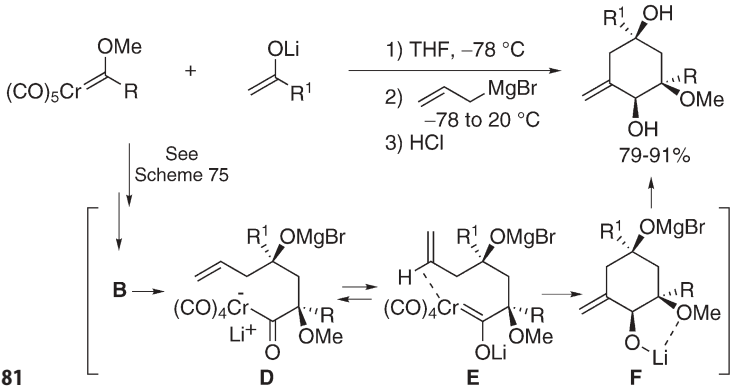
Aryl- and alkenylcarbene complexes are known to react with alkynes through a [3_C+2_S+1_{CO}] cycloaddition reaction to produce benzannulated compounds. This reaction, known as the "Dötz reaction", is widely reviewed in Chap. "Chromium-Templated Benzannulation Reactions", p. 123 of this book. However, simple alkyl-substituted carbene complexes react with excess of an alkyne (or with diynes) to produce a different benzannulated product which incorporates in its structure two molecules of the alkyne, a carbon monoxide ligand and the carbene carbon [128]. As referred to before, this [2_S+$2_{S'}$+1_C+1_{CO}] cycloaddition reaction can be carried out with diyne derivatives, showing these reactions give better yields than the corresponding intermolecular version (Scheme 80).



Scheme 80

Another example of a [2_S+$2_{S'}$+1_C+1_{CO}] cycloaddition reaction was observed by Barluenga et al. in the sequential coupling reaction of a Fischer carbene complex, a ketone enolate and allylmagnesium bromide [120]. This reaction produces cyclopentanol derivatives in a [2_S+$2_{S'}$+1_C] cycloaddition process when β-substituted lithium enolates are used (see Sect. 3.1). However, the analogous reaction with β-unsubstituted lithium enolates leads to the diastereoselective synthesis of 1,3,3,5-tetrasubstituted cyclohexane-1,4-diols. The ring skeleton of these compounds combines the carbene ligand, the enolate framework, two carbons of the allyl unit and a carbonyl ligand. Overall, the process can be considered as a for-

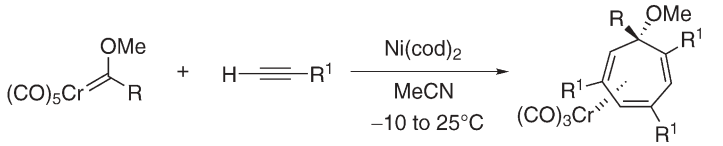
mal [2_S+$2_{S'}$+1_C+1_{CO}] cycloaddition reaction (Scheme 81). A plausible explanation for the formation of these cyclohexanediol derivatives involves initial 1,2-addition of the lithium enolate to the carbene complex to generate a lithium 1-methoxy-3-oxoalkyl pentacarbonylchromate intermediate. Subsequent addition of the organomagnesium reagent to the corresponding ketone functional group produces a 5-hexenylchromate derivative, which undergoes migratory insertion of carbon monoxide to provide a lithium acyl tetracarbonylchromate intermediate. These species lead to the final 5-methylenecyclohexane-1,4-diols after intramolecular insertion of the carbene carbon atom into the secondary vinylic C–H bond and subsequent protonation (Scheme 81).



Scheme 81

4.2
[2_S+2_S+2_S+1_C] Cycloaddition Reactions

It has been shown how alkenylcarbene complexes participate in nickel(0)-mediated [3_C+2_S+2_S] cycloaddition reactions to give cycloheptatriene derivatives (see Sect. 3.3). However, the analogous reaction performed with alkyl- or arylcarbene complexes leads to similar cycloheptatriene derivatives, but in this case the process can be considered a [2_S+2_S+2_S+1_C] cycloaddition reaction as three molecules of the alkyne and one molecule of the carbene complex are incorporated into the structure of the final product [125] (Scheme 82). The mechanism of this transformation is similar to that described in Scheme 77 for the [3_C+2_S+2_S] cycloaddition reactions.



Scheme 82

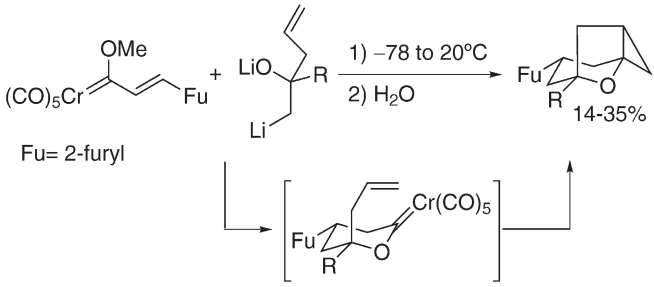
68-92%

5
Tandem Cycloaddition Reactions

In recent years the strategic use of tandem reactions has been well recognised as a powerful method for increasing molecular complexity and thereby synthetic efficiency [129]. In the field of Fischer carbene complexes this strategy has also been widely applied to the synthesis of complex structures. Some of these sequences have been mentioned in previous sections within this chapter (for example [2+2]/[5_C+1_S] [36a,c], [3_C+2_S]/[5_C+1_S] [47a] and [4_S+2_C]/[5_C+1_S] [111]). Other interesting tandem sequences are those involving an initial [4_S+2_C] cycloaddition followed by several intramolecular cyclisations [104a, 130]. In the present section we would like to summarise only a few recent examples of tandem cycloaddition processes involving Fischer carbene complexes, which are intended to highlight the incredible potential of these complexes to give access to complex structures from simple starting materials.

5.1
[3_C+3_S]/[2_S+1_C] Sequences

β-Oxygen-functionalised sp^3 organolithium compounds react with alkenylcarbene complexes to generate the corresponding cyclic carbene complexes in a formal [3+3] process (see Sect. 2.8.1). In those cases where the organolithium derivative contains a double bond in an appropriate position, tricyclic ether derivatives are the only products isolated. These compounds derive from an intramolecular cyclopropanation of the corresponding cyclic carbene complex intermediate [89] (Scheme 83).

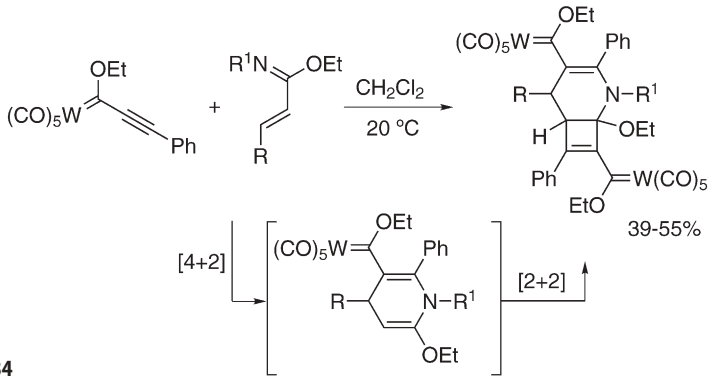


Scheme 83

5.2
[4_S+2_C]/[2_S+1_C] Sequences

Aumann et al. have described the synthesis of biscarbene complexes by the reaction of 1-alkylimidates with two equivalents of a tungsten alkynylcarbene complex [131]. An initial [4_S+2_C] cycloaddition generates an intermediate which further reacts with a second molecule of the alkynylcarbene complex

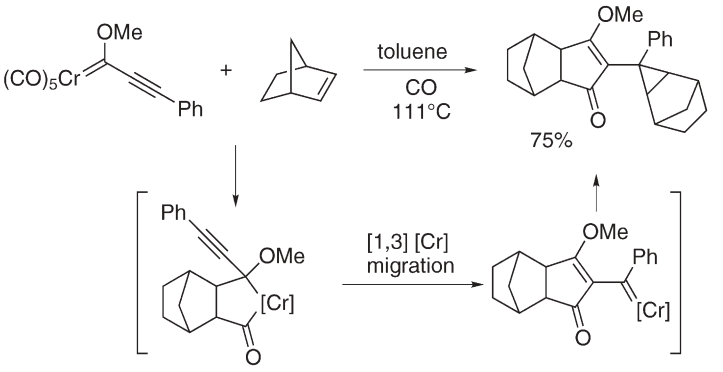
through a [2+2] cycloaddition to produce the final azabicyclo[4.2.0]octa-3,7-diene biscarbene derivatives (Scheme 84).



Scheme 84

5.3
$[2_C+2_S+1_{CO}]/[2_S+1_C]$ Sequences

Alkynylcarbene complexes react with strained and hindered olefins yielding products that incorporate up to four different components by the formation of five new carbon–carbon bonds [15b]. This remarkable transformation is explained by an initial [2+2] cycloaddition followed by CO insertion. The resulting intermediate suffers a well precedented [1,3]-migration of the metal fragment to generate a non-heteroatom-stabilised carbene complex intermediate which reacts with a new molecule of the olefin through a cyclopropanation reaction (Scheme 85).



Scheme 85 [Cr] = $Cr(CO)_n$

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