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Review

Group 6 Fischer carbene complexes: "chemical multitalents" for multi-component reactions

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Abstract

The ability of heteroatom stabilized Fischer carbene complexes (FCCs) to participate in multicomponent reactions, which has allowed the construction of a large variety of highly functionalized structures through several patterns of reactivity, will be disclosed along the following lines. One of the main reasons for the high versatility and often unexpected behavior of FCCs relies on the possibility of incorporation of carbonyl ligands along the reaction pathway, depending on the reaction conditions. Thus, in this review there will be presented examples where up to five components react in a multicomponent sequence to create up to nine carbon–carbon bonds or to lead to the formation of up to seven stereogenic centers what points out the undisputable synthetic potential of FCCs.

Contents

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1. Introduction, scope and limitations of the review

Heteroatom stabilized Fischer carbene complexes (FCCs), prepared for the first time in 1964 [1], are valuable reagents in synthetic organic chemistry, and their role in this field has experienced an extraordinary increment in recent years [2]. Furthermore, the versatility of these complexes, labelled as "chemical multitalents" by de Meijere [3], has allowed the construction of a large variety of highly functionalized structures in a stereoselective manner through several patterns of reactivity.

On the other hand, multi-component reactions (MCRs) [4], which could be briefly defined as *processes in which at least three reagents, added at the same time and under the same conditions, come together in a single reaction vessel to form a new product which contains portions of all of them*, have received great attention because of their higher atom economy and their applications in combinatorial chemistry and diversity-oriented synthesis.

In this review, we present the recent developments of group 6 FCCs as building blocks in MCRs. FCCs very often act as a source of two or more components in those reactions: the carbene ligand and one or several carbonyl ligands. For a better understanding of the connectivity of each reaction and the origin of each fragment, we have decided to use colour schemes along the review. Thus, the carbene ligand will be represented in red colour; the green colour will be restricted to the carbonyl ligands which very often are incorporated into the final reaction product. The third party will be blue coloured and the fourth different component will be depicted in purple. A fifth reagent, when it exists, will be drawn in brown colour. According to this colour code, the black colour will usually indicate the new bonds formed in the chemical reaction.

Along the review we will cover the chemistry of FCCs represented in Fig. 1. Other specific carbene complexes will be numbered as they appear.

This review does not pretend to be comprehensive; moreover, its scope will be somehow limited by the following considerations. Reactions of Fischer carbene complexes involving sequential additions, such as the addition of a nucleophile followed by the one-pot trapping of the intermediate with an electrophile, leading to products that, combine three or more components this way will not be generally considered and only occasionally will be discussed. Transformations that require a modification of the reaction conditions to proceed from an intermediate compound to the final product such as, for example, the warming of a second step of a reaction at higher temperatures than a first step, will be occasionally commented, specially if they represent relevant results relative to the main topic of the review.

We will not cover either of the two cornerstones of the synthetic chemistry of Fischer carbene complexes that involve three or more components which are Dötz benzannulation reaction (Scheme 1) or Hegedus photochemical ketene generation (Scheme 2), as these reactions have been thoroughly and recently reviewed. The third leg of the Fischer carbene complexes synthetic tripod, which is the cyclopropanation reaction, only involves two reagents and therefore it is not a MCR. However, we will also present intramolecular reactions in which only two components take part, provided that the corresponding intermolecular version, including three or more components, has also been developed.

In the Dötz benzannulation reaction [5], a Fischer alkenyl or aryl carbene complex reacts with an acetylene to form, after the insertion of a carbonyl ligand from the carbene complex, the [3 + 2 + 1] cycloadduct which may be either a phenol or a naphtol derivative, when the

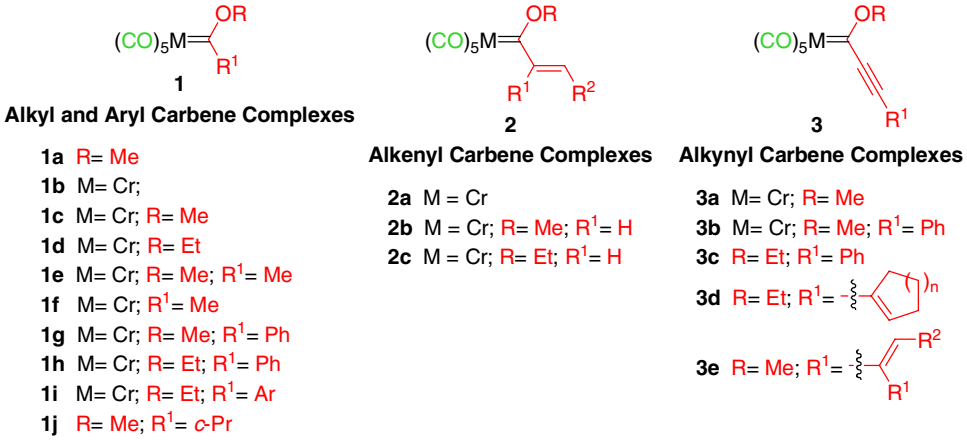
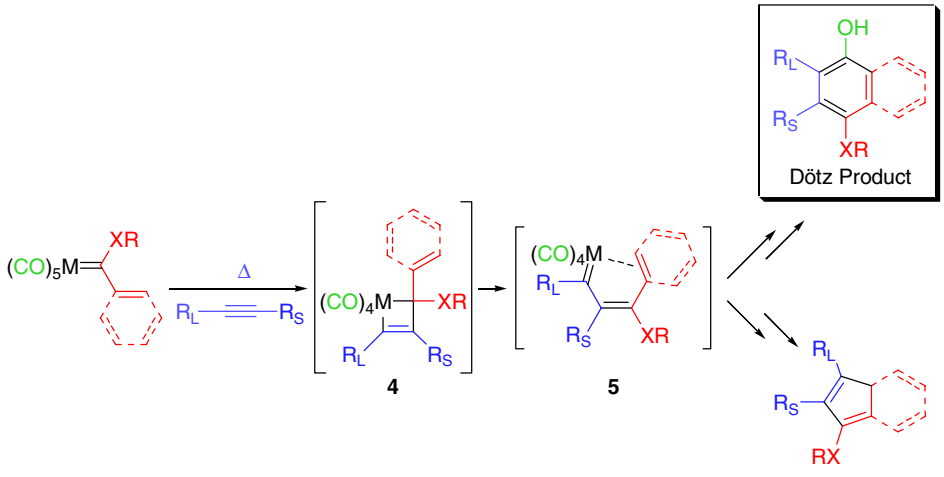
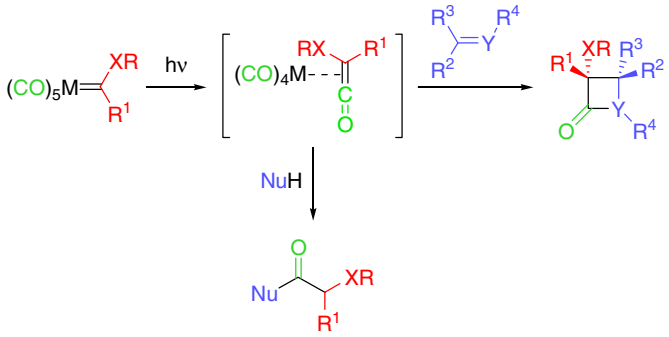


Fig. 1. Principal carbene complexes treated along the review.



Scheme 1. The Dötz benzannulation reaction.



Scheme 2. Hegedus photochemistry of FCCs.

starting material is, respectively, an alkenyl or aryl carbene complex (Scheme 1). However, depending on the nature of the substituents of the starting carbene complex, a variety of different multi-component products may be obtained under the reaction conditions and, although the Dötz reaction will not be discussed along the review, those transformations will be pointed out. We will also describe many related transformations involving 1-metallahexatrienes which some times lead to benzannulated products.

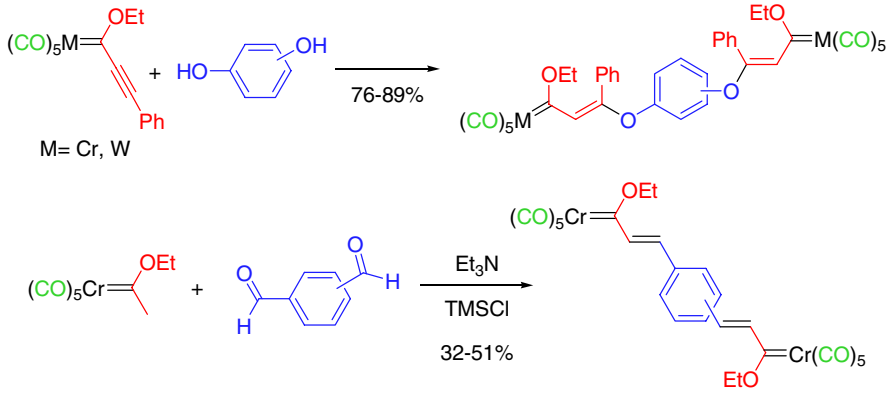
On the other hand, the photochemistry of Fischer carbene complexes, satisfactorily developed by Hegedus and co-workers, leads to multi-component products when the ketene is trapped either with nucleophiles or with compounds having multiple bonds, such as for example, olefins, imines or carbonyl compounds. Recent revisions of that useful chemistry have been published [6].

A very simple way to achieve a MCR involving Fischer carbene complexes is the addition of dinucleophiles [7] or dielectrophiles [8] to the appropriate carbene complex to get bis-carbene complexes (Scheme 3). However, the chemistry involved in their synthesis as well as the reactions performed with those bis-carbene complexes, such as, for example, Dötz benzannulations, are just applications of well-known transformations, and they have been adequately covered in the reviews by Sierra [2f] and de Meijere et al. [3b], so they will not receive further treatment along these lines.

According to the previous considerations, we will center mainly in newly developed MCRs of Fischer carbene complexes with a more detailed treatment of those reactions reported from our labs.

2. Reactions initiated by alkyne insertion

MCRs involving FCCs initiated by alkyne insertion have been known for a long time. Thus, (alkoxycarbene)iron complexes are known to form four-component pyrones [9] by treatment with alkynes while the analogous reaction with (aminocarbene)iron complexes produces three-component amino-furans [10]. Regarding group 6 FCCs, the Dötz benzannulation is a [3 + 2 + 1] cyclization between an alkenyl or aryl carbene and an alkyne to form an aromatic ring where three carbon atoms of the carbene ligand, the two acetylenic carbons and a carbonyl ligand are joined together. As indicated in Scheme 1, the reaction is initiated by a [2 + 2] cycloaddition between the alkyne and the metal–carbon double bond followed by a ring-opening reaction which results in alkyne insertion into the



Scheme 3. Synthesis of bis-carbene complexes.

metal–carbon double bond forming a 1-metallahexatriene intermediate **5**. Most of the reactions involving alkynes are presumed to be initiated following that sequence. We will present in this section several different ways of evolution for the alkenyl carbene complex intermediate **5**, involving or not CO insertion, into the final reaction products.

2.1. Reactions involving single alkyne insertion

2.1.1. Reactions with bulky acetylenes

The reaction of bulky electron-deficient alkynes with FCCs provides mainly cyclobutenone products. Thus, the reaction of *tert*-butyl substituted alkynes **6** with FCC **1g** does not result in the formation of Dötz cycloadducts but instead it leads only to cyclobutenones **7** in 73% and 93% yield, as pointed out by Harrity and co-workers [11] and Yamashita and Toy [12] (Scheme 4).

Two-component 2-alkenyl-4-cyclopentene-1,3-diones **9** are obtained when 1-alkynylcyclobutenols **8** are treated with chromium carbene complexes **1c** by a tandem carbene insertion-semipinacol rearrangement in moderate to good yields [13]. However, 1-alkynylcyclobutanol **10** did not experience ring expansion in its reaction with FCC **1g**; cyclobutenone **11**, which incorporated a carbonyl ligand, was the only identifiable product observed (yield not reported) [14].

However, when the also bulky stannylacetylenes are reacted with alkenylcarbene complexes, the Dötz benzannulation products are obtained although a constrasteric regiochemical effect has been observed [15].

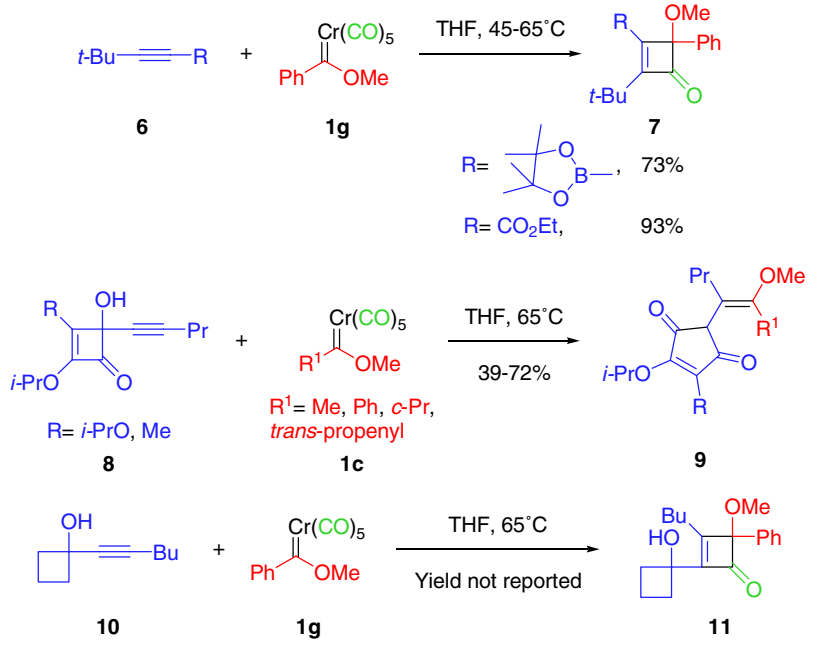
Also, the reaction of bulky acetylenes with β-isopropyl substituted β-dimethylamino substituted alkenylcarbene complexes (see Section 2.4) has been found to produce [5 + 2] cycloadducts [16].

2.1.2. Reactions with ketoalkynes

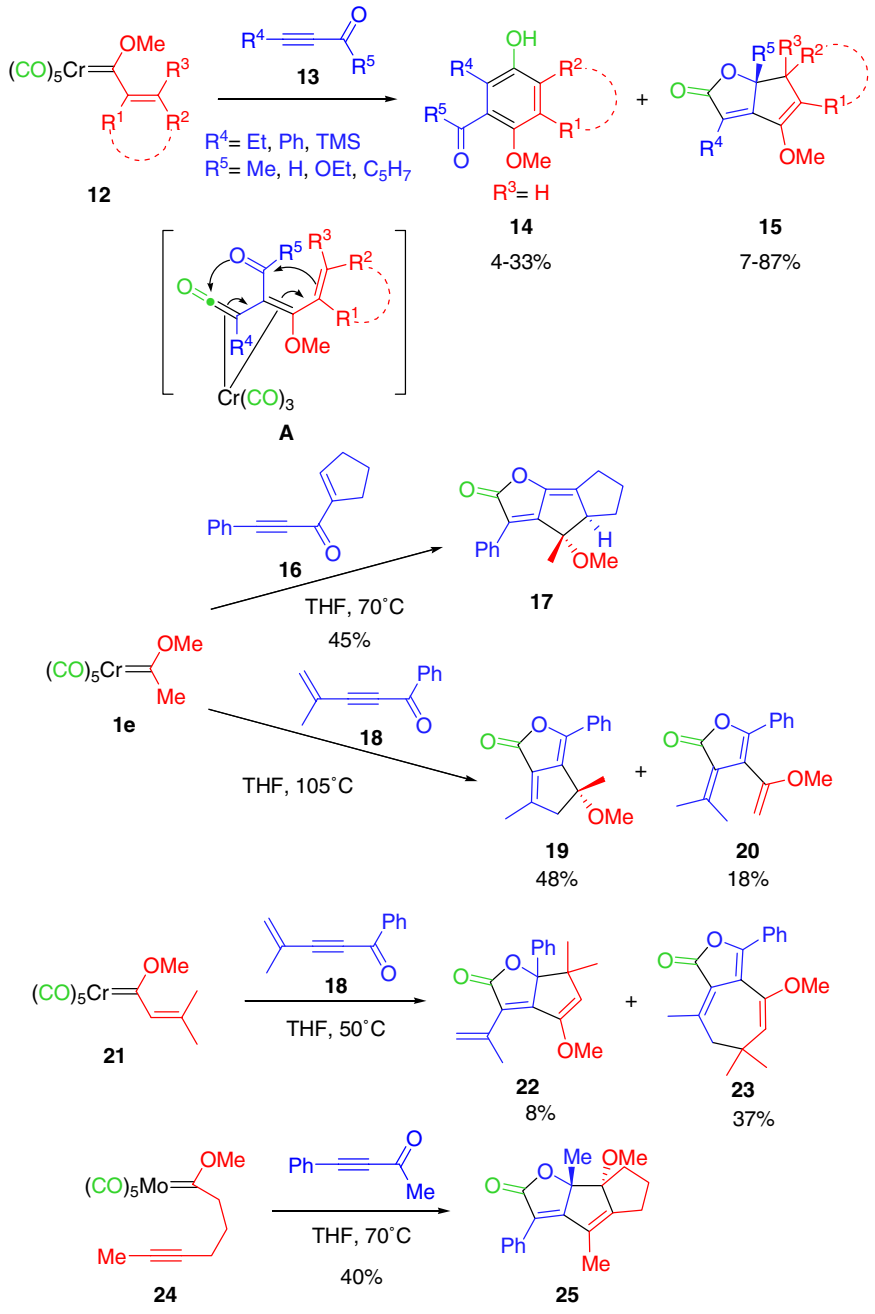
The reactions of ketoalkynes **13** with alkoxyalkenyl carbene complexes **12** give mixtures of the expected Dötz benzannulation phenol (or naphthol) **14** and bicyclic lactones **15** that are formed by double-cyclizations of cross-conjugated metal-complexed ketoketene intermediates **A** in an overall process that involves 8π electrons [17]. Yields up to 87% of bicyclic lactones **15** have been obtained (Scheme 5).

The product partition is shifted towards the lactone product when aminocarbene complexes are employed instead of alkoxycarbene complexes, which suggests that electronic interactions may account for the chemoselectivity of the reaction [18]. This supposition was further confirmed by performing the reaction with substituted aryl alkynyl ketones or substituted phenoxyalkenyl carbene complexes [19].

Similar cyclizations involving 8π electrons can be achieved also with alkyl carbene complexes, provided that the corresponding ketoalkyne bears a conjugated double bond. Thus, lactones **17** and a mixture of **19** and **20** are obtained in the reaction of carbene complex **1e** with ketoalkynes **16** and **18**, respectively. When ketoalkyne **18**, bearing a conjugated double bond, is treated with an alkenyl carbene complex, such as **21**, a mixture



Scheme 4. Reactions with bulky alkynes.



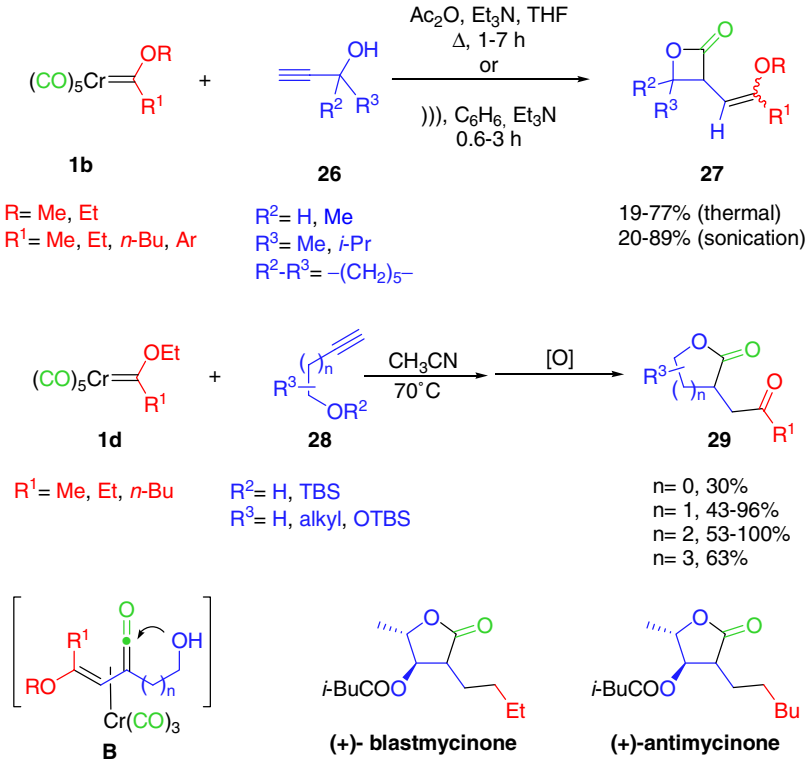
Scheme 5. Reactions with ketoalkynes.

of the 8π electron cyclized lactone **22** and the unexpected bicyclic lactone **23** was obtained. Lactone **23** arises from a 10π electron reorganization that creates a seven-membered ring into which both alkenyl groups, one from the carbene complex and one from the ketoalkyne, have been incorporated [18].

The reaction may also take place with molybdenum FCC **24** which in situ forms an alkenyl carbene complex by an initial intramolecular cyclization and then undergoes the 8π electron reorganization to the tricyclic lactone **25** in a triple annulation overall process [17].

2.1.3. Reactions with terminal propargylic alcohols or with other alcohols/silyl ethers bearing terminal triple bonds

The reactions of chromium alkyl or aryl carbene complexes **1b** with propargylic alcohols **26** lead to the formation of functionalized β-lactones **27** with moderate to good yields (Scheme 6). This cyclization, which was developed by Kerr, may be either thermally promoted [20] or induced by the application of ultrasound techniques, what besides improves the overall efficiency of the process [21].



Scheme 6. Reactions with terminal propargylic alcohols or with other alcohols/silyl ethers bearing terminal triple bonds.

Mori has simultaneously developed a similar transformation with alkynes **28** bearing either a hydroxy group or a *tert*-butyldimethylsilyloxy group and Fischer carbene complexes **1d**. After the cyclization, the crude enol ethers were treated with an oxidizing reagent to give, after the work-up, the corresponding ketones. Four-, five-, six- and seven-membered lactones **29** were obtained in moderate to excellent yields under the reaction conditions [22].

The formation of the lactones is attributed to an intramolecular attack by the hydroxyl group to the carbonyl carbon in the metal complexed ketene intermediate **B** [20a].

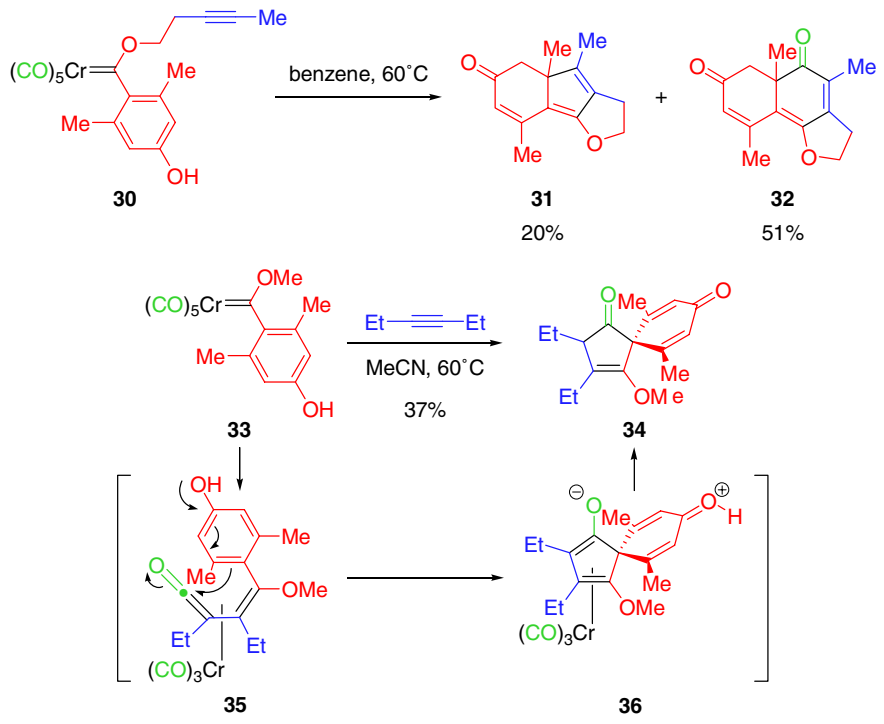
This procedure has been applied to the synthesis of γ-lactone natural products (+)-blastmycinone and (+)-antimycinone, by using an optically active homopropargylic alcohol, derived from (*S*)-ethyl lactate [22].

2.1.4. Inter- and intramolecular reactions with 2, 6-disubstituted aryl carbene complexes

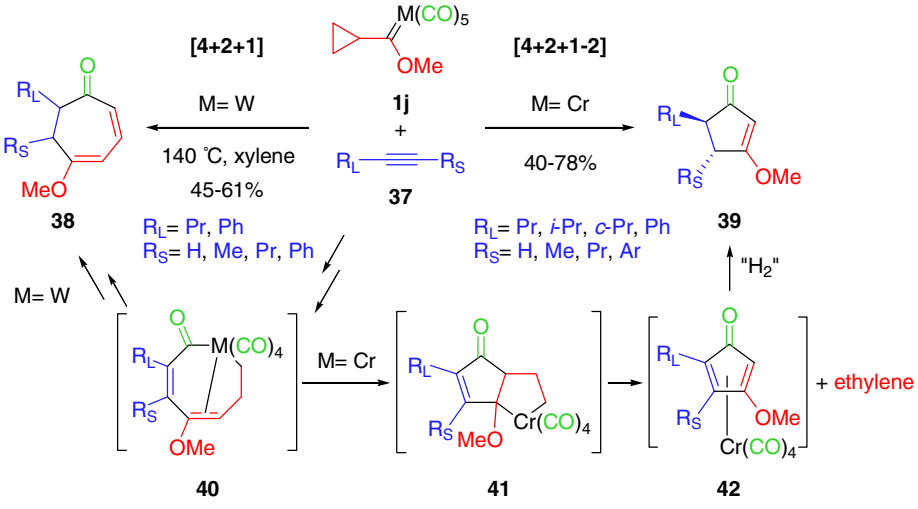
Instead of forming naphthols, the reaction of 2, 6-disubstituted aryl carbene complexes with alkynes usually produces either indenes or hydrindenones depending on the reaction conditions. When carbene complex **30** bearing a triple bond was warmed in benzene, the indene derivative was not detected and a mixture of hydrindenone **31** and cyclohexadienone **32** was obtained, being this one the first example were a cyclohexadienone was obtained from the reaction of a 2,6-disubstitued phenyl carbene complex [23] (Scheme 7). However, the reaction of carbene complex **33** with 3-hexyne, which in benzene produces the corresponding hydrindenone, originates spirocyclohexadienone **34** as the only observed product by warming in acetonitrile. This solvent is supposed to stabilize the charge separated intermediate **36**, that would be formed by an ipso attack of the electron-rich aryl ring on the ketene carbon of complex **35**.

2.1.5. Reactions of cyclopropylcarbene complexes

Treatment of cyclopropyl carbene complexes **1j** with alkynes **37** would supposedly lead to seven-membered carbocycles **38**, on the basis of a mechanism analogous to the proposed for the Dötz benzannulation but incorporating the cyclopropyl ring opening. However, only tungsten carbene complexes undergo this [4 + 2 + 1] cyclization, in moderate to good yields, through intermediate **40**; on the other hand, with chromium carbene complexes a different process takes place, leading to cyclopentenones **39** as main reaction products in moderate to good yields (Scheme 8). The reaction is proposed to proceed by a ring contraction on intermediate **40** to form bicyclochromacyclopentane **41**, which extrudes ethylene before originating the reaction products **39**. Accordingly, Herndon et al. [24] have labelled the reaction as a [4 + 2 + 1 – 2] cyclization.



Scheme 7. Reactions with 2,6-disubstituted aryl carbene complexes.

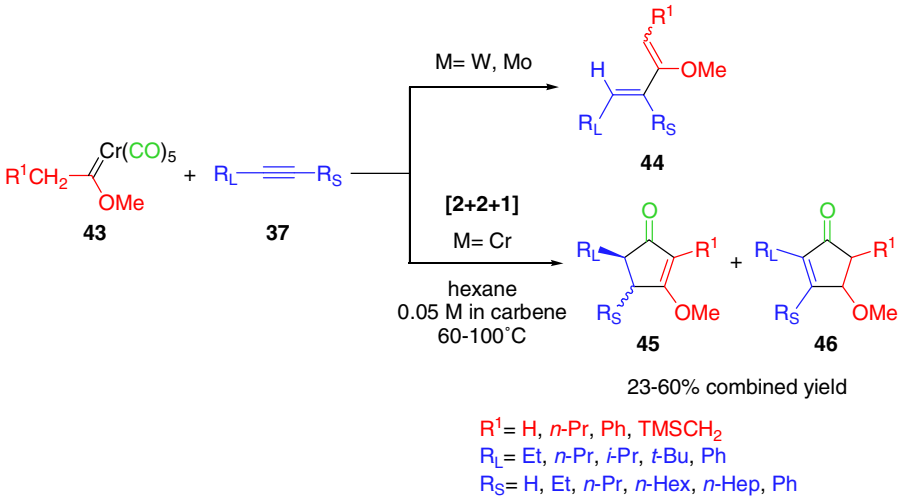


Scheme 8. Reactions of cyclopropyl carbene complexes.

2.1.6. Reactions of carbenes bearing α-hydrogen atoms

Cyclopentenones are versatile polifunctional intermediates in organic synthesis, readily accessible by Pauson–Khand cyclizations [25]. A second alternative for the synthesis of cyclopentenones involving FCCs is the treatment of alkyl chromium FCCs **43**, bearing an α-hydrogen in the alkyl group, with 1–2 equiv. of alkyne **37** in a non-polar solvent such as hexane and employing diluted conditions (0.05 M). Under these conditions, cyclopentenones **45** and **46**, obtained as the result of a [2 + 2 + 1] cyclization, are the major products with yields which range from moderate to good (Scheme 9); a wide number of by-products have also been observed in those reactions.

The formation of cyclopentenones requires the metal-mediated activation of the α-hydrogen of the alkyl group. Although every group 6 metal is able to promote the α-activation, chromium is unique in generating cyclic products while tungsten or molybdenum usually provide either dienes **44**, or their corresponding hydrolysis



Scheme 9. Reactions of carbenes bearing α-hydrogen atoms: synthesis of cyclopentenones.

products in moderate yields; a exception to this general behavior where a molybdenum carbene complex leads to a cyclopentenone is reported in Section 2.2.1. α-Activation of a chromium alkenyl carbene complex can be also achieved if a silicon group is present in the β-position [26].

2.1.7. Reactions of pentacarbonyldimethylaminomethylene chromium(0) with acetylenes and aldimines

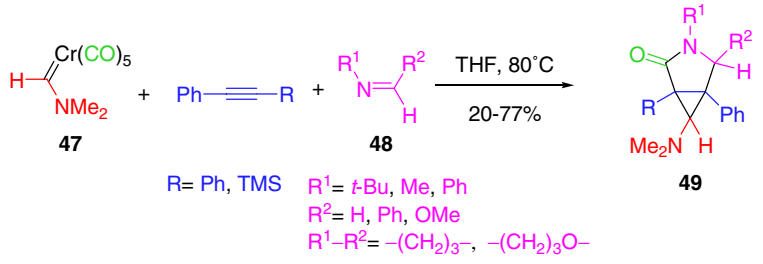
Fischer aminocarbene complexes are considered less reactive than their oxygen counterparts and their ability to undergo CO insertion under thermal conditions was questioned for a long time. However, four different components are joined together when a mixture of aminocarbene complex **47** and diphenylacetylene or phenyltrimethylsilylacetylene is warmed in THF at 80 °C (sealed tube) in the presence of imines **48**; bicyclic lactams **49** are obtained in yields that range from 20% to 75% (Scheme 10). Both terminal akynes and other internal alkynes failed to give this transformation [27].

2.1.8. Reactions of aminocarbene complexes through formation of nitrogen ylides [28]

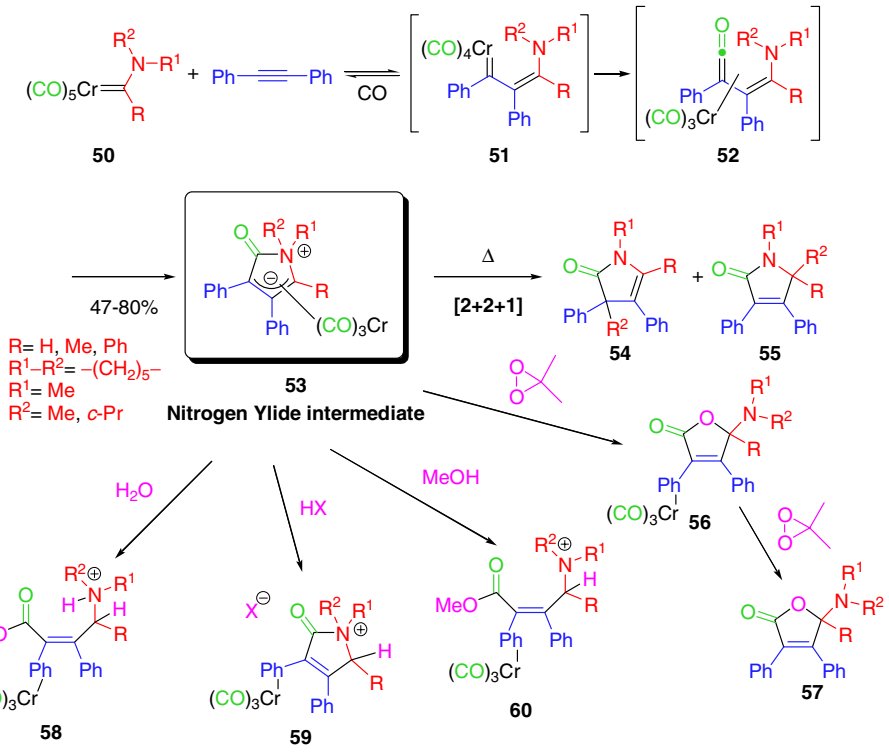
Rudler and co-workers have reported a different reaction pathway for aminocarbene complexes **50**, which are capable of inserting a unit of diphenylacetylene and a carbonyl ligand, leading to a mixture of regioisomeric pyrrolidones **54** and **55**. The reaction takes place through the formation of a nitrogen ylide intermediate **53**; an X-ray structure of this complex could be obtained after careful crystallization due to its easy hydrolysis and air oxidation (Scheme 11).

The formation of the nitrogen ylide intermediate **53** should involve an initial alkyne insertion, with release of CO, to give vinylogous aminocarbene **51** followed by a carbonyl insertion to generate an aminoketene complex **52**, which undergoes a cyclization to form ylide complex **53** [29].

Nitrogen ylides **53** are fairly stable; in fact, they can be isolated in moderate to good yields (47–80%), provided that the substituents in the nitrogen are different from allyl or benzyl or that the nitrogen does not belong to strained systems. In such cases, the nitrogen ylides are unstable and pyrrolidones **54** and **55** are formed by direct insertion-rearrangement reactions. However, for stable nitrogen ylides, the rearrangement to pyrrolidones **54** and **55** may be thermally promoted in refluxing toluene; this transformation resembles the Stevens rearrangement of other carbonyl-stabilized ammonium ylides [30].



Scheme 10. Reactions of pentacarbonyldimethylaminomethylene chromium(0) with acetylenes and aldimines.



Scheme 11. Intermolecular reactions of aminocarbene complexes through formation of nitrogen ylides.

Nitrogen ylides **53** can be oxidized to lactone complexes **56** with stoichiometric amounts of dimethyldioxirane which, when used in excess, renders metal-free lactones **57**. Other processes involving nitrogen ylides include protonation by strong acids to give ammonium salts **59**, and conversion to amino acids **58** and amino esters **60** during silica gel chromatography and by treatment with methanol, respectively (Scheme 11).

Similar transformations can be carried out intramolecularly with carbene complexes **61** leading to the formation of complex bicyclic or polycyclic nitrogenated frameworks **63** [31]. Although nitrogen ylides **62** have been proposed to participate, they have not been isolated. This methodology has been applied to the construction of alkaloids bearing the pyrroloquinoline skeleton **64** and substituted lycoranes **65** [32] (Scheme 12).

In these intramolecular reactions, when starting from azetidine and azidirine-substituted carbene complexes, products **66** and **67** arising from the insertion of two CO groups into the organic ligand of the corresponding carbene complexes have also been obtained [31]. The formation of such compounds has been rationalized in terms of organometallic or di-radical intermediates (Scheme 12).

When the intramolecular reaction is performed with carbene complexes **68** bearing the alkyne moiety linked to the nitrogen as a substituent, functionalized quinolizines **69** and homoquinolizines **70** are obtained [33] (Scheme 13).

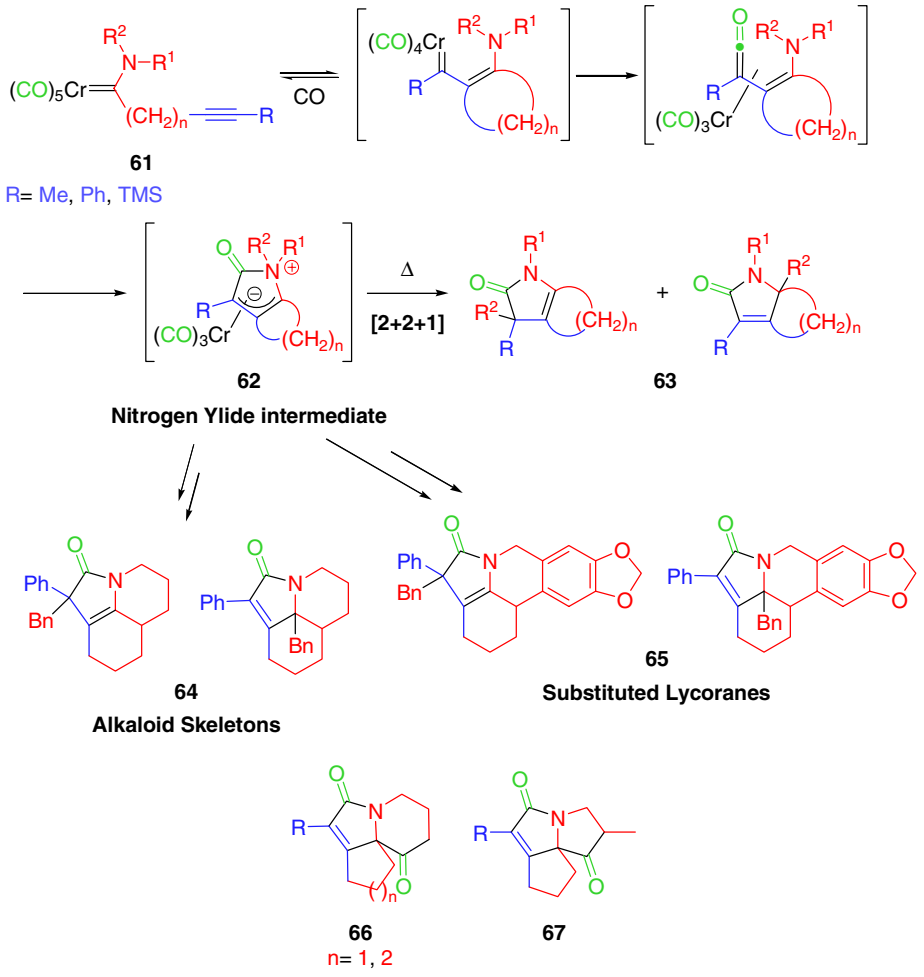
2.2. Reactions with enynes

2.2.1. Reactions with α,ω-enynes

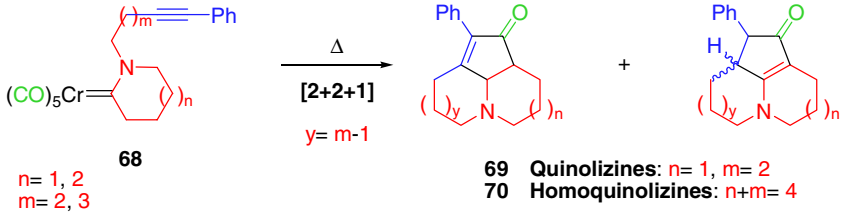
The intermolecular reaction of alkyl FCCs with α,ω-enynes **71** leads generally to complex mixtures of products bearing four different skeletons. Thus, for chromium carbene complex **1e**, after the initial alkyne insertion and once the alkenylcarbene is formed, competition between CO insertion (leading to **72** and **73**), cyclopropanation (leading to **74**) and olefine metathesis (to **75**) takes place (Scheme 14). Tungsten carbene complexes fail to give this type of reaction. These cyclizations are highly dependent on the length and composition of the tether between the alkyne and the alkene; a three-atom tether produces the best results and any increase or decrease in the length of the tether generally causes a significant reduction in the efficacy of this reaction.

Harvey and co-workers have noted that CO insertion is faster than intramolecular cyclization with the pendant alkene for chromium carbene complexes and 1,7-enynes, while the intramolecular olefin insertion is faster than the insertion of carbon monoxide for 1,6-enynes. However, for molybdenum carbene complexes, intramolecular cyclization is more favourable than CO insertion for both 1,6- and 1,7-enynes, provided that the olefin is activated by the presence of several electron-withdrawing groups [34].

Thus, when molybdenum carbene complexes are used, the reactions with enynes can be induced to



Scheme 12. Intramolecular reactions of aminocarbene complexes through formation of nitrogen ylides.

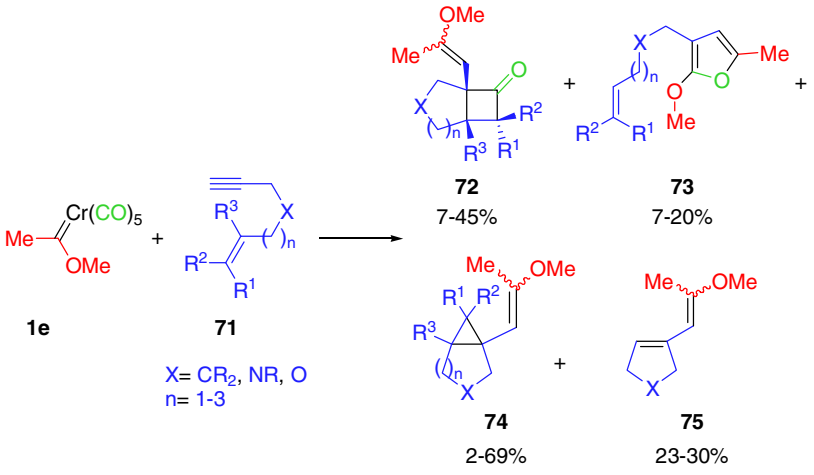


Scheme 13. Synthesis of quinolizines and homoquinolizines.

produce alkenylcyclopropane products by the proper positioning of an ester or ether functionality adjacent to the olefin moiety [35]. Alternatively, for chromium carbene complex **1e**, Katz and Yang [36] have pointed out that cyclopropanes **74** can also be favoured by performing the reaction with the metal–carbene complex adsorbed on silica gel, while cyclobutanones **72** are the main products if the reaction is carried out in acetonitrile [36,37]; those bicyclo[3.2.0]heptanones **72**, which arise via intramolecular [2 + 2] cycloaddition, are prepared with high diastereoinduction when chiral enynes are used, with yields between 33% and 73%, which enhances their synthetic potential [38].

On the other hand, the metathesis product **75** has usually been the main compound (29–62%) in the reaction of an aryl-enyne bearing a N-Ts substituted-tether in acetonitrile [39]. A significant role in the outcome of these reactions was played by the substituent placed in the aryl group; in fact, cyclopropanation was the main process if that substituent is a nitro group.

Another example of the influence of the tether length in the outcome of the reaction is given by the fact that

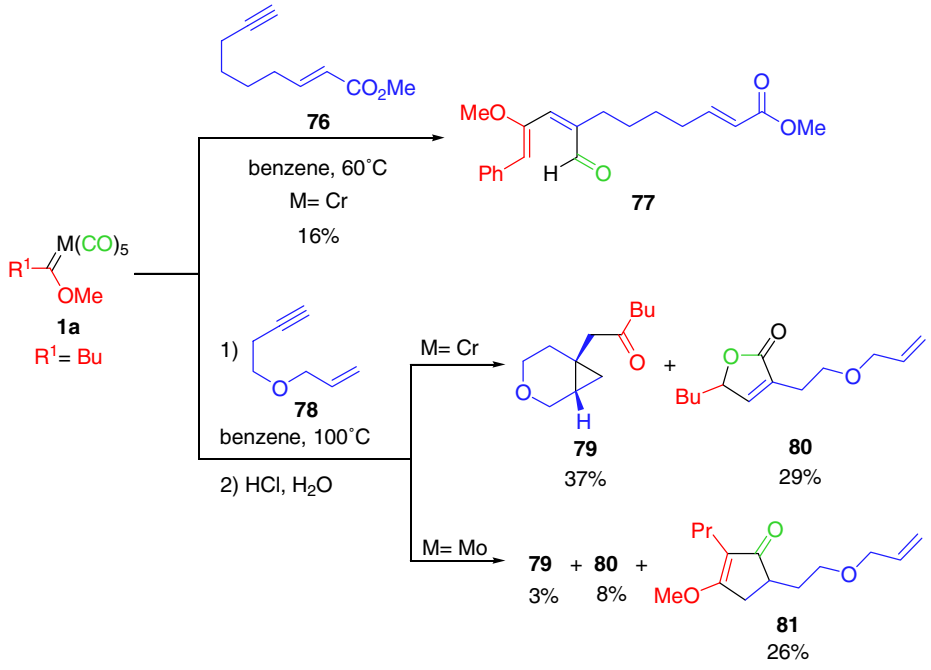


Scheme 14. Reactions with α,ω-enynes.

the furan derivative **73** was isolated in appreciable quantities (20% yield) for the reactions of carbene complex **1e** with 1,*n*-enynes **71** (X = $C(CO_2Me)_2$, *n* = 7, 8) in benzene at 70 °C [40]; actually, in the last case the furan derivative **73** was the only significant product observed. Furan derivatives **73**, which are occasionally found as additional by-products when the reaction of **1e** with 1,6-enynes is carried out in THF, are formed by migration of the methoxy group after the insertion of a carbonyl ligand.

Other different skeletons have also been reported by Harvey in this type of reactions [34]. Thus, the reaction of carbene complex **1a** (M = Cr, R^1 = Bu) with enyne **76** gave only aldehyde **77** in 16% yield, while with enyne **78**, it led to a mixture of cyclopropane **79** and butenolide **80** (Scheme 15); the last one came from the hydrolysis of the corresponding furan derivative. However, with the corresponding molybdenum complex **1a** (M = Mo, R^1 = Bu) small amounts of **79** and **80** were obtained, being cyclopentenone **81** the major product. The formation of cyclopentenone structures, such as **81**, has been already described for chromium carbene complexes (Section 2.1.5).

When one of the carbons of the enyne double bond is substituted by two methyl groups, a different behavior was noted [38,41]. Thus, as part of their research towards the synthesis of Taxol, Wulff and co-workers found that bicyclo[3.1.1]heptanone **83**, that resulted



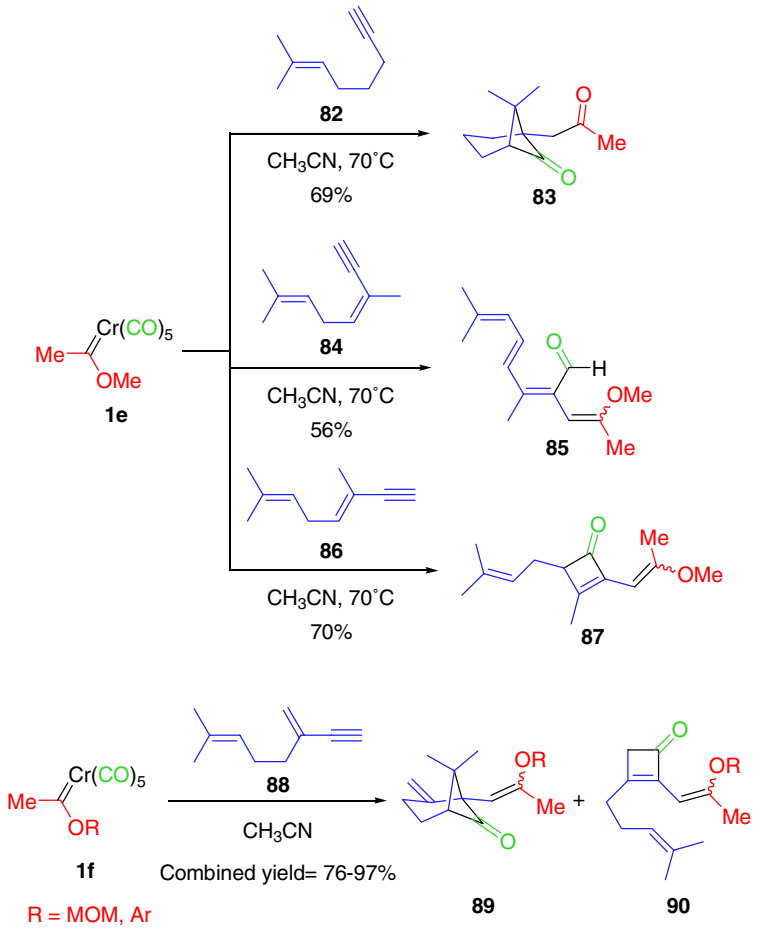
Scheme 15. Other skeletons obtained in the reactions with α,ω-enynes.

from a crossed [2 + 2] cycloaddition, was isolated in 69% yield in the reaction of carbene complex **1e** with enyne **82** in acetonitrile, while acyclic aldehyde **85**, structurally related to **77**, can be prepared in 56% yield if dienyne **84** is used instead. On the other hand, cyclobutenone **87** is obtained in 70% yield when **1e** is treated with diastereoisomeric dienyne **86** (Scheme 16).

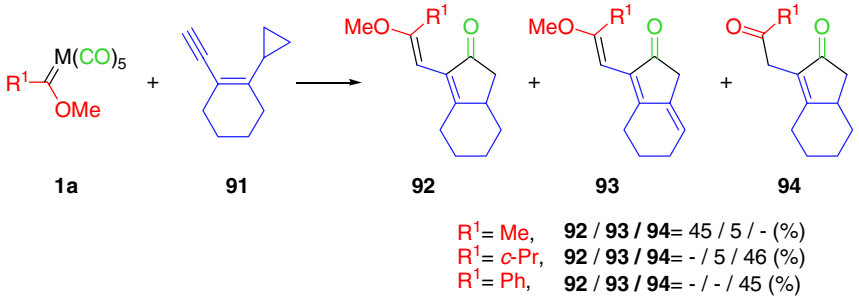
Treatment of **1f** with isomeric exo-methylene dienyne **88** led to a mixture of bicyclo[3.1.1]heptanone **89** and cyclobutenone **90** in a ratio which depended on the reaction temperature. It was also found that the electronic tuning of the alkoxy substituent of the carbene moiety could control the products ratio to an extent where good yields of bicyclo[3.1.1]heptanone **89** (66–71%) could be reached.

2.2.2. Reactions with cyclopropyl-conjugated enynes

Cyclopentenones **92–94** are obtained as main products when cyclopropyl-conjugated enynes **91** react with chromium FCC **1a**. After ethylene extrusion takes place, the nature of the major component depends on the stability of enol ethers **92** towards hydrolysis [42] (Scheme 17).



Scheme 16. Reactions with 1,1-dimethyl-1,6-enynes.



Scheme 17. Reactions with cyclopropyl-conjugated enynes.

2.2.3. Reactions with dienylacetylenes

Alternative benzannulation reactions can also occur with alkyl carbene complexes provided that the alkyne component also incorporates either a conjugated diene or both a conjugated double bond and an aromatic ring. Herndon and co-workers have developed this chemistry.

Thus, the treatment of carbene complexes **1c** with phenylalkenylacetylenes **95a** or dienylacetylenes **95b** usually leads to naphtofuran ketal derivatives **96** or to benzofurans **97**, respectively, in good to excellent yields [42] (Scheme 18). In this occasion, the 1-metallahexatriene **98** generated after the alkyne insertion evolves, as in the Dötz benzannulation, through intermediate **99** and further cyclization to **100**. Usually, under the reaction conditions naphtols **100a** cyclize to ketal derivatives **96** while phenols **100b** require the addition of iodine or acid to form benzofuran derivatives **97** in good yields [43]. This methodology has been applied to the total synthesis of nor-neolignan natural product egonol [44].

These same authors have also explored the behavior of chromium methoxymethylcarbene complex **1e** with a variety of alkynes bearing conjugated double bonds. Thus, the reaction with alkenylphenylacetylenes **101** involves just two components and leads to indane derivatives **102** [45] (Scheme 19); however, three components are incorporated into cyclopentenone **104**, structurally related to **45** (Section 2.1.6, Scheme 9), which is obtained when carbene **1e** was treated with alkenylphenylacetylene **103**. The reaction with biphenylacetylene [46] **105** originates a mixture of two three-component products, **106** (which comes from the ring-closure and spontaneous air oxidation of **108**) and cyclopentenone **107**.

2.2.4. Reactions with enediynes

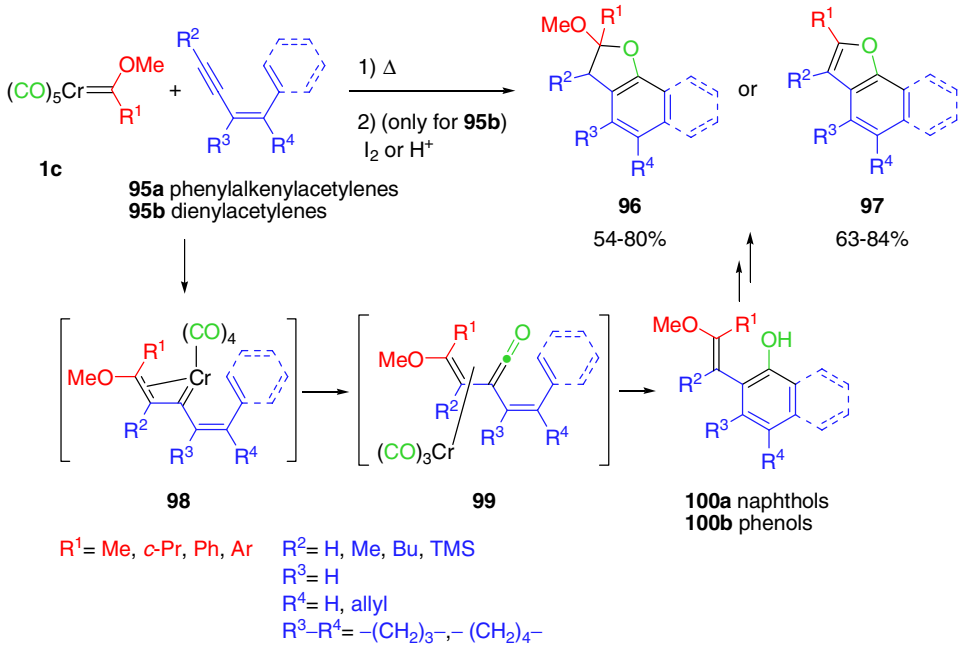
When chromium methoxymethylcarbene **1e** was treated with enediyne **109** a mixture of benzofurane derivatives **110** and **111** was obtained in moderate yields [47]. In the proposed mechanism, intermediate **112**, formed by terminal alkyne insertion, is able to insert a carbonyl ligand leading to intermediate **113**; a Moore cyclization [48] will then form di-radical species **114**, which will evolve to the final products (Scheme 20). The remote functionalization process involved in the final transformations to **110** and **111** can be effectively controlled [49]. Enediynes bearing a diverse array of alkyl substituents have been shown to undergo this process.

Related cyclizations, which are also initiated by alkyne insertion, occur when FCCs are treated with conjugated enyne-aldehydes, ketones or structurally related systems. However, the products can participate in subsequent reactions and this chemistry will be covered within the cascade reactions in Section 7.4.

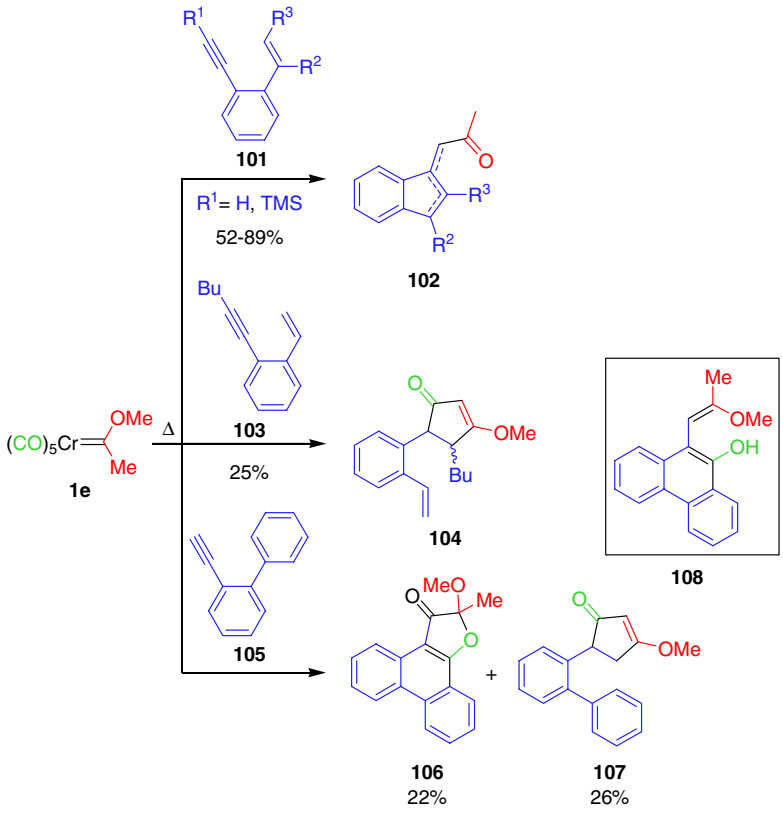
2.3. Multiple insertion of alkynes

2.3.1. [2 + 2 + 1 + 1] Cyclization involving two alkyne units and related reactions

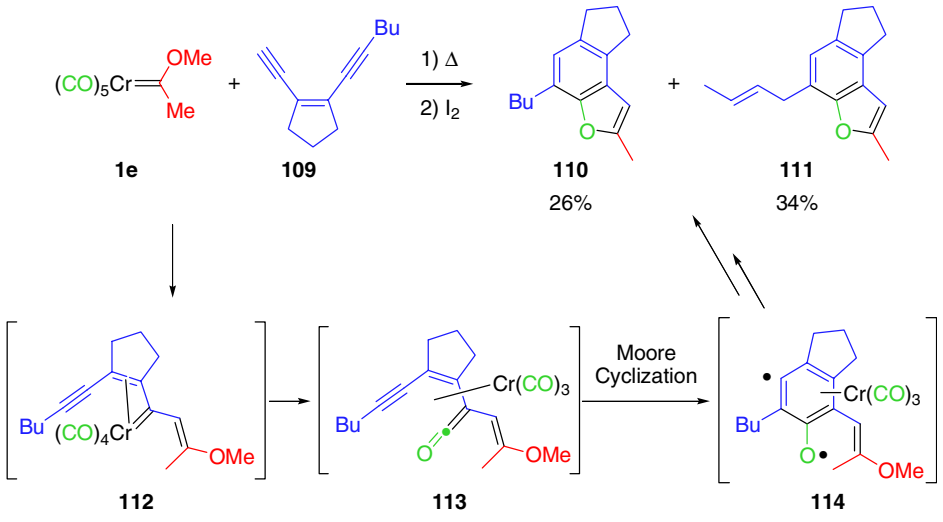
Chromium carbene complex **1e** can also participate in six-membered annulations involving the incorporation of two equivalents of an acetylene, a carbon monoxide ligand and the carbene carbon. The reaction takes place with a high excess of a terminal alkyne **115** in THF providing only moderate yields of phenols **116** [50] (Scheme 21). This pattern of reactivity has also been encountered



Scheme 18. Reactions with phenylalkenylacetylenes or dienylacetylenes.



Scheme 19. Reactions with arylacetylenes bearing conjugated double bonds.

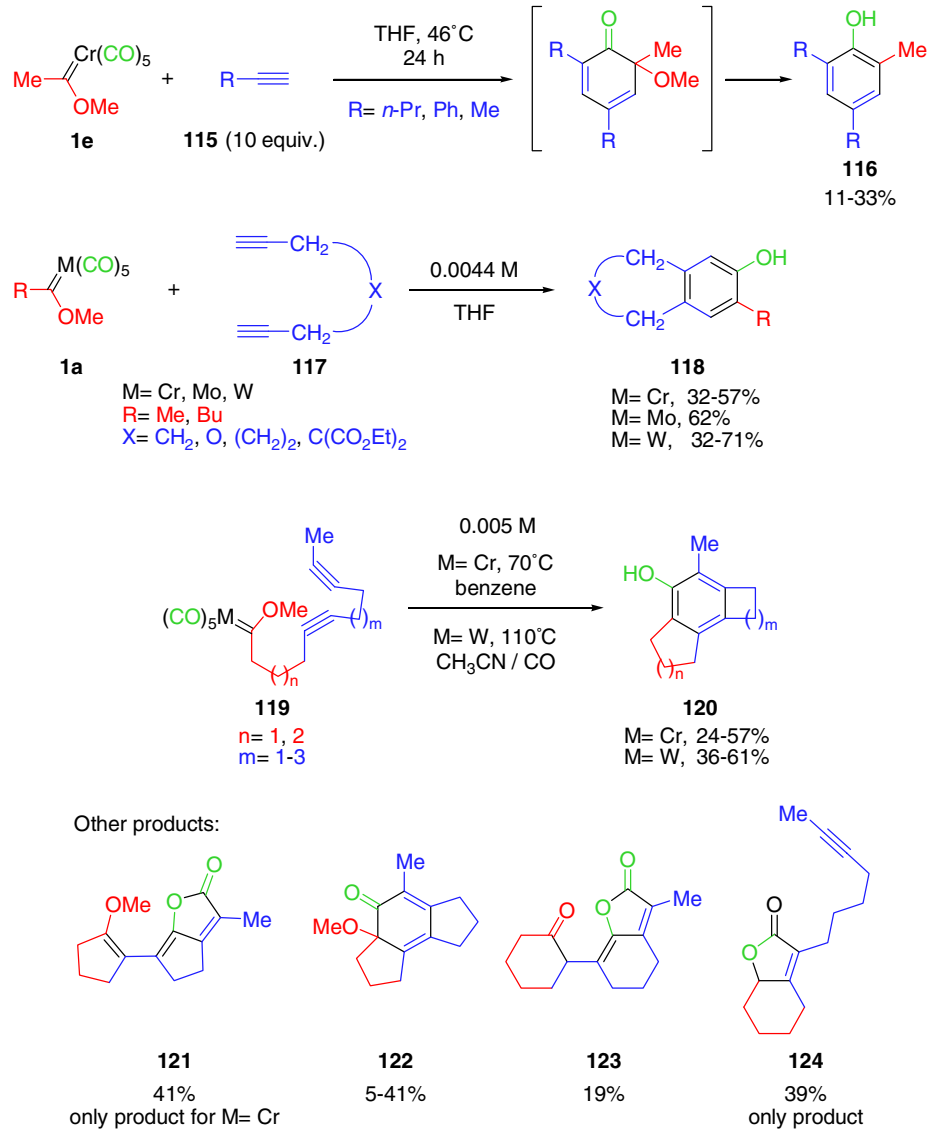


Scheme 20. Reactions with enediynes.

in the reaction of molybdenum carbene complex **1a** (M = Mo, R^1 = Bu) with an 1,7-enyne (9% yield) [34].

An intramolecular version of this reaction occurs for alkyl carbene complexes of chromium, tungsten or molybdenum **1a** with α,ω-diynes **117**. The reaction is quite general, it has to be performed in THF under quite diluted conditions (0.0044 M) and usually gives moderate to good yields of adducts **118** for 1,6-diynes while only moderate yields are achieved for 1,7-diynes. Also, an inversion in the direction of addition of the second alkyne causes a substitution pattern of the products different from that in the intermolecular reaction.

A completely intramolecular reaction has also been examined with carbenes **119** which include both alkyne



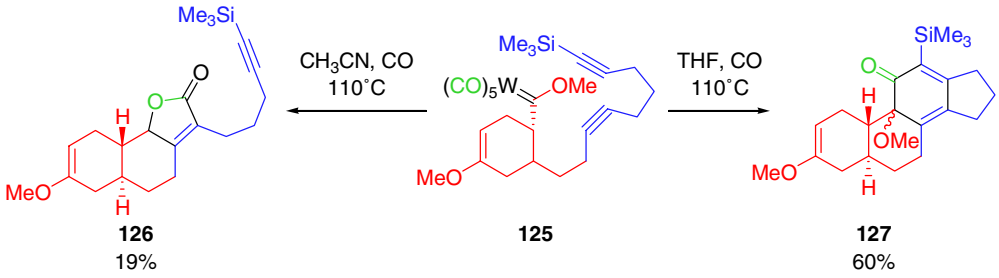
Scheme 21. [2 + 2 + 1 + 1] Cyclization involving two alkyne units.

units in the same molecule. The reaction has to be performed in benzene at 70 °C for chromium carbene complexes while tungsten carbene complexes require acetonitrile as solvent at 100 °C in the presence of carbon monoxide; moderate to good yields of adducts **120** have been obtained. In several cases, other products with different skeletons **121**–**124** that incorporate three or more components have been isolated and occasionally they were the only detected products (i.e. **121** for M = Cr, and **124**) [51].

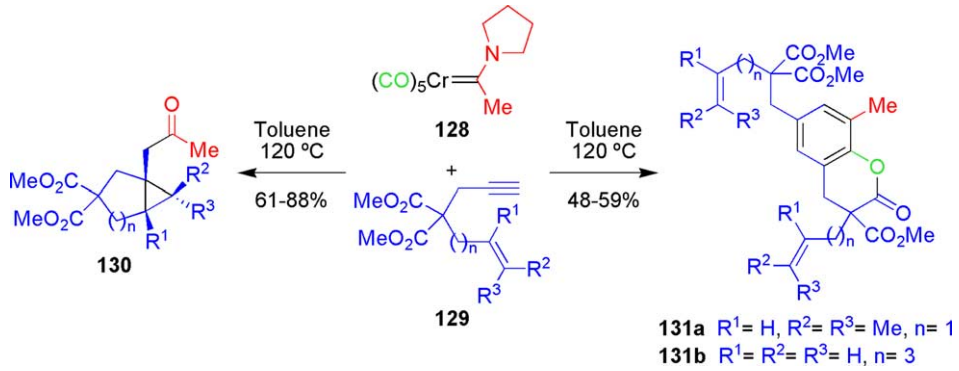
The intramolecular cyclization in acetonitrile of the less flexible tungsten carbene complex **125** led to butenolide **126** with low mass balance. However, its thermolysis in THF gave a 60% of the desired [2 + 2 + 1 + 1] annulation product **127** (Scheme 22).

Although the amino group in amino carbene complexes slows the rate of carbon monoxide insertion, this [2 + 2 + 1 + 1] cyclization has also been observed for amino carbene complexes. In general, when enynes **129** were exposed to the pyrrolidinocarbene **128** in refluxing toluene, the expected two component with no CO insertion ketocyclopropanes **130** were isolated in good yields. However, in two specific cases, for enynes which contained either additional hindrance on the alkene ($R^2 = R^3 = Me$) or a longer tether ($n = 3$), the [2 + 2 + 1 + 1] cyclized aromatic lactones **131** were the only identified products isolated in moderate yields (Scheme 23) [52].

The reactions of FCC with acetylenes **37** are known to be sensitive to solvents. This is indeed the case of the reactions of alkoxy carbene complexes bearing an internal triple bond, that are proposed to be initiated by intramolecular alkyne insertion. For chromium carbene complexes **132**, indanol derivatives **133**, which are



Scheme 22. Cyclizations of FCC **126**.



Scheme 23. Cyclizations of aminocarbene complex **128**.

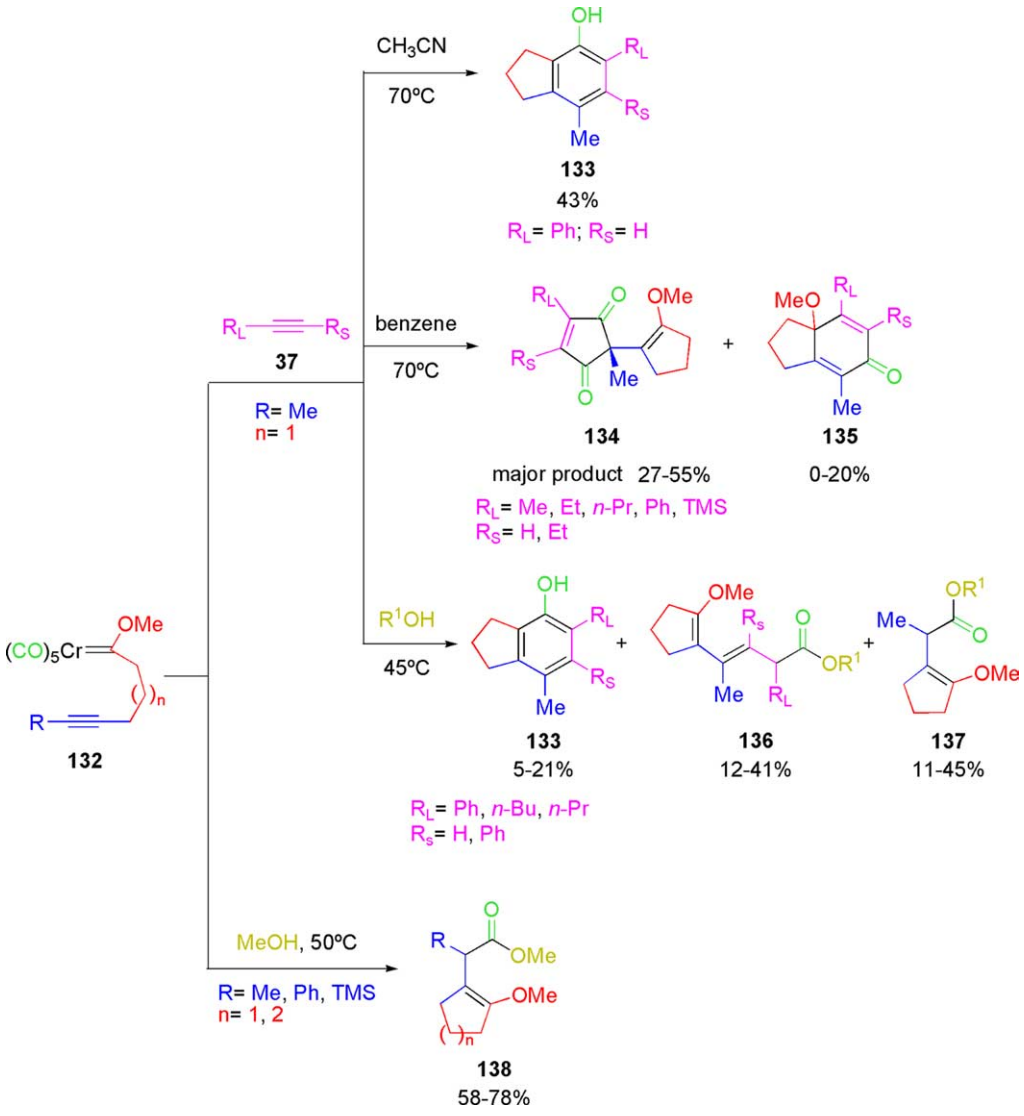
formed by a [2 + 2 + 1 + 1] cyclization, are the main products when the reaction is performed in acetonitrile [53]; on the other hand, cyclopentenediones **134** are the major products if the reaction is carried out in benzene or in hexane; in this case a remarkable [2 + 1 + 1 + 1] cyclization has occurred, as cyclopentenediones **134** can be obtained in moderate yields with the proper choice of solvent and concentration [54] (Scheme 24). Although it has also been observed for intermolecular reactions, the formation of cyclopentenedione products **134** is greatly favoured for intramolecular processes. Cyclohexadienones **135** are occasionally obtained among the minor products under these reaction conditions; they are the result of an unusual two-alkyne annulation, that requires a CO insertion prior to the external alkyne insertion to place the carbene carbon and the carbonyl group in relative para positions.

If the reaction is carried out in a protic solvent, such as an alcohol, it leads to a mixture of three structurally different products; these are the formerly described indanols **133**, and two cyclopentenes, **136** and **137**. Those cyclopentenes are, respectively, obtained by the insertion of an alkyne unit followed by carbonyl insertion and trapping of the intermediate with the alcohol and by direct carbonyl insertion followed by alcohol trapping without insertion of the second alkyne unit. On the other hand, cyclopentenes **138** are the only products formed when the starting carbene complexes **132** are warmed in methanol in the absence of the alkyne.

Wulff and co-workers have also observed that, besides the effect of the solvent, the nature of the metal of the FCC has also an important influence in the ratio of the reaction products. Thus, for the reaction of **132** with 1-pentyne, while cyclopentenedione **134** (R_L = *n*-Pr, R_S = H) is favoured for chromium carbene complexes, indanol **133** (R_L = *n*-Pr, R_S = H) is the main reaction product when tungsten and molybdenum complexes are employed [55].

Aminoalkynylcarbene complexes **139** do also undergo this type of transformation to produce cyclopentenediones **143** and indanols **144**–**146**, after a reductive treatment. In this case, the indanols **144** and **145**, which may even be the major products if the reaction is carried out in THF, proceed from the before-mentioned unusual "para"-two-alkyne derived cyclohexadienones **141**, while the more common "ortho"-two-alkyne derived indanols **146** are barely detected (Scheme 25).

The direct warming of aminocarbene complex **139b** in benzene allowed the isolation of η^4-alkenylketene complex **147** (X-ray) in 52% yield. Heating **147** in THF in the presence of *n*-pentyne led to a mixture of products with almost the same distribution obtained when the reaction was carried out with carbene complex **139a**, being this an evidence of the role of η^4-alkenylketene complex **147** as an intermediate in these reactions. Complex **147** can also be treated with a variety of nucleophiles such as pyrrolidine or sodium methoxide in methanol to form multi-component adducts **148**. The



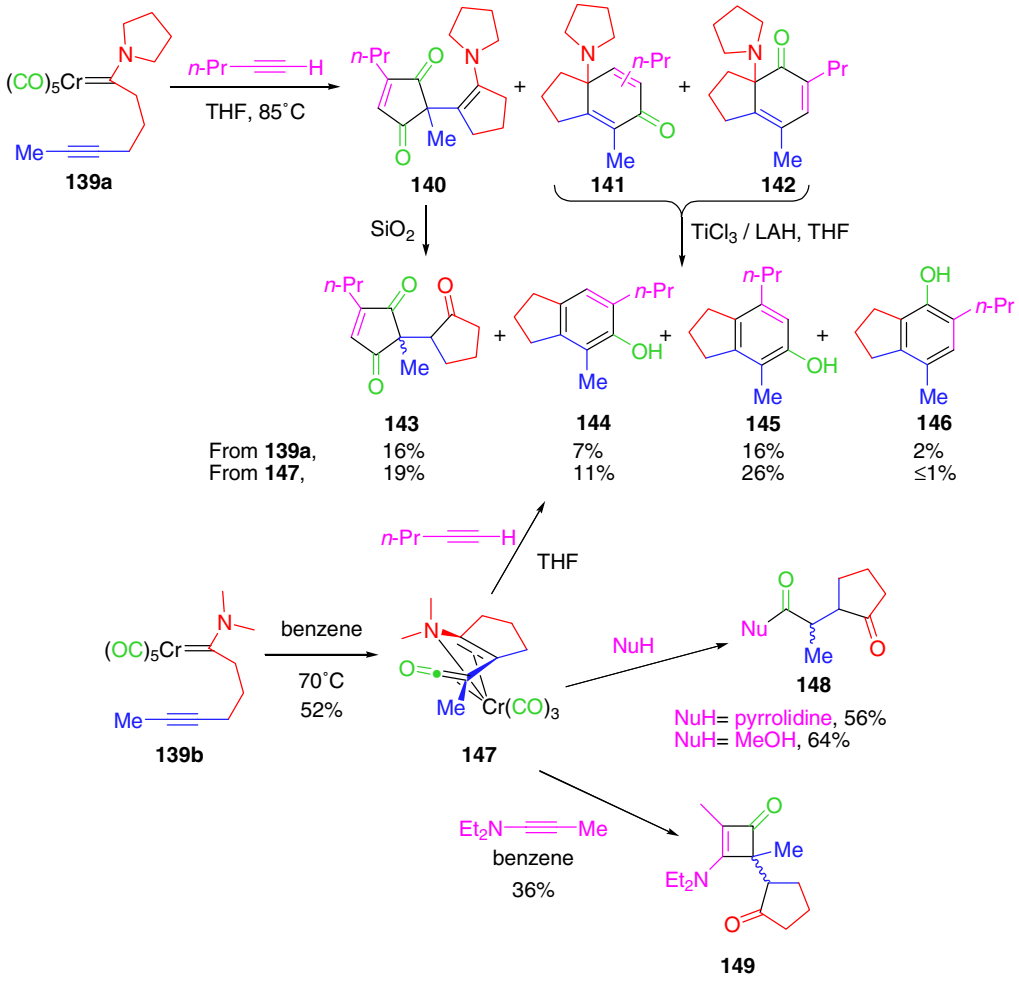
Scheme 24. Cyclizations of FCCs bearing an internal triple bond.

regioisomeric indanols **144** and **145** are obtained by a formal [4 + 2] cycloaddition of **147** with 1-pentyne; in contrast, the reaction of **147** with diethylpropynylamine leads to cyclobutenone **149** in 36% by a formal [2 + 2] cycloaddition [56].

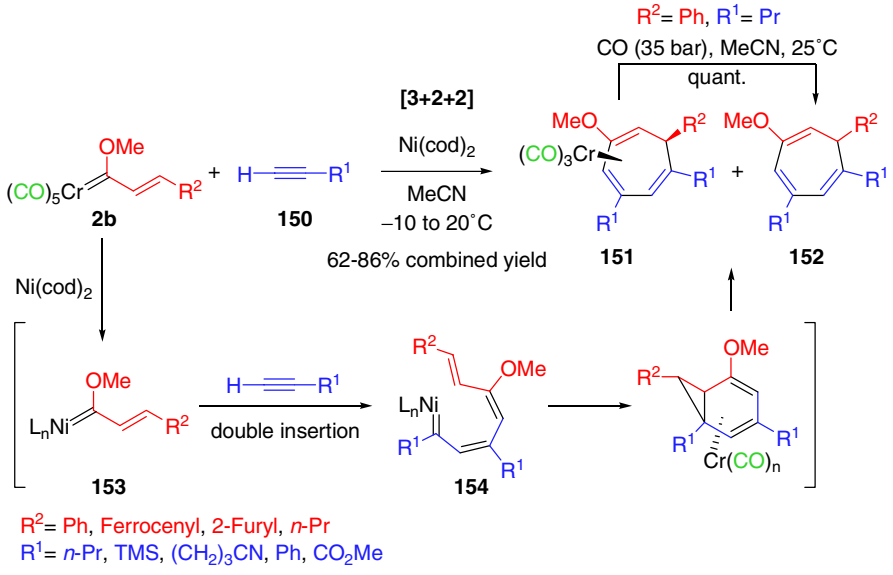
2.3.2. Reactions involving transmetallation to late transition metals

Transmetallation to late transition metals has been presented as a feasible strategy to discover a different pattern of reactivity for FCCs; in this sense, multiple alkyne insertion has been observed for nickel FCCs. Thus, Barluenga et al. have postulated the active role of nickel alkoxy carbene species **153** and **154** in the reaction of chromium Fischer alkenyl carbene complexes **2b** with terminal alkynes **150** at −10 °C in acetonitrile in the presence of stoichiometric amounts of [Ni(cod)$_2$]. Under the reaction conditions a [3 + 2 + 2] cyclization takes place with complete regio- and stereo-selectivity, to form the *endo* isomer of a cycloheptatriene tricarbonylchromium complex **151** and/or the corresponding demetallated cycloadduct **152** in good yields. The reaction takes place with neutral and electron-deficient alkynes. Two equivalents of the alkyne are therefore incorporated into the final product. The metal-free systems **152** are quantitatively accessed by CO exchange under pressure [57] (Scheme 26).

The proposed mechanism is initiated by a chromium–nickel exchange to form **153**, which is presumably facilitated by the formation of pentacarbonyl(acetonitrile)chromium(0). The subsequent double regioselective alkyne insertion produces a new nickel–carbene complex **154** which evolves, probably by intramolecular cyclopropanation and isomerization to give **151** and **152**.



Scheme 25. Cyclizations of aminocarbene complexes bearing an internal triple bond.



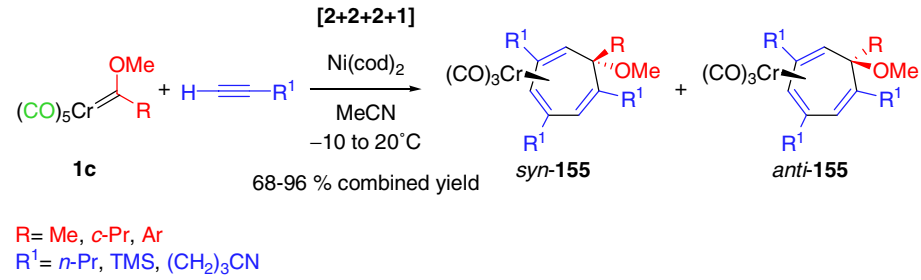
Scheme 26. Nickel mediated [3 + 2 + 2] cycloaddition of chromium alkoxy alkenylcarbene complexes with terminal alkynes.

When simple carbene complexes **1c** are treated with terminal acetylenes under the conditions described above, complexes **155** are isolated in high yields. These products are the result of a [2 + 2 + 2 + 1] cyclization which requires the consecutive incorporation of three alkyne units in a regioselective manner (Scheme 27). The *syn* isomer was the sole or the major isomer obtained and its structural assignment was confirmed by an X-ray analysis of one of the adducts.

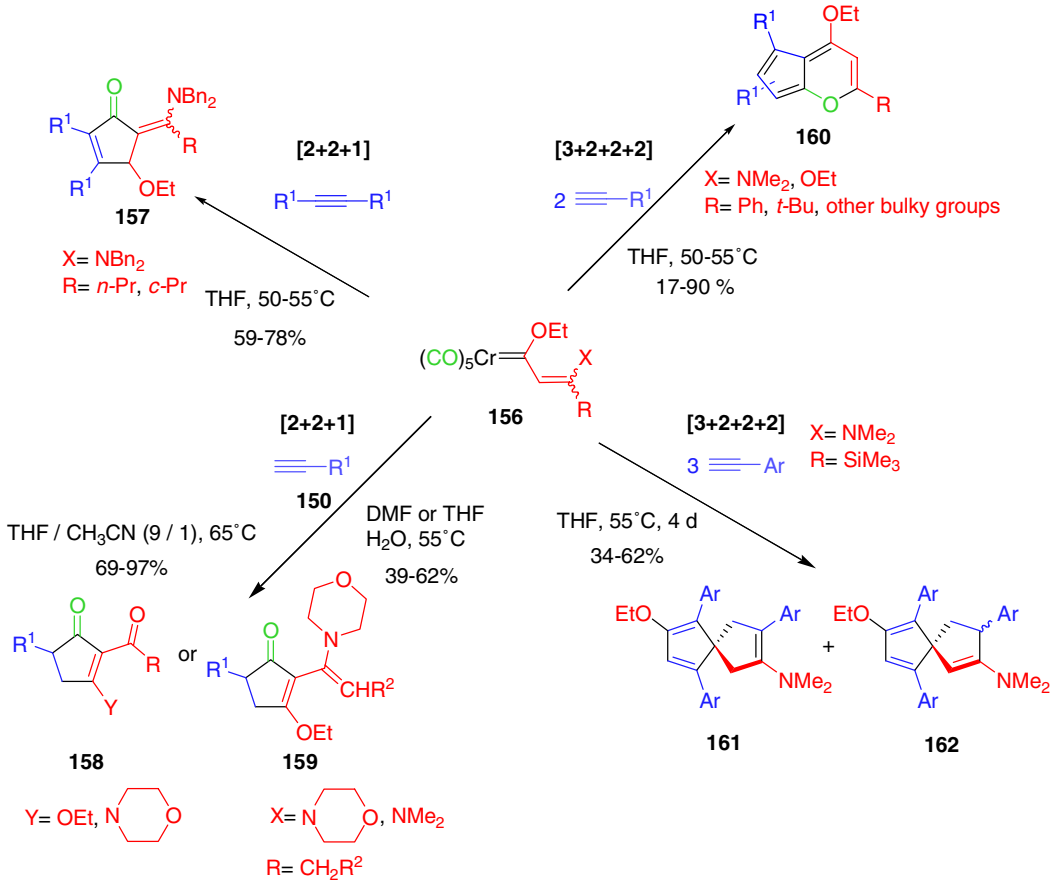
Therefore, nickel-transmetallation presumably allows the formation of nickel carbene complexes which readily undergo consecutive alkyne insertions to produce hept-annulated compounds.

2.4. Reactivity of β-donor substituted alkenylcarbene complexes with alkynes: from single to multiple insertions of alkynes into chromium–carbon bonds

The reaction of β-donor substituted alkenylcarbene complexes with alkynes represents a well established preparation of formal [3 + 2] cycloaddition products, although it only involves two components [3c,58]. De Meijere and co-workers have developed new reaction patterns when they found that internal alkynes may add to (2-dibenzylaminoalkenyl)carbene chromium complexes **156** (X = NBn_2) followed by CO insertion to give 5-(1-dibenzylaminoalkylidene)cyclopent-2-en-



Scheme 27. Nickel mediated [2 + 2 + 2 + 1] cycloaddition of chromium alkoxy alkyl or arylcarbene complexes with terminal alkynes.



Scheme 28. Reactivity of β-donor substituted alkenylcarbene complexes with alkynes.

ones **157** in a formal [2 + 2 + 1] cyclization with moderate to good yields. Terminal alkynes may also react in the same fashion when the reaction is performed in DMF (Scheme 28) [59].

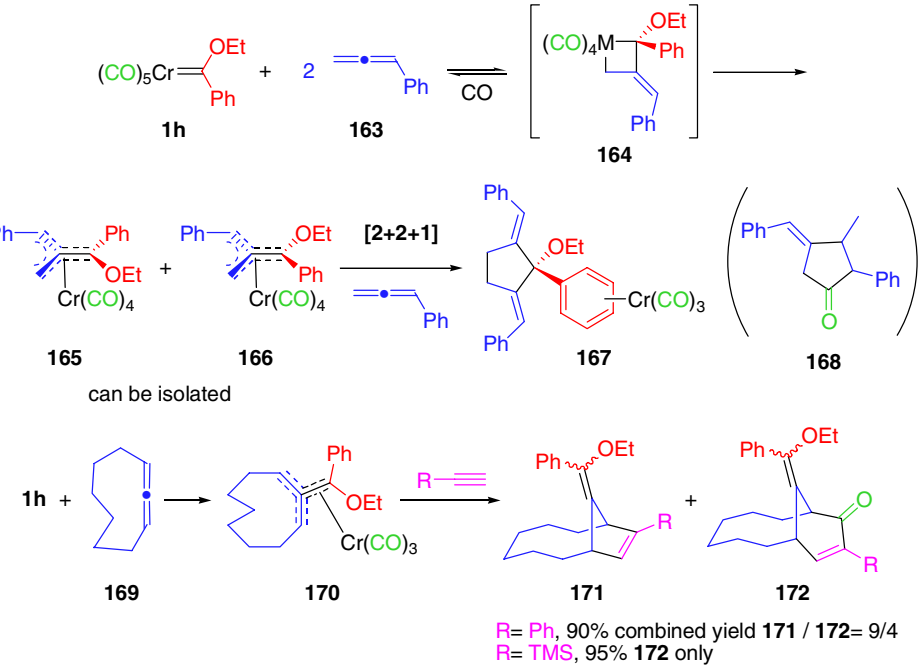
However, if the solvent is a mixture of THF and acetonitrile (9/1), cycloadducts **158** are obtained in good to excellent yields in the reaction of β-morpholino substituted alkoxy alkenylcarbenes with terminal alkynes. On the other hand, when the reaction is performed in aqueous DMF or THF, compounds **159** are synthesized in moderate yields. The formation of cyclopentenones **158** and **159** is the result of two different [2 + 2 + 1] cyclizations, both of them involving the incorporation of two carbons from the carbene complex, one unit of the terminal alkyne and a carbonyl ligand [60].

A more relevant finding was reported for β-donor substituted alkoxy alkenylcarbenes of chromium which may undergo the consecutive incorporation of two molecules of a terminal alkyne and a carbonyl ligand, with elimination of dimethylamine or ethanol, to form cyclopenta[*b*]pyrans **160** in yields up to 90%. Steric effects may be causing this surprising behavior as the higher yields are obtained when R is a bulky (tertiary or large secondary) substituent. The final product **160** is a bicyclic system, which results from a formal [3 + 2 + 2 + 2] cyclization [61].

However, the incorporation of three units of alkyne was reported for the first time five years ago when de Meijere and co-workers warmed 3-dimethylamino-3-trimethylsilylpropylidenchromium complex **156** (R = TMS, X = NMe_2) with an excess of terminal aromatic alkynes, to find a new process that can also be formally considered as a [3 + 2 + 2 + 2] cyclization. Unexpectedly, the reaction product was identified as a mixture of regioisomeric spiro[4.4]nonatrienes **161** and **162**; when Ar = Ph, the structure of the major adduct **161** was unequivocally ascertained by X-ray crystal analysis [62]. Due to the unusual behavior found for the carbene complex, which involves losing the original connectivity of the carbene ligand in the products, no mechanistic proposals for this transformation have been reported so far.

3. Reactions with allenes

The reaction of allenes with Fischer carbene complexes has been scarcely studied. Aumann and Uphoff obtained three-component cyclopentanes **167** by treating phenyl carbene **1h** with allenes **163**. In this reaction, which can be initiated thermally or photochemically, two units of allene become part of the final framework; the reaction presumably proceeds via the metallacyclobutane **164**, which rearranges to yield a mixture of isolable diastereoisomeric trimethylenemethane complexes **165** and **166** (Scheme 29). The metal moiety is crucial to control both the reactivity of the carbene complex (Mo > Cr > W) and the regiochemistry of metallacyclobutane **164**, which is determined by the steric demand of the tetracarbonyl metal fragment and by the charge distribution of the reactants **1h** and **163**. The diastereomeric trimethylenemethane complexes **165** and **166** slowly react with allene **163** at 25 °C to give carbocyclic five-membered ring compound **167**. The overall



Scheme 29. Reactions with allenes.

[2 + 2 + 1] cycloaddition process may be achieved either stepwise, with isolation of **165** and **166**, or in one step just by prolonging the reaction at the expense of complexes **165** and **166** [63].

In a parallel reaction, 4-methylenecyclopentanone **168** is a by-product formed in a template-directed [2 + 2 + 1] cycloaddition involving one equivalent of the CO released during the former synthetic reaction.

On the other hand, the isolated trimethylenemethane derivative **170**, obtained in the reaction of **1h** with cyclic allene **169**, is able to react with a molecule of alkyne to form different structures depending on the substituent on the alkyne. Thus, for R = TMS, the only isolated compound is alkylidenecyclohexenone **172** which is a three-component coupling product because of carbonyl insertion; however, for R = Ph, alkylidenecyclopentene **171** is the major product [64]. The preparation of compounds **172** represents a case of sequential MCR, as four different moieties are integrated into the final compound taking into account the whole sequence from the starting carbene complex **1h**.

4. Reactions with isocyanides

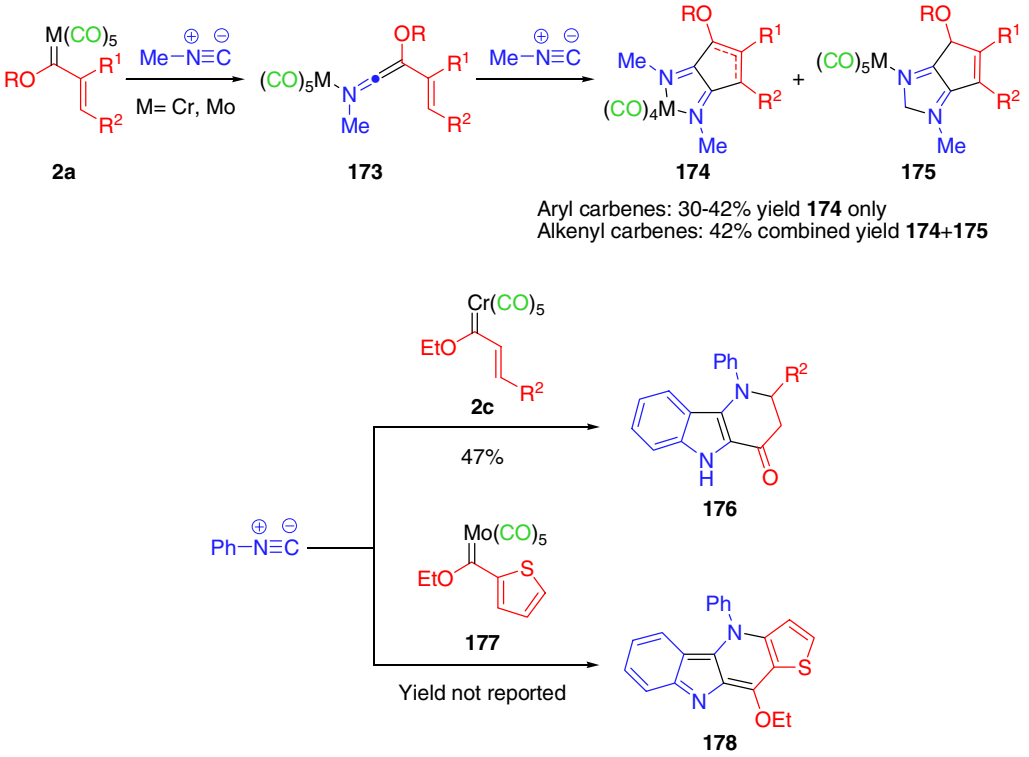
Aryl or alkenylcarbene complexes **2a** are capable of coupling with two units of methyl isocyanide to afford indane-diimine derivatives **174** and **175** with moderate yields. The reaction is proposed to proceed through intermediate **173** which comes from the insertion of methyl isocyanide into the metal–carbene carbon double bond [65] (Scheme 30).

On the other hand, phenyl isocyanide reacts with chromium alkenylcarbene complexes **2c** to give partially hydrogenated δ-carbolinones **176** in a double cyclization process. An analogous transformation takes place with particularly reactive molybdenum thienylcarbene complex **177** to spontaneously form tetracyclic molecule **178** in an unreported yield [66].

5. Free radical-mediated MCRs

Although free radical intermediates are valuable tools in synthetic organic chemistry, there is a limited number of examples in which these intermediates have been generated from Fischer carbene complexes. In 1997, Barluenga et al. [67] reported that difluoroboroxy Fischer carbene molybdenum complexes may act as precursors to acyl radicals under very mild reaction conditions and in the absence of an oxidant. The chemistry of such systems has been developed and expanded more recently and it has been found that they may be trapped with electron-deficient olefins and can participate in MCRs depending on the nature of the reagents which are present while the radicals are generated.

Pentacarbonyl(difluoroboroxy)carbene molybdenum complexes **180** are obtained by treatment of the corre-



Scheme 30. Reactions with isocyanides.

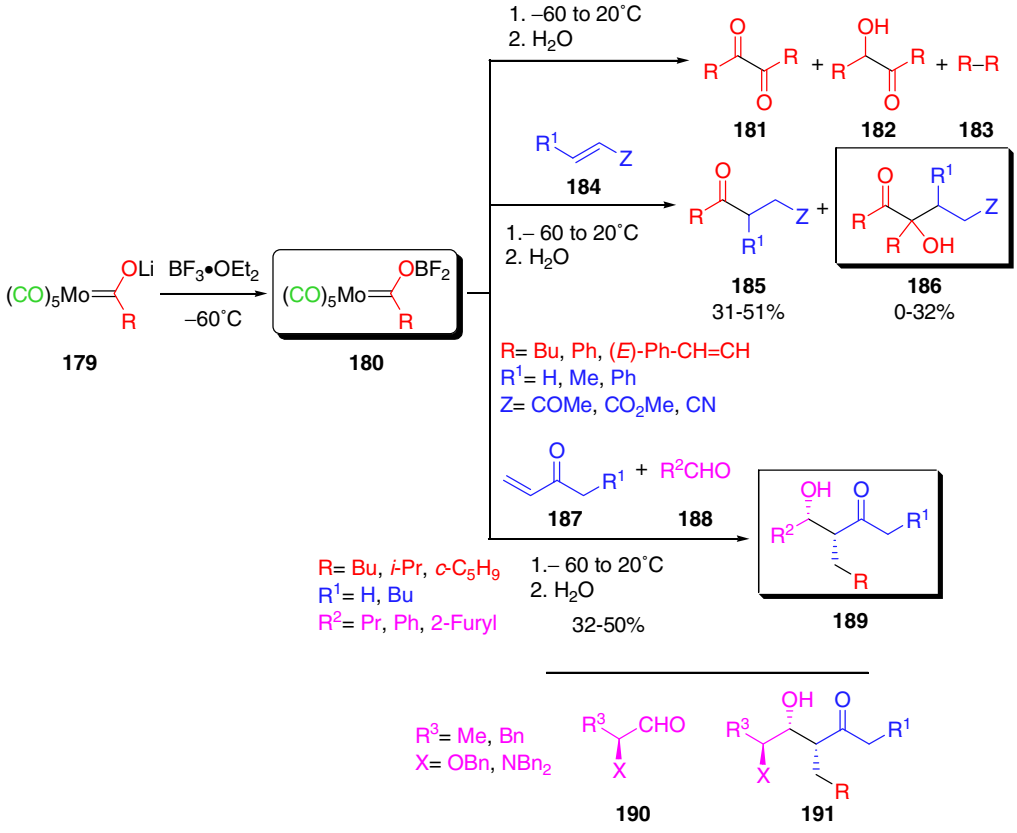
sponding lithium acyl metalates **179** with boron trifluoride diethyl ether complex in diethyl ether at −60 °C. Initial results showed that they are thermally unstable and, upon warming to room temperature, undergo loss of the metal fragment leading, after hydrolysis, to mixtures of 1,2-diketones **181**, 1,2-hydroxy ketones **182** and/or dimers **183** depending on the nature of the starting molybdate (Scheme 31).

However, when the decomposition is carried out in the presence of electron-deficient olefins **184**, Michael adduct products **185** are obtained. In several occasions, three-component addition products **186** have also been detected [68].

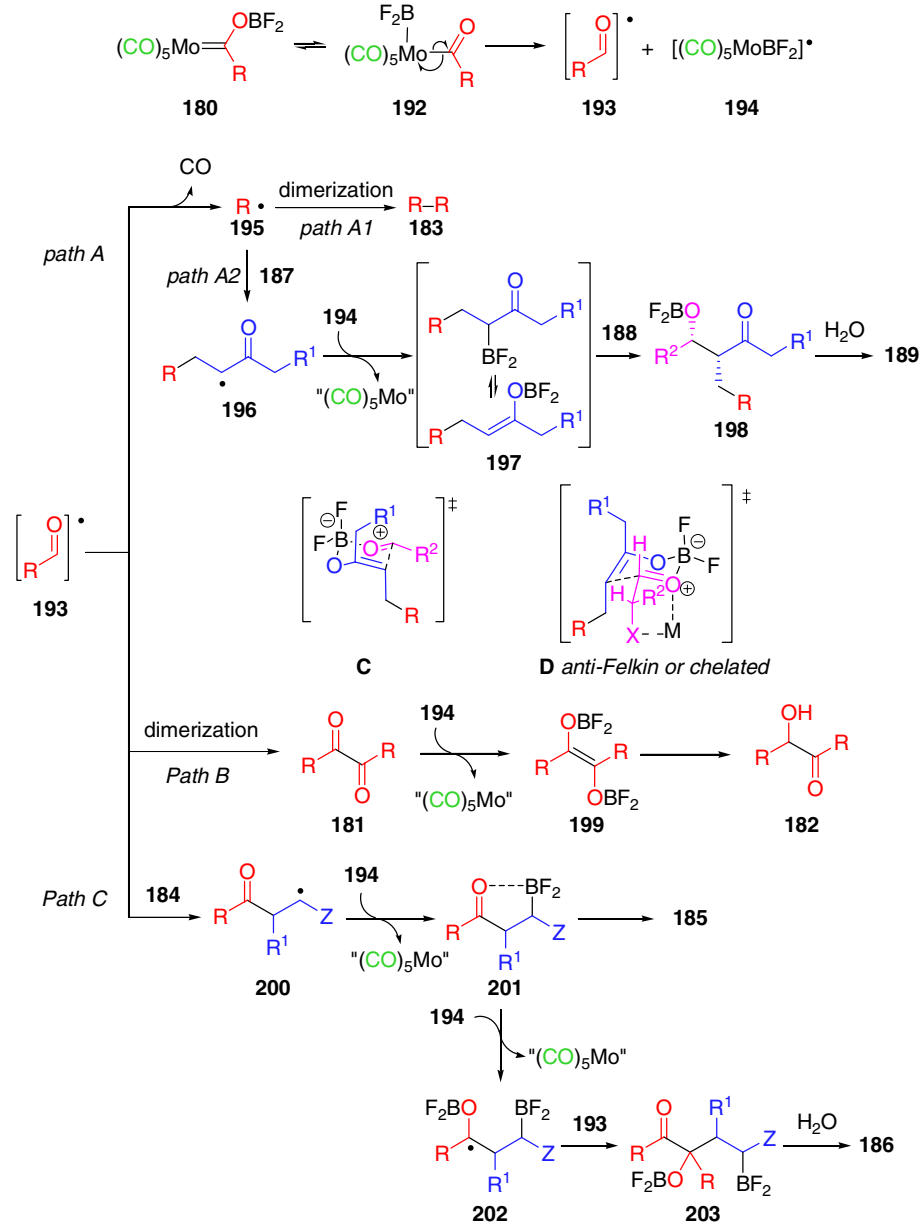
On the other hand, when difluoroboroxycarbene molybdenum complexes **180** are treated with vinyl ketones **187** and aldehydes **188** in diethyl ether at temperatures from −60 to 20 °C, they lead exclusively to the *syn* isomers of β-hydroxyketones **189** in moderate yields. Due to the complete stereoselectivity observed, the reaction was extended to chiral aldehydes **190** to study the diastereofacial selectivity of the process; thus, enantiomerically enriched adducts **191** are obtained with moderate yields and diastereoselectivities above 99% in most cases [69].

The formation of the products described above is considered to proceed by an initial homolytic scission of the carbon–molybdenum bond of tautomeric species **192**, with formation of acyl radicals **193** and the radical species **194**. Acyl radicals **193** can evolve by any of the following options (Scheme 32):

- By losing carbon monoxide (*path A*) to form alkyl radicals **195** which may either couple (*path A1*) to form **183** or add to vinyl ketones **187** (*path A2*) to generate radical intermediates **196**. Further electron transfer from **194** to intermediate **196**, with loss of the $Mo(CO)_5$ fragment, would produce boron enolates **197**, which thereafter would add to aldehydes **188** (or **190**) to afford the adducts **198**. The final hydrolysis leads to the β-hydroxy ketone derivatives **189** (or **191**). The 1,2-*syn* induction in the aldol step can be explained on the basis of the Zimmermann–Traxler chair-like transition model **C**, assuming that the geometry of the formed enolate is exclusively Z. In the case of the chiral aldehydes **190**, the major diastereomer obtained can be explained assuming that the reaction proceeds by a chelated or anti-Felkin transition state **D**, due to the presence in the reaction media of species with high coordinating capacity such as boron derivatives or organometallic species derived from the starting carbene complex.



Scheme 31. Free-radicals from molybdenum FCCs **180**: reactions with electron-deficient olefins.

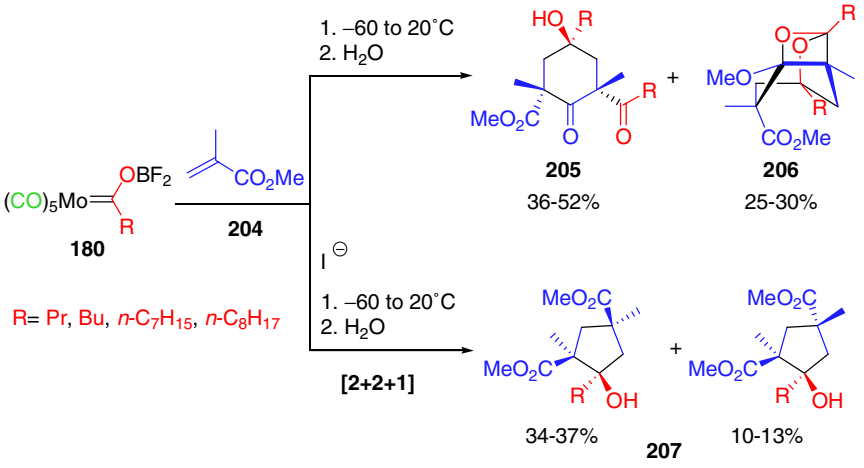


Scheme 32. Mechanistic proposals for free radical-mediated MCRs.

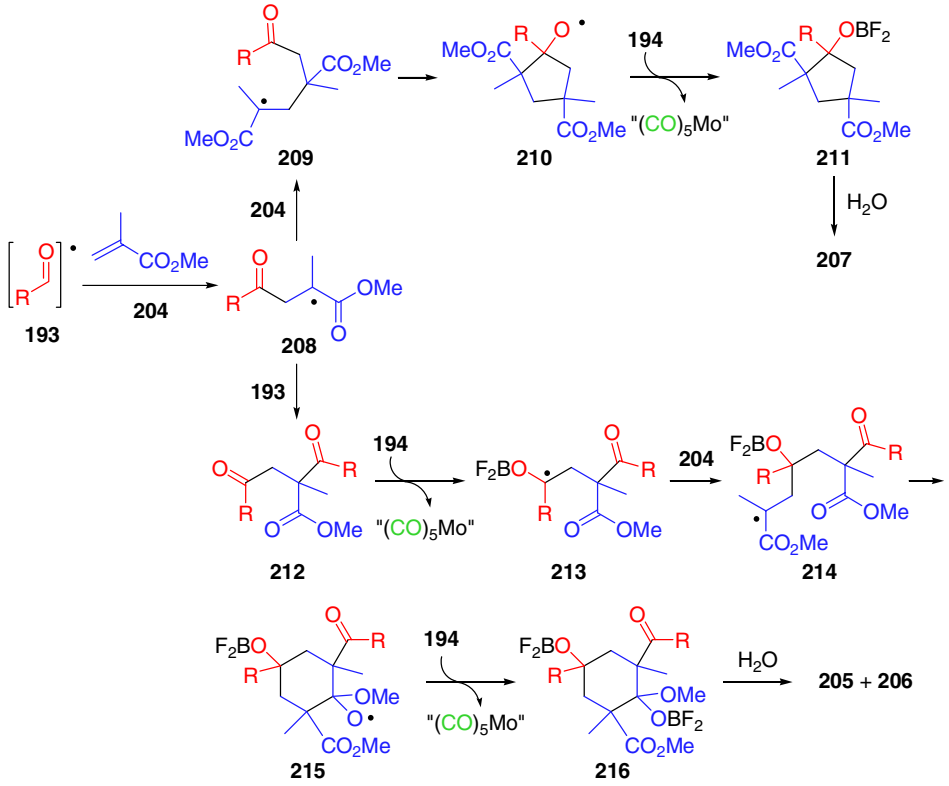
- By coupling (*path B*) with another acyl radical to form 1,2-diketones **181**. The formation of 1,2-hydroxy ketones **182** may be explained considering that the reduction of 1,2-diketones **181** takes place through a double electron transfer from radical species **194**, with release of "$Mo(CO)_5$", to give enediol derivatives **199**. Hydrolysis of **199** would then afford 1,2-hydroxy ketones **182**.
- By being trapped (*path C*) with electron-deficient olefins **184**. A further electron transfer followed by hydrolysis would explain the formation of the two-component Michael-addition product **185**. However, a second electron transfer would afford radical intermediate **202**, which would react with another equivalent of acyl radical **193** to generate products **203** which, after hydrolysis, lead to hydroxy ketone derivatives **186**. Compounds **186** were only observed in the reaction of *n*-butyl substituted carbenes with methyl acrylate and acrylonitrile, which was attributed to the lower reactivity of these olefins compared with 3-buten-2-one. Compounds **186** were neither obtained when disubstituted olefins were employed as trapping agents nor when the R group of the carbene complex is alkenyl or a bulky group, which can be attributed either to steric hindrance or to electronic effects.

A different outcome was observed when methyl methacrylate **204** was employed as electron-deficient olefin [68]. In these cases, a mixture of cyclohexanone derivatives **205** or tricyclic compounds **206**, both of them incorporating four components (two units of methyl methacrylate and two units of the acyl radical), was obtained as the main reaction products (Scheme 33). Surprisingly, if the reaction is performed in the presence of iodide (LiI, NaI, KI), the cyclopentanedicarboxylate derivatives **207** are isolated as a mixture of diastereomers. Other halides (F, Cl, Br) did not produce the change in reactivity: compounds **205** and **206** were obtained as the major products while cyclopentanedicarboxylate derivatives **207** were not observed. The reaction only takes place when the R group of the boroxy Fischer carbene complex is a primary alkyl substituent; with secondary alkyl groups, the reaction product is the result of the direct Michael addition of the acyl radical to methyl methacrylate.

This 1,4-addition of acyl radical to methyl methacrylate is proposed to be a key step in the reaction mechanism. The new radical **208** generated in this way is



Scheme 33. Free radicals from FCCs: reactions with methyl methacrylate.



Scheme 34. Mechanistic proposal for the free radical reactions with methyl methacrylate.

relatively stable as the unpaired electron is placed on a tertiary carbon, which allows its reaction with another unit of acyl radical **193** to form compound **212** (Scheme 34). Species **194** then transfers an electron to the more accessible carbonyl group of **212** to form **213**, which adds to another molecule of methyl methacrylate leading to **214**. This new intermediate will intramolecularly cyclize to cyclohexane derivative **215** which will evolve to **216** by a new electron transfer. The final hydrolysis step will originate tricarbonyl compound **205** or tetracyclic product **206**, which is, in fact, an acetal derivative of **205**. The formation of **205** or **206** may rely on the relative stereochemistry of the stereogenic centers formed in the reaction.

Cyclopentanecarboxylate derivatives **207** are the result of a [2 + 2 + 1] cyclization. Their formation can be understood considering that tertiary radical **208** evolves in a different way, now adding to a new molecule of methyl methacrylate to form a new tertiary radical **209**. The intramolecular cyclization of **209**, by addition of the radical carbon to the ketone carbonyl to form **210**, will be followed by a rapid electron transfer to **211** and the final hydrolysis will produce cyclopentane derivatives **207**.

The role of iodide remains still unclear although it appears to act either in the formation of acyl radicals or, more reasonably, in their concentration in the reaction media. Thus, in the absence of iodide, there would be a high concentration of acyl radicals **193** which would be trapped by intermediate radical **208** and would evolve to generate products **205** and **206**. However, in the case of low concentration of acyl radicals **193**, intermediate radicals **208** would react with methyl methacrylate leading to cyclopentane derivatives **207**.

6. MCRs by insertions in metallates

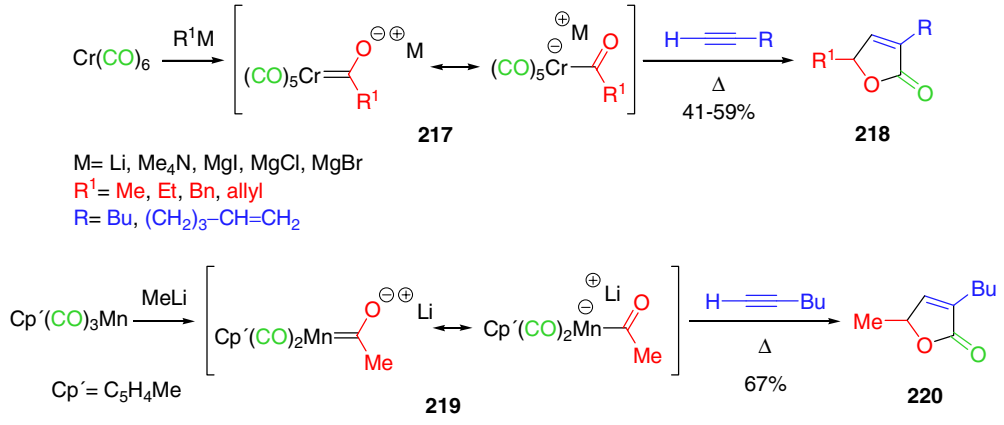
Several MCRs are based in the generation of metallates, which are able to trigger inter- or intramolecular insertions of unsaturated compounds. The following reactions will be presented according to the method employed to generate the corresponding metallates.

6.1. Alkyl addition to metal carbonyls followed by reaction with alkynes

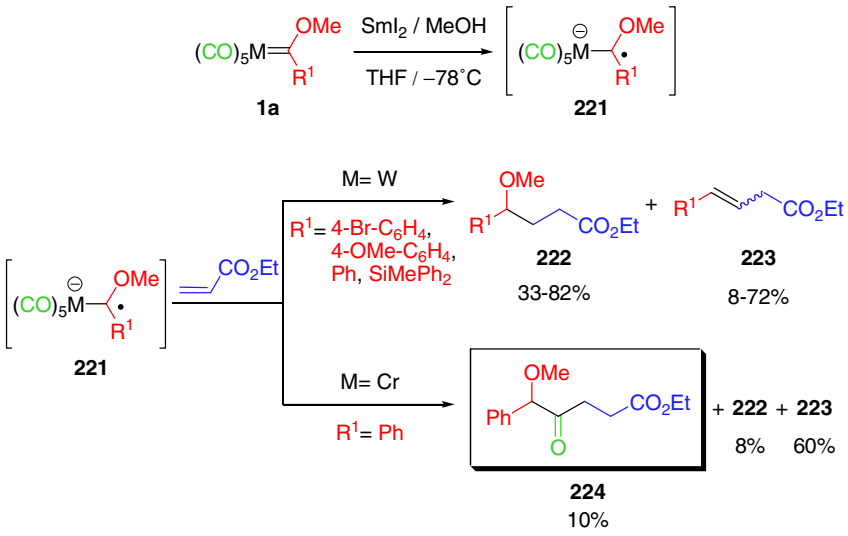
The addition of alkyl carbanions to hexacarbonyl chromium easily generates acyl chromates **217** that have been employed by Hoye and Rehberg and by Katz in a MCR. Therefore, acyl chromates **217**, which are intermediates in the classical synthesis of alkoxy chromium carbene complexes, were found to undergo thermal successive insertion of 1-hexyne and a carbonyl ligand to give three-component butenolides **218**, in moderate yields [36,70] (Scheme 35). Similarly, the acyl manganate **219** affords the butenolide **220** in 67% yield [71].

6.2. One-electron reduction of alkoxy carbene complexes and trapping with electron-deficient olefins

One-electron reduction of carbene complexes **1a** is a well-known reaction that leads to anion radicals **221**, which are stable in highly diluted solution at low temperature. Fuchibe and Iwasawa [72] employed these species, generated by samarium(II)-mediated reduction of carbene complexes **1a**, in carbon–carbon bond-forming reactions. Therefore, radical anions **221a** (M = W, R^1 = Ar, SiR_3), derived from tungsten aryl or silyl carbene complexes **1a**, underwent radical conjugated addition reactions to ethyl acrylate to afford a mixture of methyl ethers **222** and olefins **223** in good combined yields and variable ratio. Nevertheless, when the reaction was performed with chromium phenyl carbene complex **1g** (M = Cr, R^1 = Ph), a 10% yield of the three-component product **224**, which results from a carbonyl insertion prior to a 1,4-addition to the olefin, was obtained along with the corresponding methyl ether **222** and olefin **223** in 8% and 60%, respectively (Scheme 36).



Scheme 35. Alkyl addition to metal carbonyls followed by reaction with alkynes.



Scheme 36. One-electron reduction of alkoxy carbene complexes: trapping with ethyl acrylate.

However, ketone **224** became the only reaction product and it was isolated in good yield (75%) when the reaction was performed in a sequential way: the olefin was added in a second step, after treatment of the carbene complex with samarium diiodide. This result was an evidence of the participation of an acyl chromate complex, derived from the anion radical **221** and stable at low temperatures, as intermediate in the reaction.

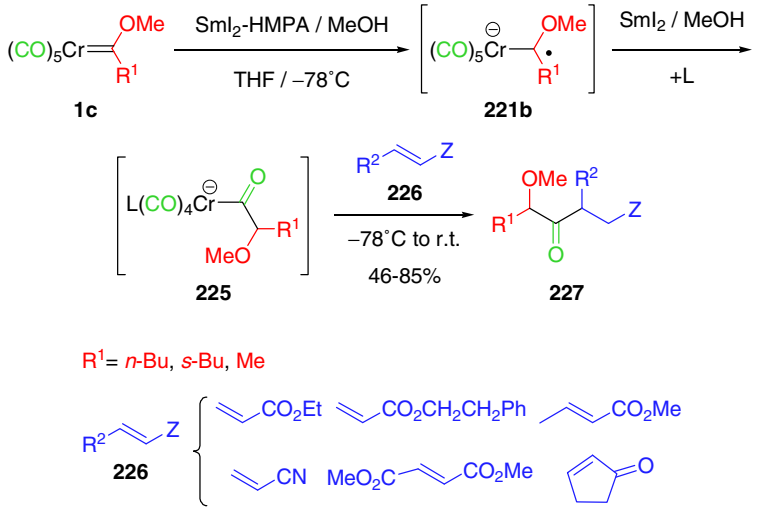
This sequential MCR was further examined and extended to chromium alkyl carbene complexes **1c** and several electron-deficient olefins **226** (Scheme 37). Thus, ketones **227** were obtained as single products in moderate to good yields by using samarium(II) iodide-HMPA complex as one-electron reducing agent.

As shown in Scheme 37, the proposed mechanism is initiated by one-electron transfer to chromium carbene complexes **1c** to form the corresponding anion radicals **221b**. A second electron transfer followed by protonation and carbonyl ligand insertion (not necessarily in that order) originates acyl chromate complexes **225**, which, finally, undergo a 1,4-addition to electron-deficient olefins **226** to furnish ketones **227**.

The different reaction pathways observed for tungsten and chromium carbene complexes is attributed to the lower bond energy of the chromium–carbon single bond that prompts the insertion of a carbonyl ligand to afford acyl chromate complexes.

6.3. Dihydropyridine-induced reduction of carbene complexes and addition to multiple bonds

The reduction of chromium and tungsten alkoxycarbene complexes **1** to pyridinium metallates **228** with dihydropyridine derivatives has been extensively



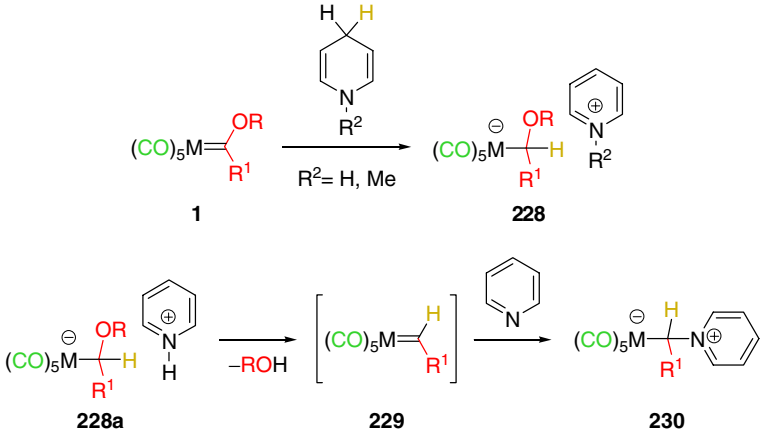
Scheme 37. Acyl chromates by samarium(II)-mediated reduction of chromium FCCs: reaction with electron-deficient olefins.

developed by Rudler and co-workers [28,73]. Metallates **228a** ($R^2 = H$) rapidly evolve to stable and isolable pyridinium ylide complexes **230** in high yields when unsubstituted dihydropyridine is used; the reaction proceeds by alcohol elimination and addition of pyridine to the carbene carbon of alkylidene complexes **229** (Scheme 38). As this interaction is reversible, a general approach to non-stabilized carbene complexes **229** has also been established.

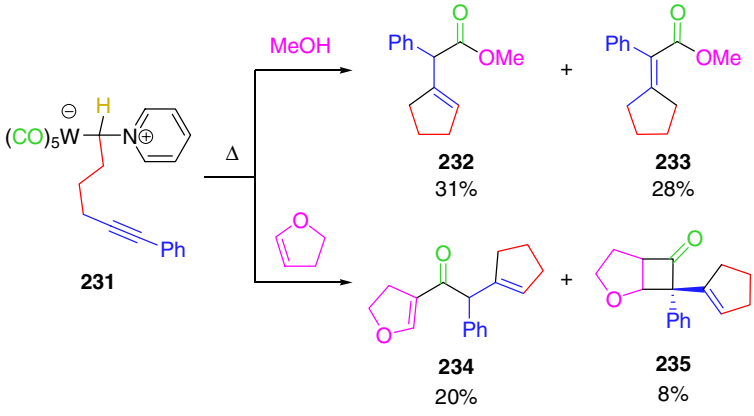
Complexes **230** do not react in an intermolecular fashion with non-activated alkynes, although intramolecular MCRs can be achieved when the pyridinium ylide complex bears an acetylene unit in its structure. Thus, heating complex **231** in refluxing benzene with a slight excess of methanol led to a mixture of three-component regioisomeric alkenyl esters **232** and **233** in good combined yield. Moreover, when the thermolysis was carried out with an excess of dihydrofuran, multi-component polycyclic ketones **234** and **235** were obtained in moderate combined yields (Scheme 39) [74]. The formation of both series of cycloadducts should be initiated by an intramolecular insertion of the acetylene into the non-stabilized alkylidene complex derived from pyridinium ylide **231**, by pyridine elimination, followed by a CO insertion. The resulting intermediate would either undergo methanolysis to form esters **232** and **233** or evolve to cycloadducts **234** and **235**, in the presence of dihydrofuran.

Otherwise, *N*-methylpyridinium metallates **228b**, formed by addition of *N*-methyldihydropyridine to carbene complexes **1**, undergo CO insertion processes to give oxycarbenes complexes **236** (Scheme 40), which take part in MCRs with reagents bearing multiple bonds.

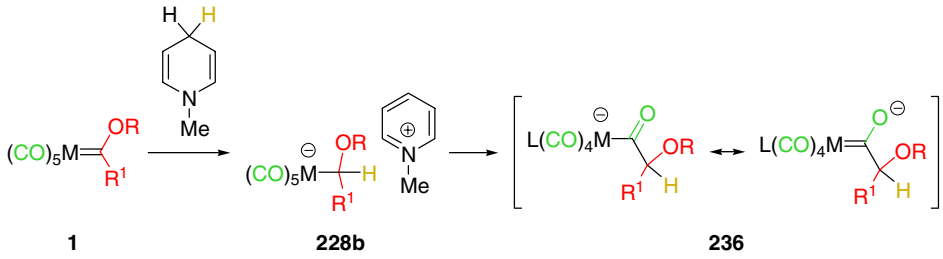
Thus, the addition of *N*-methyl dihydropyridine to a mixture of chromium carbene complex **1** and cyclopentenone at −10 °C, followed by slow warming to room temperature, led to 1,4-dicarbonyl compound **237** in moderate yield through a conjugated addition of the acyl metallate **236** to cyclopentenone. Moreover, when the addition of *N*-methyl dihydropyridine was performed over chromium or tungsten carbene complexes **238** containing a tethered double bond, two possible products **239** and **240** were isolated in variable amounts



Scheme 38. Reduction of FCCs **1** with dihydropyridine derivatives.



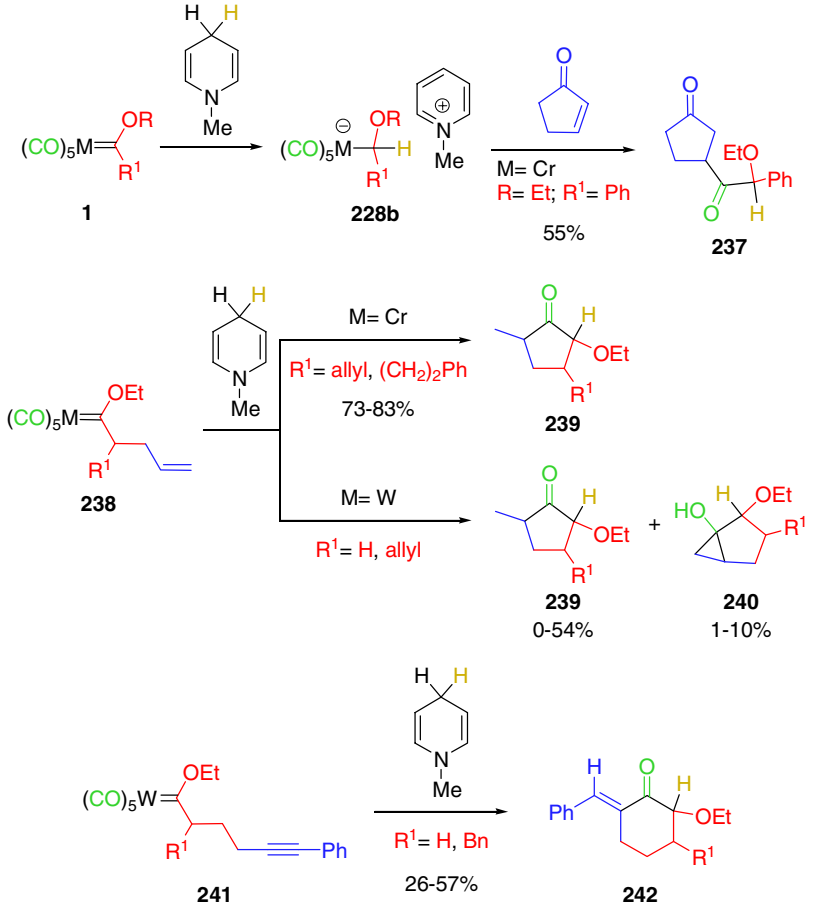
Scheme 39. MCRs with complex **231**.



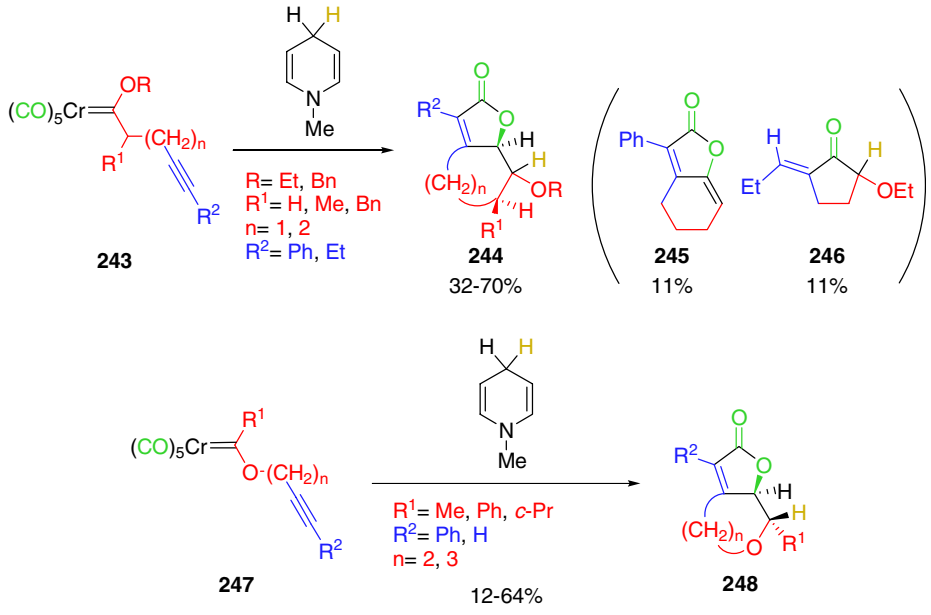
Scheme 40. CO insertion in *N*-methylpyridinium metallates **228b**.

depending on the metal of the starting carbene complex (Scheme 41) [73b,75]. Therefore, while chromium carbene complexes led to cyclopentanones **239** in good yields, tungsten complexes afforded a mixture of cyclopentanones **239** and cyclopropanols **240** in variable ratios. Cyclopentanones **239** are the result of an intramolecular insertion of the terminal double bond of the carbene complex in the acyl metallate **236** while bicycloadducts **240** were produced through an intramolecular cyclopropanation between the double bond and the oxycarbene function. In an analogous reaction, tungsten carbene complexes **241**, bearing an acetylene in their structure, furnished cyclohexanones **242** as a mixture of two isomers in moderate yields, due to an intramolecular alkyne insertion in acyl metallate **236**. If we consider the hydrogen from the dihydropyridine as an independent unit, all of these transformations involve the participation of four components in an inter- or intramolecular fashion.

However, when analogous chromium carbene complexes **243** were used, a different pathway takes place affording five-component butenolides **244** in moderate to good yields as a mixture of two isomers (Scheme 42) [73b,75,76]. This MCR involves the participation of two molecules of CO from the coordination sphere of the starting chromium carbene complex, the



Scheme 41. MCRs promoted by the addition of *N*-methyldihydropyridine to FCCs.



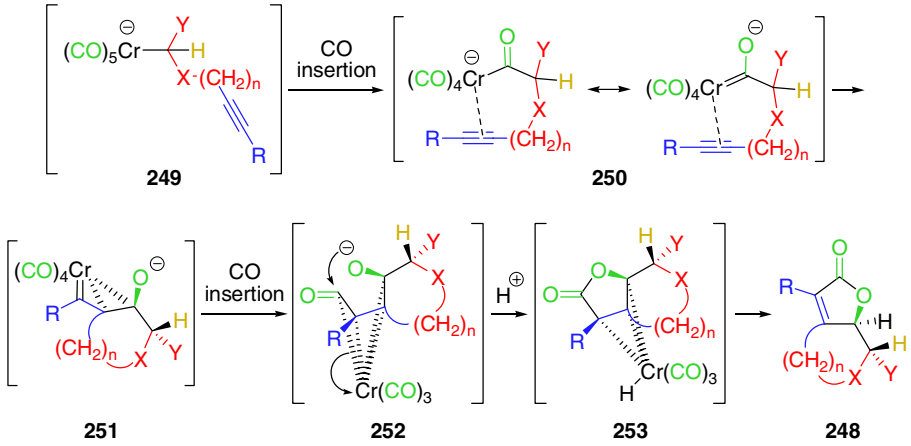
Scheme 42. Butenolides by *N*-methyldihydropyridine promoted MCRs of chromium FCCs bearing triple bonds.

hydrogen from the reducing agent, an acetylene moiety and the carbene ligand. Cycloadducts **245** and **246**, formed by ethanol elimination from **244** and single insertion of CO, respectively, were isolated in small amounts in particular examples.

Similarly, chromium carbene complexes **247** which bear the triple bond in the alkoxy unit led to the expected butenolides **248**, as single isomers, in moderate yields. In this case, no by-products were observed (Scheme 42). An approach to scalemic butenolides **248** was carried out by using chiral dihydropyridines as reducing agents to obtain enantiomeric excesses up to 55% [77].

The mechanism proposed to explain these transformations is depicted in Scheme 43. Thus, chromate **249**, generated by reduction of the starting carbene complex with *N*-methyldihydropyridine, inserts a carbonyl ligand to afford acyl chromate **250**, which is stabilized by intramolecular coordination with the acetylene unit. The insertion of the alkyne produces a new carbene complex **251** (these types of intermediates led to cycloadducts **242** when tungsten carbene complexes were employed, Scheme 41). Then, a second CO ligand insertion takes place in chromium carbene complex **251** to give ketene complex **252**, which bears a negatively charged oxygen in a suitable position to undergo a nucleophilic attack to the carbonyl carbon. At this point, protonation of the metal atom furnishes intermediate **253** which, after reductive elimination, produces butenolides **248** (or **244**).

More recently, the same research group has discovered that, not only hydrides generated from dihydro-



Scheme 43. Proposed mechanism for the formation of butenolides **248** (or **244**).

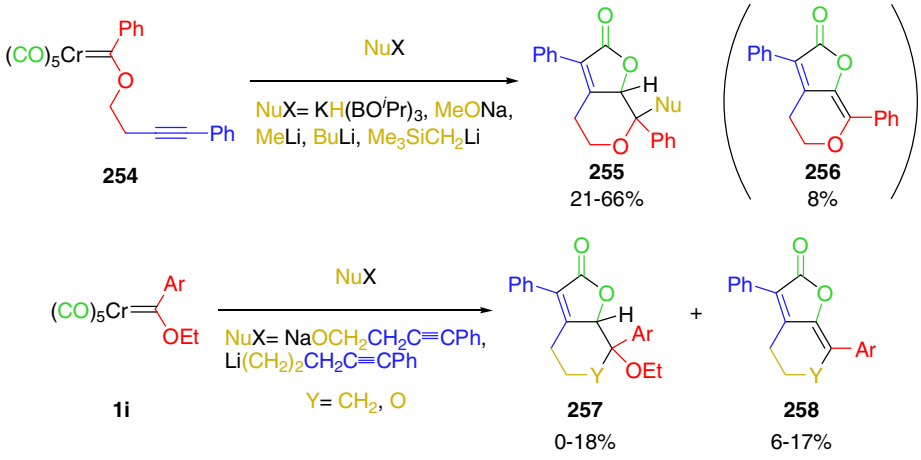
pyridines, but also simple metal hydrides, alkoxides and various nucleophilic alkyl lithium reagents give five-component substituted butenolides **255** in low to good yields with variable diastereoselectivities; a small amount of four-component butenolide **256**, originated by methanol elimination, was isolated when sodium methoxide was used as nucleophile [78] (Scheme 44). Furthermore, butenolides **257** and/or **258** could also be formed albeit in low yields, from simple chromium arylcarbene complexes **1i**, by using suitable nucleophilic agents containing a triple bond.

6.4. Sequential addition of lithium enolates and allyl magnesium bromide

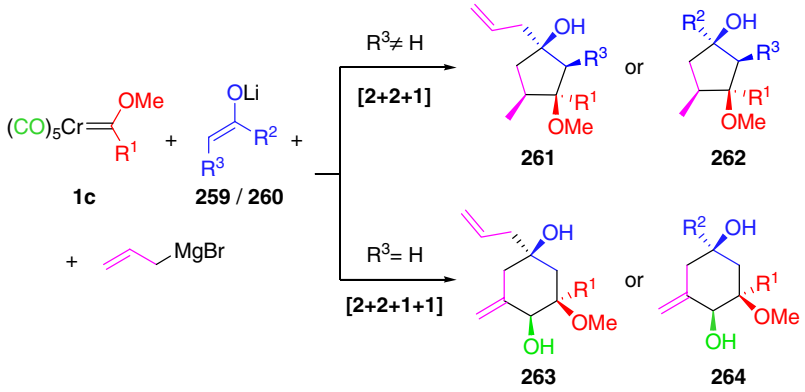
Recently, a novel selective MCR that leads to substituted cyclopentanols **261/262** or cyclohexane-1,4-diols **263/264**, in formal cycloadditions [2 + 2 + 1] and [2 + 2 + 1 + 1], respectively, was presented by Barluenga's group. Both processes involve the generation of acyl chromate species through sequential addition of a ketone or ester lithium enolate **259/260** and allyl magnesium bromide to chromium carbene complexes **1c** (Scheme 45) [79].

Thus, the successive addition of β-substituted lithium enolates **259** and allylmagnesium bromide, under suitable reaction conditions, to chromium aryl or alkyl carbene complexes **1c** led, after acidic hydrolysis and decoordination of the metal center, to 1,2,3,3,4-pentasubstituted cyclopentanols **261** or **262**, which were obtained as single diastereoisomers. 1-Allylcyclopentanols **261** were formed when ester lithium enolate **259** (R^2 = OMe) was used in a process that involves the sequential participation of four reacting components, three of them in a single step, and the formation of four new carbon–carbon bonds (Scheme 46). In a similar way, 1-substituted cyclopentanols **262** were isolated from the reactions with ketone lithium enolates **259** (R^2 = alkyl group) and represent the sequential coupling of three reacting components, two of them in a single step, with the formation of three new carbon–carbon bonds.

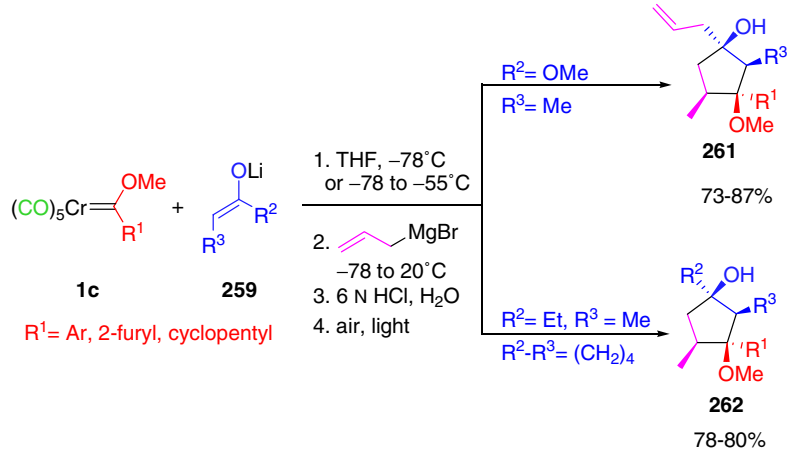
The analogous consecutive treatment of aryl, heteroaryl, alkyl, or alkynyl carbene complexes **1c** with



Scheme 44. Nucleophilic promoted formation of butenolides.



Scheme 45. MCRs by sequential addition of lithium enolates and allyl magnesium bromide to FCCs **1c**.



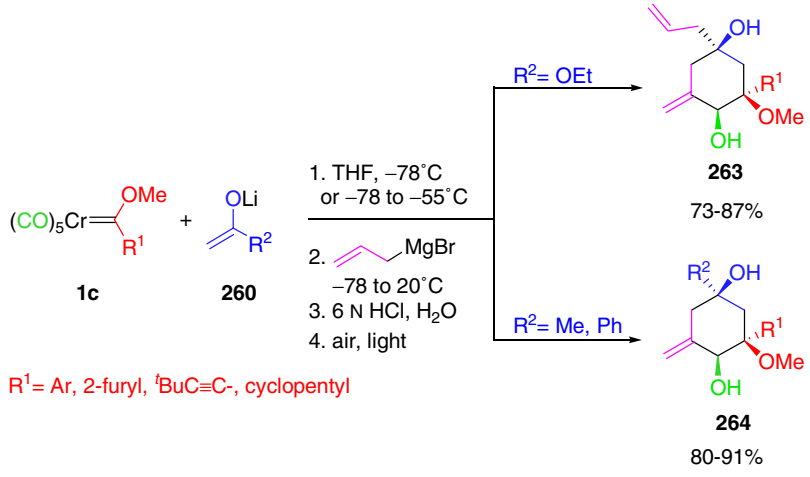
Scheme 46. 1,2,3,3,4-Pentasubstituted cyclopentanols **261** and **262** prepared by multi-component coupling of FCCs **1c**, lithium enolates **259** and allylmagnesium bromide.

β-unsubstituted lithium enolates **260** and allylmagnesium bromide resulted in the diastereoselective formation of 1,3,3,5-tetrasubstituted cyclohexane-1,4-diols **263** or **264** (Scheme 47). On one hand, ester lithium enolate **260** (R^2 = OEt) afforded 1-allylcyclohexane-1,4-diols **263** in which five reacting components have been joined together (four of them in a single step) with the formation of five new carbon–carbon bonds. On the other hand, the reactions with ketone lithium enolates **260** (R^2 = Me, Ph) provided 1-substituted cyclohexane-1,4-diols **264** by successive assembly of four reacting components, three of them in a single step, with the creation of four new carbon–carbon bonds.

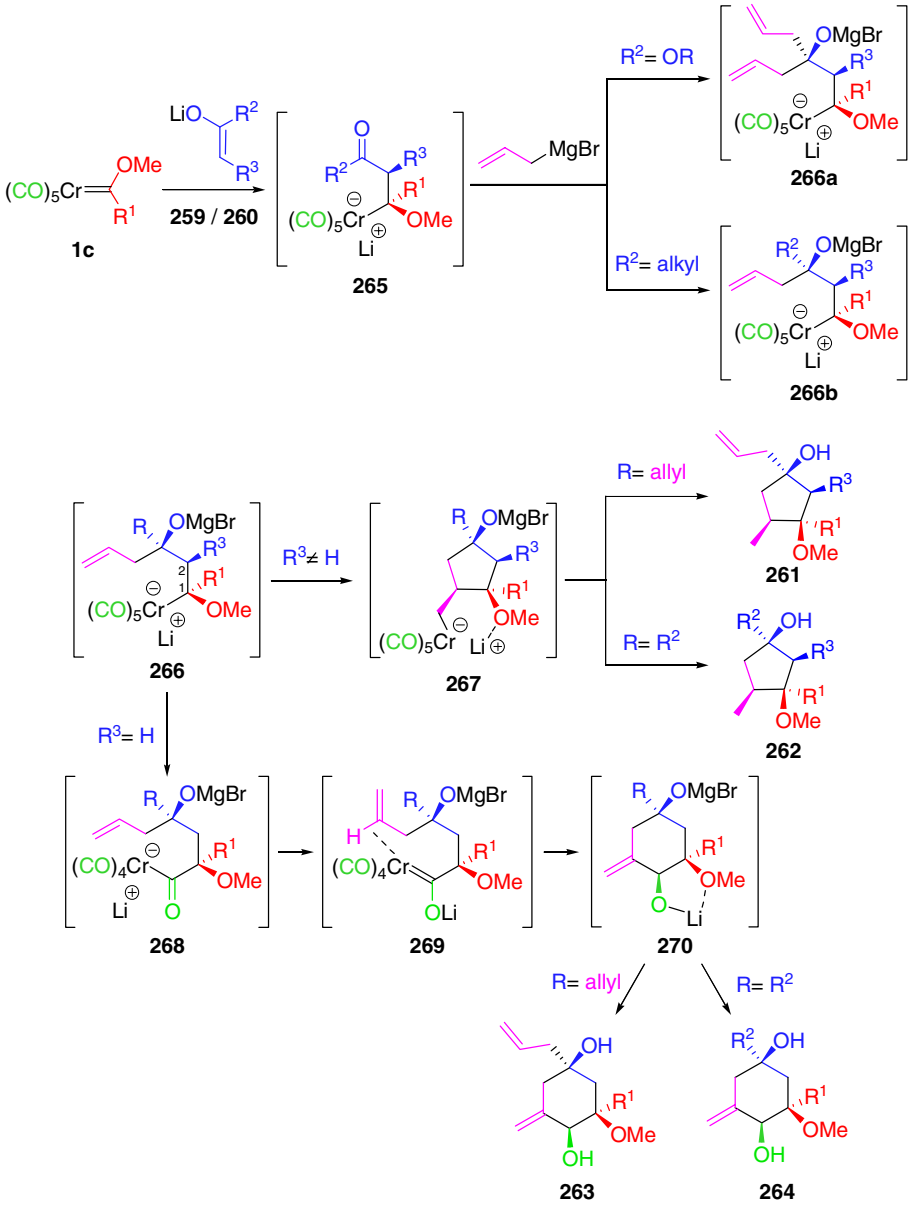
The ring skeleton of cyclopentanols **261** and **262** combines the carbene ligand, the enolate framework, and one allyl units, whereas that of cyclohexanediols **263** and **264** also incorporates a carbonyl ligand. Based on this information, a plausible mechanism shown in Scheme 48 explains the formation of both cycloadducts.

An initial 1,2-addition of the appropriate lithium enolate **259** or **260** to carbene complex **1c** affords pentacarbonylchromate intermediate **265**. Subsequent addition of the organomagnesium reagent at low temperature to the corresponding ester or ketone functional group produces chromate intermediates **266a** and **266b** as a result of di- or mono-allylation, respectively. The reactivity of species **266** depends on the degree of substitution at C2. C2-substituted complexes **266** ($R^3 \neq H$) undergo an intramolecular carbometallation reaction to give cyclopentylmethylchromate derivatives **267**, which finally furnish cyclopentanols **261** or **262** upon protonation. Evidence for the formation of intermediate **267** was provided by quenching the reaction with deuterium oxide and deuterated hydrochloric acid.

On the other hand, tetrahedral intermediates **266** that do not have a substituent at C2 (R^3 = H) undergo migratory insertion of carbon monoxide to provide acyl



Scheme 47. 1,3,3,5-Tetrasubstituted cyclohexane-1,4-diols **263** and **264** prepared by multi-component coupling of FCCs **1c**, lithium enolates **260** and allylmagnesium bromide.



Scheme 48. Proposed mechanism for the synthesis of cyclopentanols **261**/**262** or cyclohexane-1,4-diols **263**/**264**.

tetracarbonylchromate species **268**, which lead to 5-methylenecyclohexane-1,4-diols **263** and **264**, presumably after intramolecular insertion of the carbene carbon atom into the secondary vinylic carbon–hydrogen bond, as indicated in intermediate **269**, and subsequent protonation of **270**.

The diastereoselectivity observed in the first reaction step can be explained in terms of an approach topology **E**, which is favored by coordination of the lithium center to the oxygen atom of the methoxy group. The diastereoisomer formed in the second reaction step can be rationalized by a chelation-controlled transition state in which the

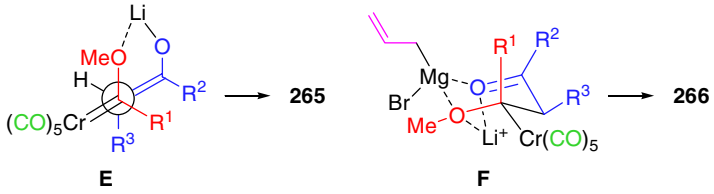


Fig. 2. Transition states proposed to account for the stereochemical results.

nucleophile (organomagnesium) adds to the less-hindered face (back face of model **F**) of the carbonyl group (Fig. 2).

7. Domino reactions

Tandem, cascade or domino processes are defined as *sequences in which a bond formation (or a bond-breaking process) is combined with the formation of a new functionality, which again forms a new bond and a new functionality, and so on* [80]. According to this definition, all MCRs are domino reactions, including the preceding reactions covered in this review; however, we have grouped in this section those transformations whose reaction sequence is clearly established, even though they could have been included in other sections. Such sequences are frequent in the chemistry of FCCs as will be pointed out below.

7.1. Tandem Diels–Alder cycloaddition/Dötz benzannulation reactions

The Diels–Alder reaction of alkynyl FCCs with dienes generates new α,β-unsaturated alkenyl FCCs which are of high synthetic value by virtue of their ability to undergo Dötz benzannulation reactions. Both the cycloaddition and the annulation reactions may also be carried out concurrently by mixing carbene complex **3a** with reactive diene **271** and acetylene **37** all in one pot. Phenol adducts **272** are obtained in good to excellent yields or cyclohexadienones **273** in moderate to good yields when starting from TMS-substituted or Me-substituted alkynyl complexes **3a**, respectively. Five carbon–carbon bonds are formed in these tandem Diels–Alder/Dötz benzannulation reactions (Scheme 49) [81].

7.2. Tandem Diels–Alder cycloaddition/double intramolecular two-alkyne annulation

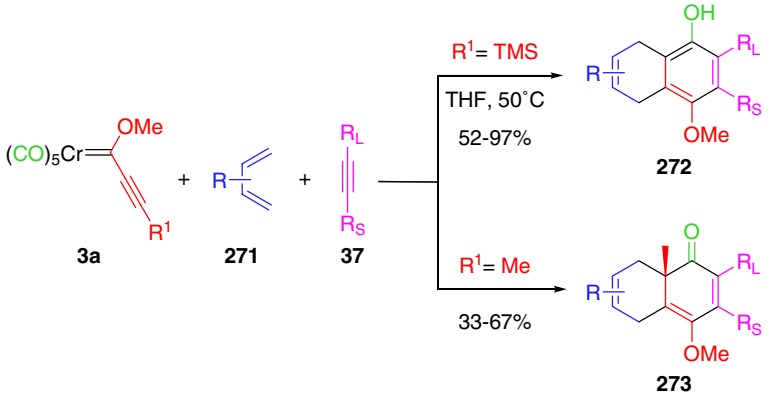
The intramolecular [2 + 2 + 1 + 1] annulation reaction (Section 2.3.1) can be coupled with a Diels–Alder reaction in a tandem sequence [82]. Thus, the reaction of **274** with diene **275** under a CO pressure followed by warming at 110 °C produces a 62% of adduct **276**, as a mixture of TBS protected and deprotected alcohols **276a** and **276b**. The reaction may also be carried out stepwise; thus, the treatment of carbene complex **274** with diene **275** in benzene produces the Diels–Alder adduct **277** which can be isolated in 82% yield. Further warming in acetonitrile under a CO atmosphere causes the [2 + 2 + 1 + 1] cyclization step to afford **276** (Scheme 50).

7.3. Tandem isocyanide insertion/Diels–Alder cycloaddition

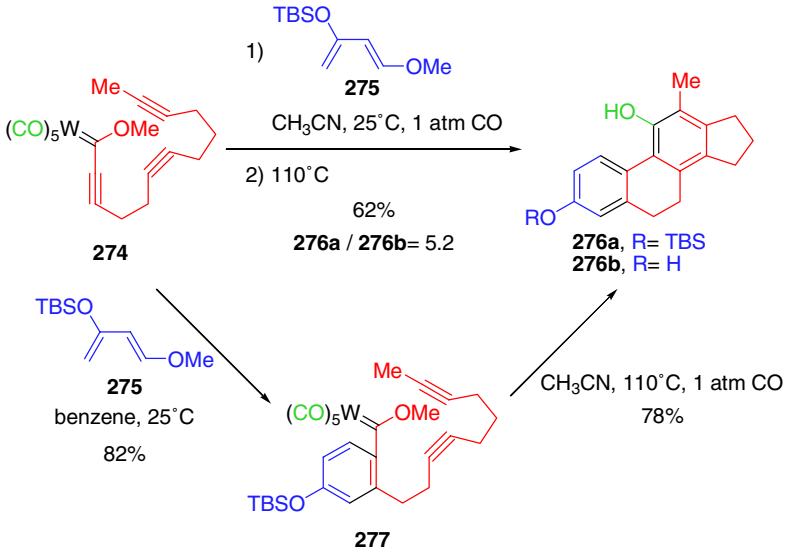
Tandem reactions consisting of an isocyanide insertion followed by a Diels–Alder cycloaddition are achieved when mixing chromium alkenyl FCCs **2c** with isocyanides **278** in the presence of maleic anhydride to form amino-ethoxycyclohexadienes **279** in moderate to good yields. These compounds can be easily oxidized in air to phthalic anhydride derivatives **280** (Scheme 51) [65b].

7.4. Isobenzofuran cyclization/Diels–Alder cycloaddition and related processes

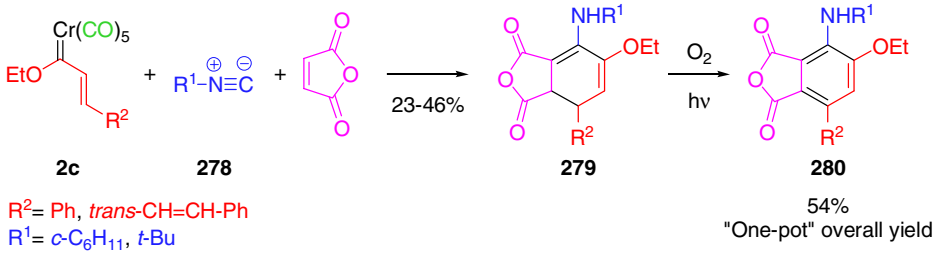
The coupling of Fischer carbene complexes **1e** with conjugated enyne-aldehydes or ketones **281** is initiated by an alkyne insertion followed by ring closure to form furan enol ethers **282** which are hydrolyzed to their ketone derivatives **283** in good yields [83] (Scheme 52). Similar transformations, including just two components, also happen with arylacetylene aldehydes or ketones **284** (X = —CH=CH—) to form isobenzofurans [84] **286** and with enyne-hydrazones **289** which lead to 1-dimethylaminopyrrols [85] **291**. However, for furyl- and thiophene-acetylene aldehydes **284** (X = O, S), three-component products furano[2,3-*c*]-pyran-3-one **288** (X = O) and thieno[2,3-*c*]-pyran-3-one **288** (X = S), both



Scheme 49. Tandem Diels–Alder cycloaddition/Dötz benzannulation reactions.



Scheme 50. Tandem Diels–Alder cycloaddition/double intramolecular two-alkyne annulation.



Scheme 51. Tandem isocyanide insertion/Diels–Alder cycloaddition.

of which incorporate a carbonyl ligand, are obtained in good yields [86].

Three-component cascade reactions can be achieved by mixing carbene complex **1e** with enyne-aldehyde or enyne-ketone **284** in the presence of dimethyl fumarate or just with enyne-aldehydes **284** (R = H) in the presence of dimethyl acetylendicarboxylate to form the isobenzofuran cyclization/Diels–Alder adducts **292** or the aromatized compound **293**, respectively, in moderate to excellent yields [84] (Scheme 53).

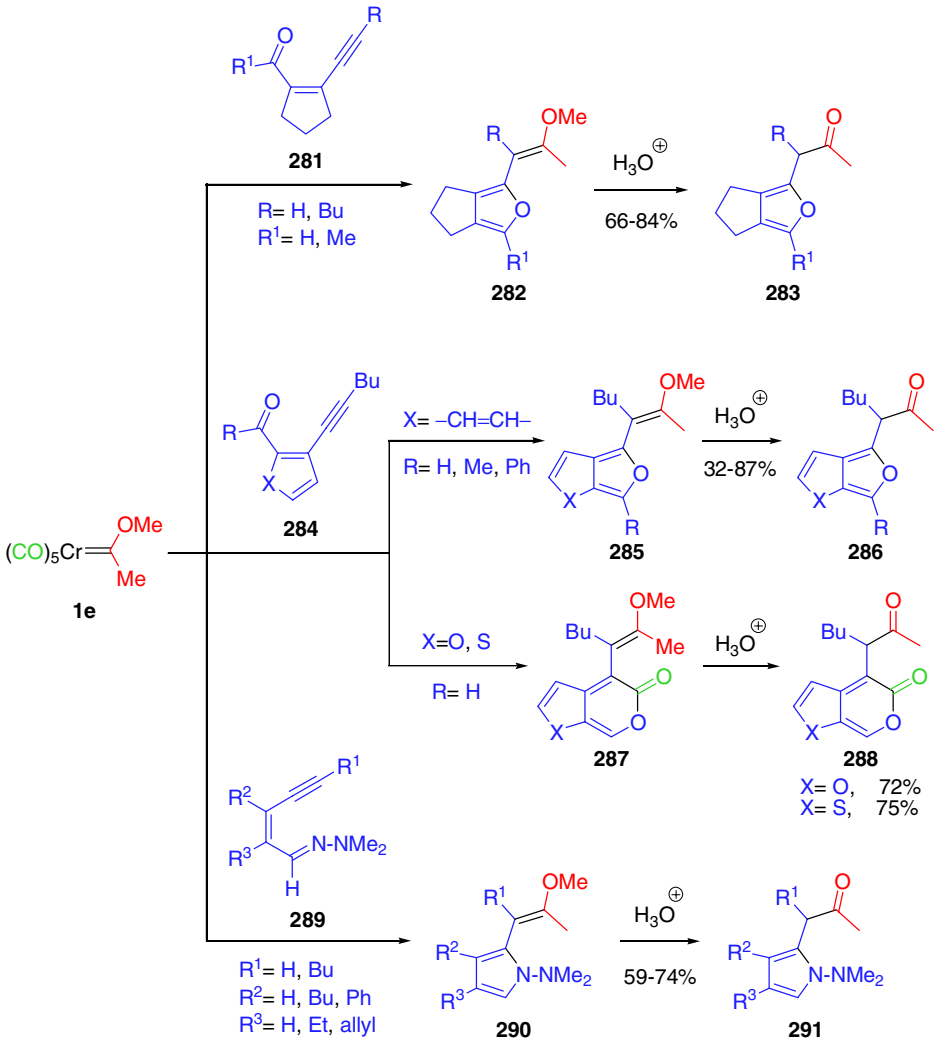
The intramolecular Diels–Alder version of this tandem reaction has allowed the formation of the steroid ring systems [87] **298** or the tetracyclic frameworks [88] **296** in moderate to good yields, when coupling carbene complexes **295** or **297** with 2-ethynylbenzaldehyde **294** (Scheme 53).

The coupling of γ,δ-unsaturated alkenyl carbene complexes **299** with acetylene-aldehydes **300** leads to the cyclization/intramolecular Diels–Alder adduct **301** or to the tetracyclic compound [85,89] **302**, in good yields. The outcome of the reaction depends on the substituent in the position 5 of the heterocyclic ring (R^1); when R^1 is an electron-withdrawing group, like the methoxycarbonyl group, adduct **301** is the major product; when R^1 is a methyl group or a hydrogen, the major product is the four-component cycloadduct **302**, which is the result of the spontaneous intramolecular Diels–Alder reaction on a furano- or thienopyranone (**288**-type) structure (Scheme 54).

More recently, a two-component coupling between FCC and *o*-alkynylbenzamides [90] and a novel synthesis of isoquinolines by an isobenzofuran cyclization/nitrile Diels–Alder [91] tandem reaction have been reported. Finally, a one-pot reaction, related to this chemistry, which involves the sequential coupling of three components, has been presented; the last step of the sequence is a [8 + 2]-cycloaddition [92] between dienylisobenzofurans **303** and DMAD that leads to the 11-oxabicyclo[6.2.1]undecane ring system **304** in moderate to good yields (Scheme 54).

7.5. Domino reactions promoted by nucleophile addition to alkynyl carbene complexes

In several cases, two or more equivalents of Fischer carbene complexes are involved in MCRs through cascade processes, as pointed out below.



Scheme 52. Isobenzofuran cyclization and related processes.

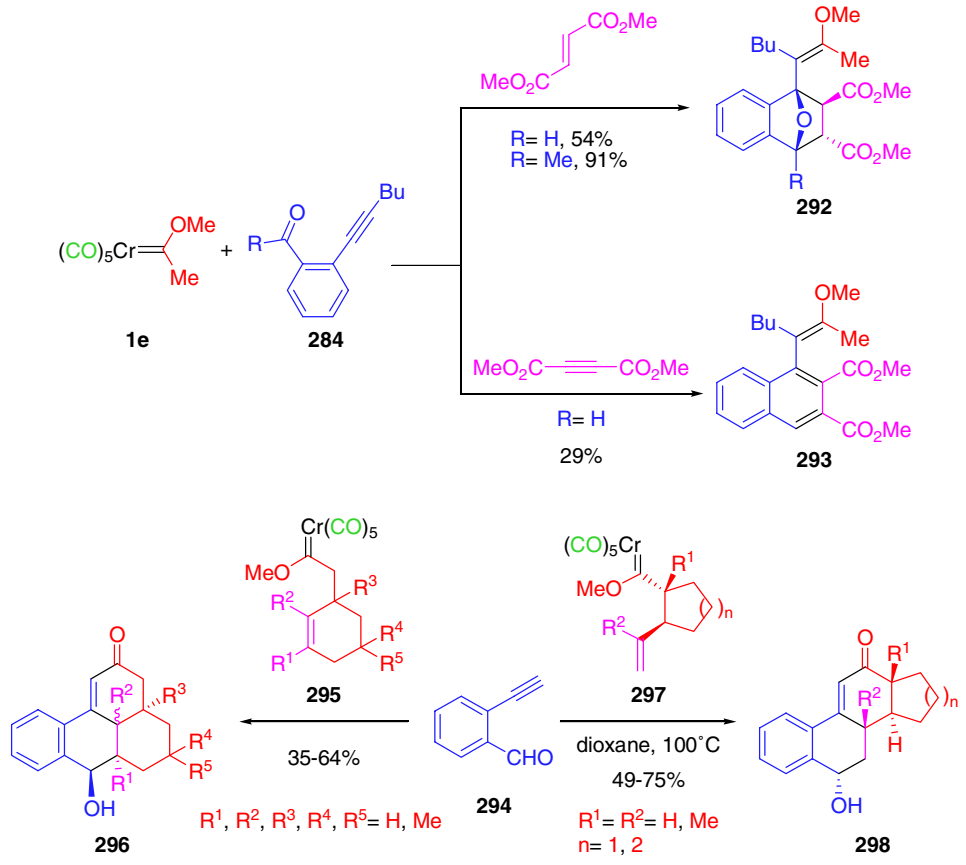
7.5.1. Cascade reactions initiated by a nucleophile addition to the carbene carbon

The addition of organometallic species to alkynylcarbene complexes **3** produces new carbene complexes by three-component reactions which involve two units of the starting carbene complex. Thus, chromium or tungsten alkoxy(phenylethynyl)carbene complexes **3** react with aryl lithium derivatives to give, after hydrolysis, a mixture of regioisomeric cyclopentenylidene complexes **305** and **306**, in variable ratios which depend on the reaction conditions (Scheme 55) [93]. On the other hand, the addition of diethylzinc to tungsten methoxy(4-methylphenyl)ethynylcarbene complex leads, after protonation, to cyclopentenylidene complex **307**, analogous to **305**, in moderate yield [94]. Complex **G**, generated by the addition of the organometallic species to the carbene carbon followed by a 1,2-shift of the metal moiety, was proposed to be an intermediate towards the final products. The formation of products **305** (and **307**) or their regioisomers **306** could be explained in terms of a 1,4- versus a 1,2-addition (which should be followed by a 1,3-metal migration) of **G** to a second equivalent of the alkynyl complex.

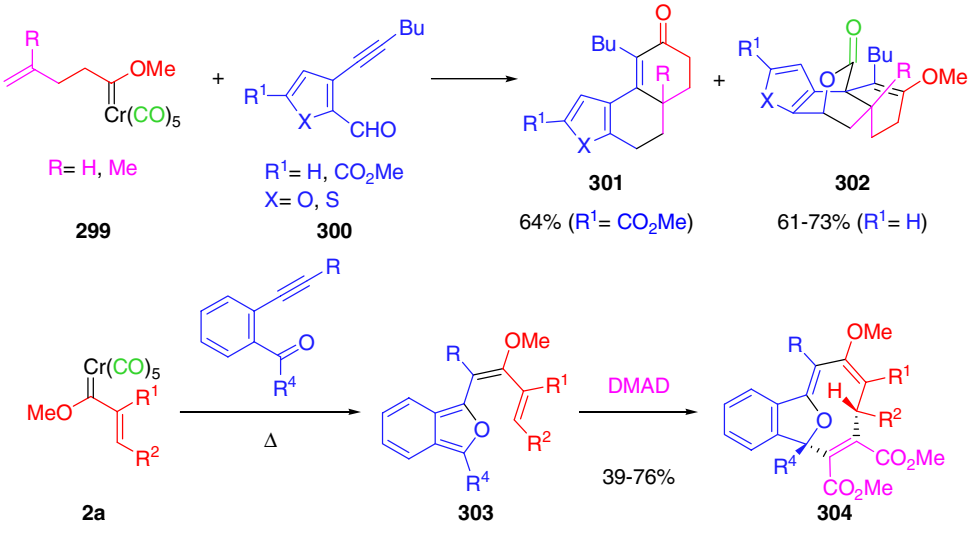
7.5.2. Cascade reactions initiated by a nucleophile addition to position 4

(1-Phenylpropynyl)carbene complexes **3c** react, under mild conditions, with alkenyl imidates **308** or cyclic imidates **312** to give, respectively, biscarbene complexes **311** and **315** (Scheme 56) [95]. In the reaction with alkenyl imidates **308**, the initially formed iminiun carbonyltungstates **309** readily undergo a cyclization to the dihydropyridyl carbene complexes **310**. These compounds, unlike those generated in the reaction with alkenyl imines [96,97], evolve to the final products **311**, in moderate rates, by a [2 + 2] cycloaddition between the electron-rich C=C(OEt)N bond and another equivalent of the alkynylcarbene complex **3c**.

On the other hand, the addition of five- or six-membered cyclic imidates **312** to alkynylcarbene complexes

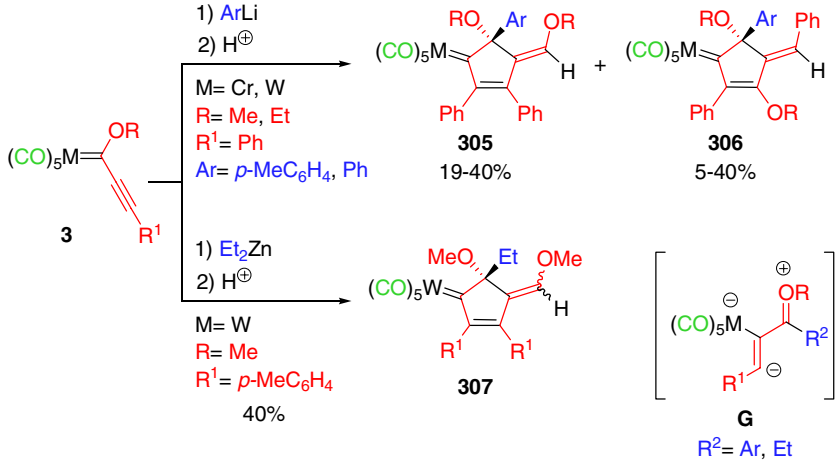


Scheme 53. Inter- or intramolecular isobenzofuran cyclization/Diels–Alder cycloaddition.

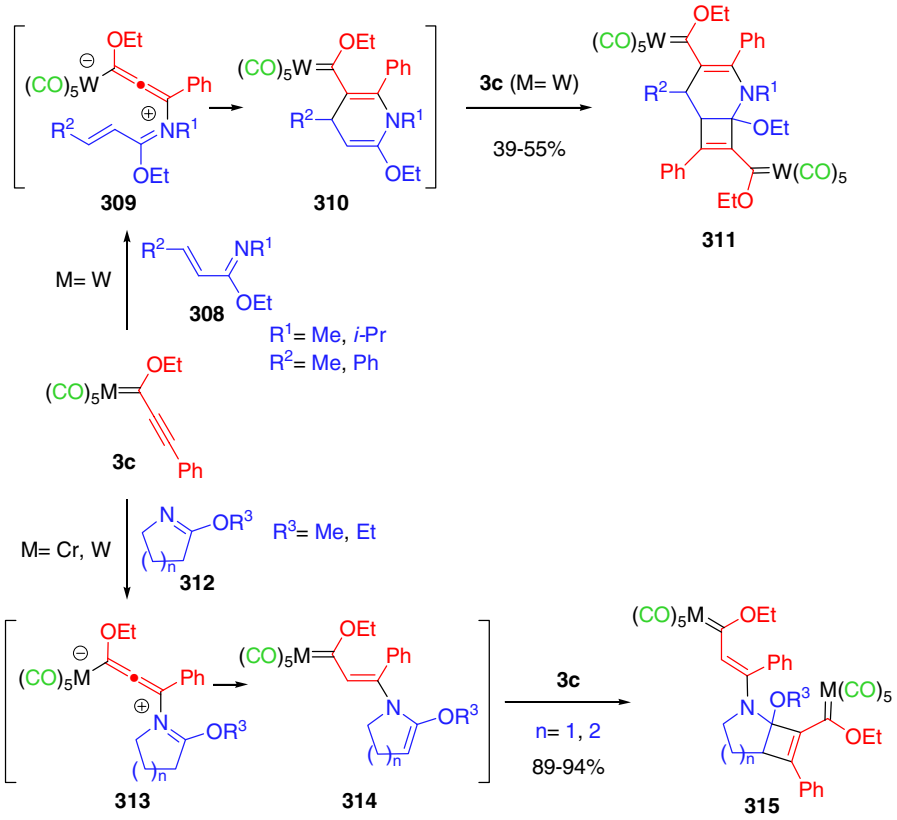


Scheme 54. Other cascade sequences involving FCCs and acetylene aldehydes.

3c generates the iminium carbonylmetallates **313** which, through a spontaneous 1,5-hydrogen shift, lead to enamine derivatives **314**. These species bear an electron-rich olefin, analogous to that in the above described compounds **310**, and experience a [2 + 2] cycloaddition with another equivalent of the carbene complex **3c** to form biscarbene complexes **315** in excellent yields. However, the reaction of seven- and eight-membered cyclic imidates **312** with complexes **3c** affords compounds **314** in good yields but no bimetallic derivatives **315**.



Scheme 55. Cascade reactions initiated by a nucleophile addition to the carbene carbon.



Scheme 56. Cascade reactions initiated by a nucleophile addition to position 4.

7.6. Domino reactions from alkenyl substituted alkynylcarbene complexes

A general method to carry out cascade reactions is the formation of 1-metalla-1,3,5-hexatrienes from alkenyl substituted alkynylcarbene complexes [98]. These species evolve, through a π-cyclization, to reactive cyclopentadienes that can undergo a cycloaddition with another molecule of the alkynylcarbene.

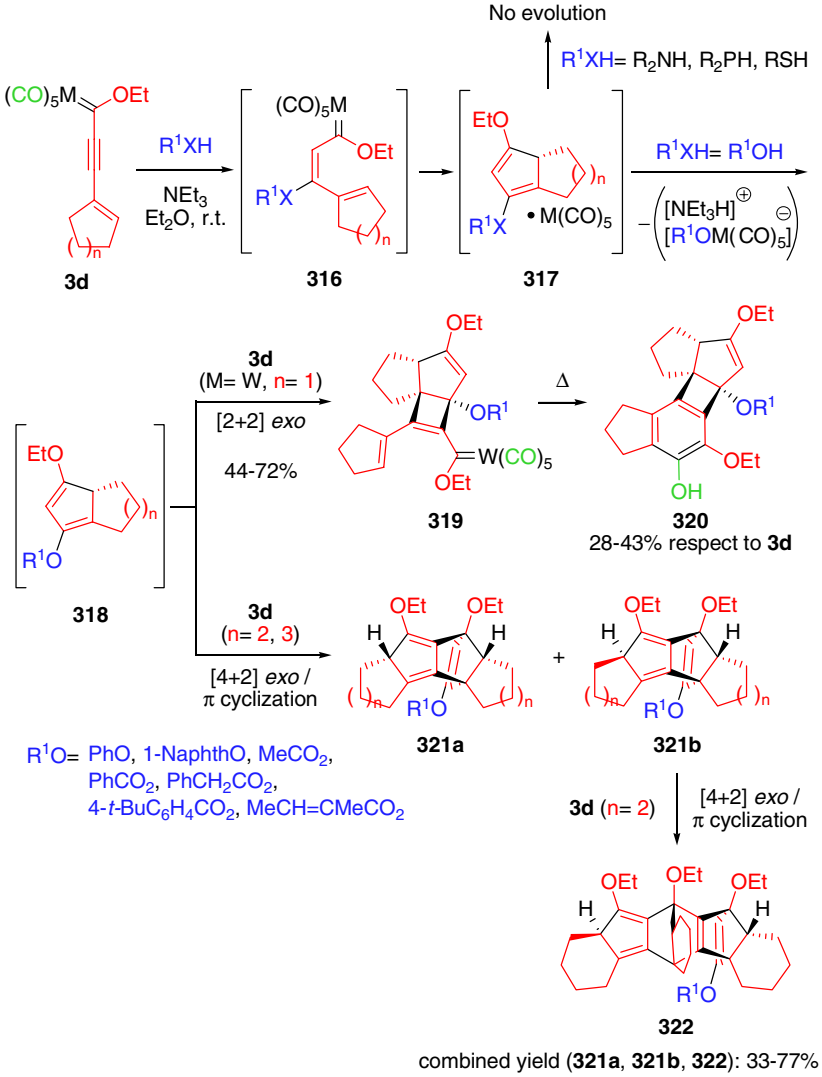
In this way, addition of protic nucleophiles R^1XH, catalyzed by NEt_3, to cycloalkenylethynyl carbene complexes **3d** affords 4-heterosubstituted-1-metalla-1,3,5-hexatrienes **316** which spontaneously cyclize to metalla-cyclopentadienes **317**. While these complexes are

stable when nitrogen, phosphorus or sulfur nucleophiles are used [99], the corresponding oxy compounds obtained with oxygen nucleophiles (phenols and carboxylic acids) could not be isolated and the metal moiety was transferred to another molecule of the oxygen nucleophile to form an oxy(pentacarbonyl)metallate. The highly reactive metal-free cyclopentadienes **318** thus generated were found to trigger cascade reactions with one or two equivalents of the starting carbene complex **3d** (Scheme 57) [100].

In particular, addition of oxygen nucleophiles to tungsten [2-(1-cyclopentenyl)ethynyl]-carbene complex **3d** (M = W, $n = 1$) furnished cyclobutenylcarbene complexes **319**, in moderate to good yields, by a regio- and *exo* stereoselective [2 + 2] cycloaddition between the vinyl ester (or ether), derived from the nucleophile, and the triple bond of a second molecule of the carbene complex **3d** (M = W, $n = 1$). Thermolysis of the cyclobutenyl carbene complexes **319** leads to pentacyclic compounds **320** in moderate rates through a benzannulation reaction, which involves a CO insertion followed by cyclization.

On the other hand, when the same oxygen nucleophiles are added to [2-(1-cyclohexenyl)ethynyl]- or [2-(1-cycloheptenyl)ethynyl]-carbene complexes **3d**, a tandem reaction, that involves an *exo* stereoselective [4 + 2] cycloaddition between the cyclopentadiene **318** and a second equivalent of the carbene complex followed by a π-cyclization, gives a mixture of pentacyclic compounds **321a** and **321b**. Cycloadducts **321b** afford octacyclic derivatives **322** by another tandem sequence *exo* [4 + 2] cycloaddition/π-cyclization when [(2-cyclohexenyl)ethynyl]carbene complex was used. The combined yields of cycloadducts **321a**, **321b**, and **322** are moderate to good, although the product ratio depends on the molar ratio of starting reagents.

The strong influence of the ring size of the starting carbene complex on the completely different courses of

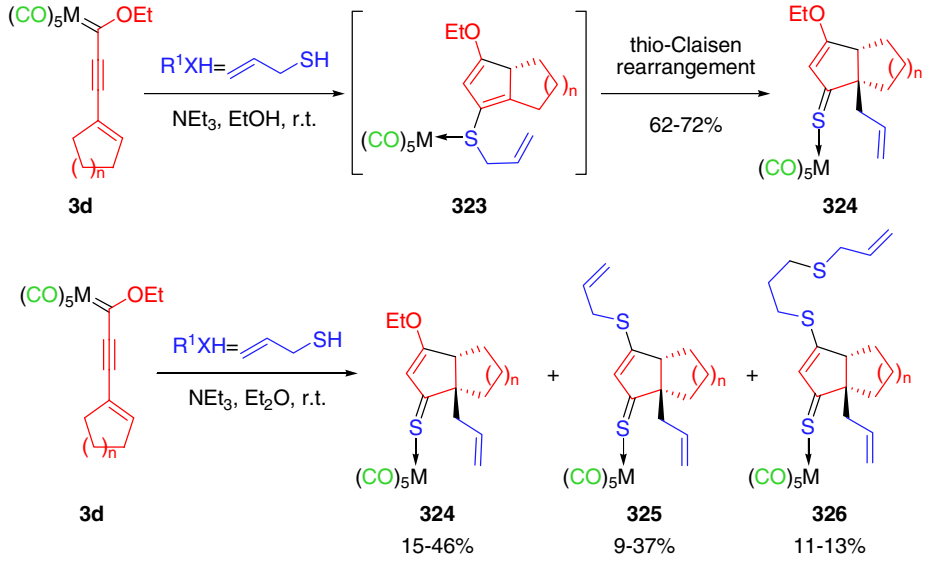


Scheme 57. MCRs in metallahexatrienes generated by nucleophilic addition to FCCs **3d**.

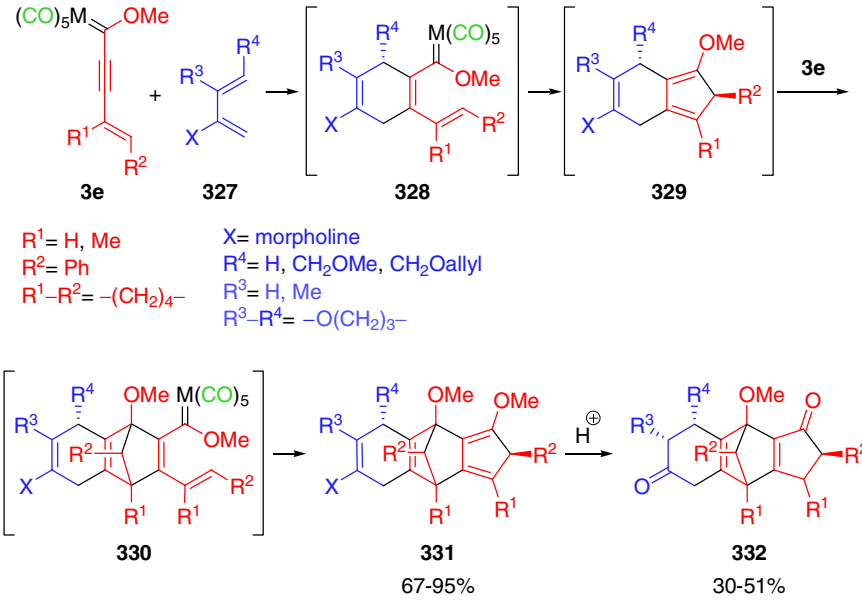
cascade processes shown in Scheme 57 can be attributed to the higher ring strain of the cyclopentadiene species **318**. Experimental evidence of intermediate species **318** was provided by competition tests, in which the oxygen nucleophile was added to a mixture of alkynylcarbene complexes to afford a mixture of cross-cycloadducts.

In connection with those studies, a marked influence of the solvent choice has been observed in the reaction with carbene complexes **3d**, when allylthiols were used as nucleophiles for the generation of the metallahexatriene (Scheme 58). If the reaction is performed in protic solvents like ethanol, the initially formed cyclobutadienes **323** undergo a thio-Claisen rearrangement to give cyclopentene-1-thione complexes **324** in good yields; however, if aprotic solvents such as diethyl ether are used, variable amounts of additional multi-component products **325** and **326** are obtained as result of the incorporation of two or three allylthiol units, respectively [99c].

Barluenga's research group was the first one to describe several MCRs based on 1-metalla-1,3,5-hexatrienes. Their initial findings were based on the in situ formation of 1-metalla-1,3,5-hexatrienes **328** by a [4 + 2] cycloaddition between 1-metallahexa-1,5-dien-3-ynes **3e** and 2-morpholine-1,3-butadienes **327** which afforded, under very mild conditions, three-component polycyclic scaffolds **331**, in good to excellent yields. (Scheme 59) [101]. Adducts **331**, when solids, were iso-



Scheme 58. MCRs in metallahexatrienes generated by allylthiol addition to FCCs **3d**.



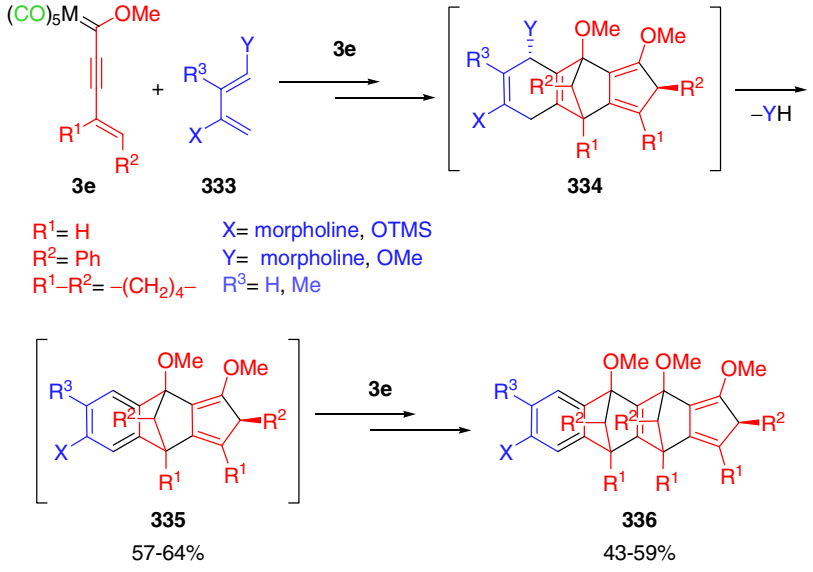
Scheme 59. Double tandem [4 + 2] cycloaddition/cyclopentannulation reaction.

lated by crystallization in cold hexane; otherwise, they could not be properly isolated due to partial hydrolysis of the enamine in the column chromathography. In these cases, the crude reaction mixture was treated with aqueous acid giving diketones **332** in moderate yields.

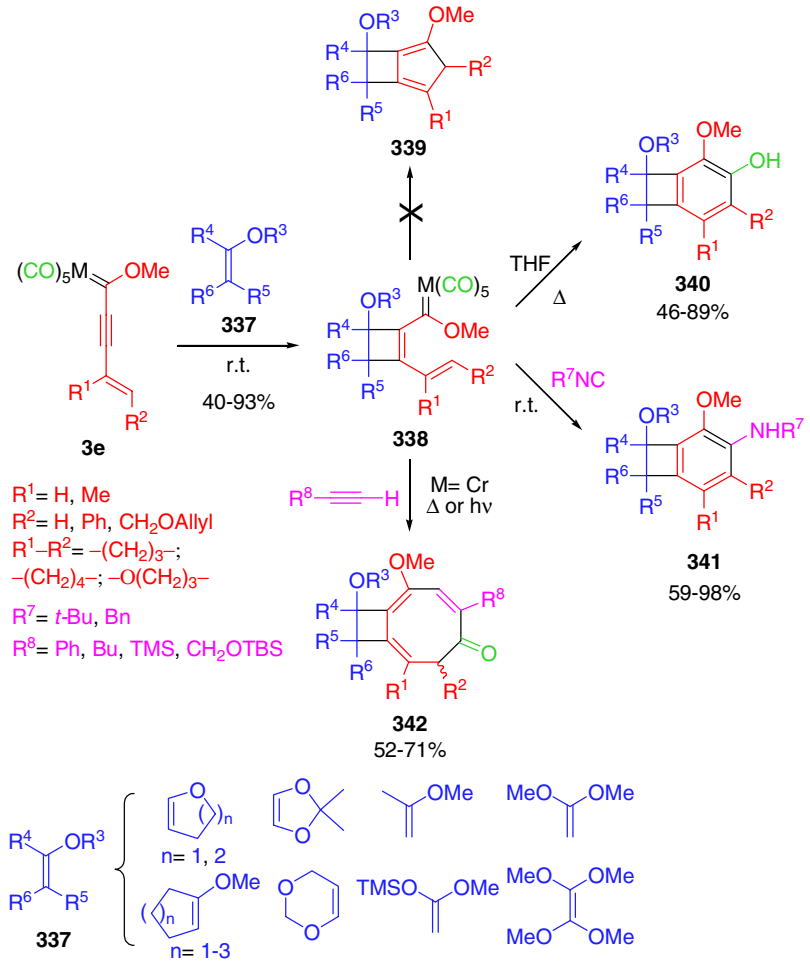
Such unexpected products **331** were the result of the consecutive incorporation of two units of the starting carbene complex by a double tandem [4 + 2] cycloaddition/cyclopentannulation cascade process. As shown in the scheme, the initial [4 + 2] cycloaddition would produce 1-metalla-1,3,5-trienes **328** which readily undergo a π-cyclization to give cyclopentadienes **329**. It had been already observed that the cyclopentadienes obtained in the reaction between arylethynylcarbene complexes and several types of dienes (including **327**) lead to fluorene derivatives [102]. However, cyclopentadienes **329** appeared to be more reactive than 2-heterosubstituted-1,3-butadienes **327** towards the starting carbene complex **3e**, and therefore underwent a second [4 + 2] cycloaddition to tricyclic 1-metalla-1,3,5-hexatrienes **330** intermediates, which was followed by a cyclopentannulation to finally form tetracyclic cyclobutadienes **331**. In this MCR, six new carbon–carbon bonds and five new stereogenic centers were created in a single step and in a stereoselective fashion. The final dienes **331** did not undergo a third cycloaddition even when warmed up in the presence of an excess of starting carbene complex. Probably, both faces of the diene moiety were blocked by the first carbocycle formed in the reaction and by the substituent R^2 in the cyclopentadiene. Thus, the approach of a third molecule of starting carbene complex **3e** was avoided.

2-Heterosubstituted-1,3-butadienes **333**, bearing a morpholine or methoxy substituent in the fourth position of the diene, provided an access to four-component hexacyclic scaffolds **336** through a triple tandem [4 + 2] cycloaddition/cyclopentannulation cascade process with the incorporation of three units of the starting carbene complex **3e** (Scheme 60) [103]. In this case, dienes **334**, which are analogous to **331** as both of them incorporate two equivalents of carbene complex, were not detected since they evolve, by a morpholine or methanol elimination, to afford cyclopentadienes **335** in moderate yields if just two equivalents of the starting carbene complex were used. However, the bottom face of dienes **335** is accessible to other reagents and therefore when the reaction was performed with three equivalents of the starting carbene complex **3e**, four-component compounds **336** were synthesized in moderate yields, by a third tandem [4 + 2] cycloaddition/cyclopentannulation sequence. This four-component cascade reaction involved the creation of nine carbon–carbon bonds and seven stereogenic centers in a stereoselective manner. The structure of the final adducts **336**, where the diene moiety is blocked as in **331**, inhibits the approach of another component; consequently, the addition of a fourth equivalent of carbene complex **3e** has never been observed.

An alternative approach to 1-metalla-1,3,5-hexatrienes was provided by the [2 + 2] cycloaddition of alkynyl carbene complexes **3e** with enol ethers **337**. This reaction, performed at room temperature, led, in moderate to good yields, to compounds **338**, which were unreactive at room temperature (Scheme 61). However, heating these metallatrienes under refluxing THF gave three-component *o*-methoxyphenols **340** in a completely regioselective fashion instead of the expected two-component cyclopentadienes [104] **339**. Furthermore, phenols **340** were obtained in moderate to good overall



Scheme 60. Triple tandem [4 + 2] cycloaddition/cyclopentannulation reaction.



Scheme 61. Reactions of metallahexatrienes generated by [2 + 2] cycloaddtion to alkynyl FCCs **3e**.

yields through a sequential MCR without isolation of cycloadducts **338**, just by removal of the excess enol ether and further heating in THF.

The formation of phenols **340** involves a CO insertion followed by cyclization and can be assumed to be a variation of the Dötz reaction that affords *p*-methoxyphenols. The different behavior observed for complexes **338** bearing a cyclobutene ring and those generated by a [4 + 2] cycloaddition or Michael addition can be explained in terms of their geometries. The proposed cyclopentannulation mechanism requires a nucleophilic attack of the terminal double bond of the metallatriene to the carbene carbon. In the case of metallatrienes **338**, this interaction cannot be achieved due to the large angles existing between the substituents of the cyclobutene ring. However, metallatrienes **338** react at room temperature with isocyanides furnishing *o*-methoxyaniline derivatives **341** in a regioselective manner and in good to excellent yields [105].

On the other hand, the unusual reactivity of metallatrienes **338** was shown in their reaction with acetylenes. Thermal and photochemical reactions of complexes **338** with terminal alkynes give, in a regioselective fashion, cyclooctatrienones **342** in moderate to good yields [106] These three-component processes can be also considered as related to the Dötz reaction since both an alkyne and CO ligand are inserted. In this case, the additional double bond present in the starting metallatriene complexes partakes in the electrocyclic ring closure affording eight-membered carbocycles. Cycloadducts **342** could also be synthesized in a one-pot sequential four-component cascade process from alkenyl-substituted alkynyl carbene complexes **3e** in slightly lower yields compared to those obtained in stepwise reactions. The construction of adducts **342** can be explained by a mechanism that involves the sequential insertion of the acetylene and a CO ligand, as in the Dötz reaction, affording a trienyl ketene complex intermediate. This species, due to the geometric restraints caused by the presence of the cyclobutene ring, undergoes an eight-electron electrocyclic ring closure, instead of the expected six-electron electrocyclization to give, after demetallation, the final products.

As pointed out before, when the inner double bond of metallahexatrienes is part of a six-membered ring, dou-

ble and triple tandem [4 + 2]-cycloaddition/cyclopentannulation sequences were observed. However, if it is part of a four-membered ring, such sequences do not occur, although these compounds are able to insert other molecules or ligands, such as CO, isocyanides or alkynes. The intermediate situation, where the inner double bond of metallahexatrienes is part of a five-membered ring, has been examined more recently.

The starting metallatrienes may be accessed by [3 + 2] cycloadditions. In this way, alkenyl-substituted alkynyl carbene complexes **3e** were reacted with nitrones **343** at room temperature to give metallatrienes **344**, which contain a heterocyclic five-membered ring, in very good yields and in a completely regio- and chemoselective fashion (Scheme 62) [107]. Most of these cycloadducts **344** are stable and can be isolated. Their treatment with isocyanides at room temperature afforded 2,3-dihydro-1,2-benzisoxazoles **345** in moderate to good yields, through an annulation reaction. Cycloadducts **345** can also be formed without isolation of the metallahexatriene in comparable yields to the stepwise process. Moreover, [3 + 2] cycloadditions can be achieved with trimethylsilyldiazomethane to afford metallahexatrienes **346** that could not be isolated, but were stable enough to be handled in solution. Thus, when treated with *tert*-butyl isocyanide, indazole derivatives **347** were prepared as single regioisomers, in good yields.

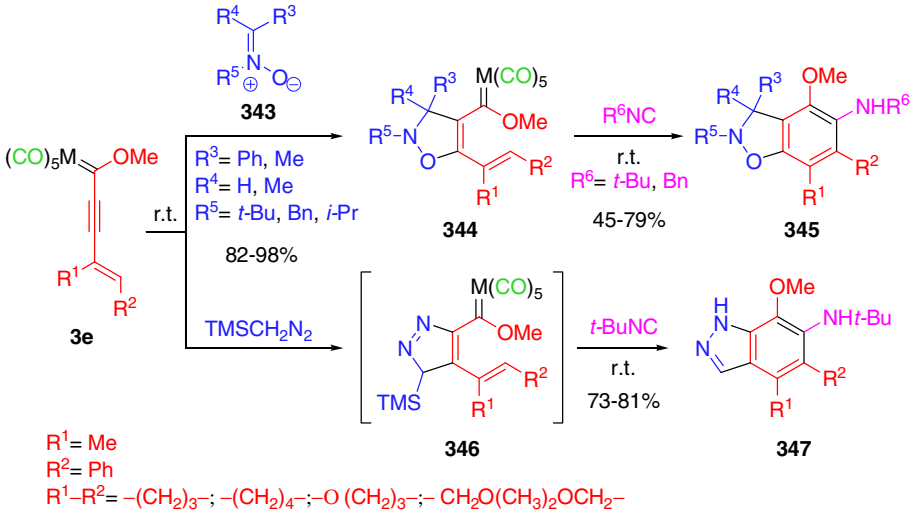
7.7. [2 + 2 + 1]/[2 + 1] Tandem cycloaddition reactions of alkynyl FCCs with strained and sterically hindered bicyclic olefins

The cyclopropanation of olefins is probably the more intensely studied reaction involving Fischer carbene complexes, as outlined in Section 1, and different conditions have been established to cyclopropanate electron-rich, electron-deficient and neutral olefins. However, when strained bicyclic olefins such as norbornene derivatives **348** were treated with Fischer alkynyl carbene complexes **3a** an unexpected behavior was found: the main products **350** incorporated two units of norbornene derivative, the carbene ligand and a carbonyl ligand with an unprecedented manner of reactivity of the alkynyl carbene complex, through the carbene carbon and both acethylenic carbons, that was also remarkable. In fact, under the reaction conditions four simple components were converted into a complex structure **350** in a single operation by the creation of five new σ carbon–carbon bonds that led to the concomitant formation of two new rings: cyclopentenone and cyclopropane moieties (Scheme 63) [108].

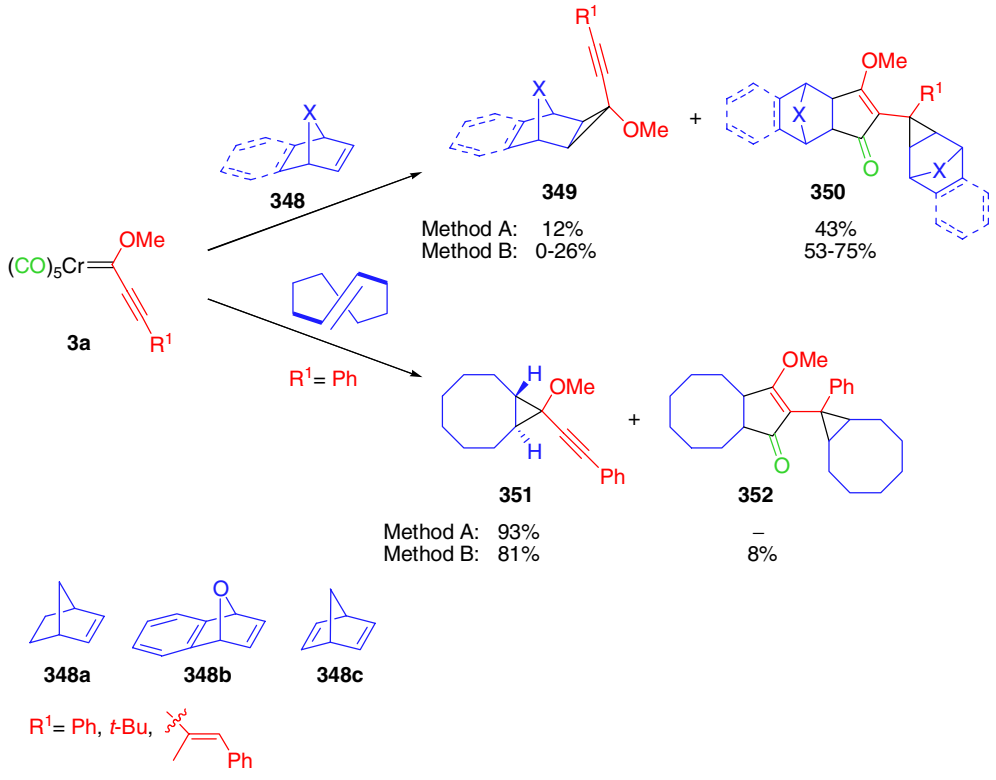
The reaction was carried out in toluene at 110 °C (method A) and the expected cyclopropanes **349** were obtained as minor products; however, the performance of the reaction with slow addition of the carbene complex to the bicyclic olefin in refluxing toluene and under CO atmosphere (method B) diminished or inhibited the direct cyclopropanation as a side reaction. Usually, the combined reaction yields range from moderate to good.

The structural assignment of the main adducts **350** was confirmed by an X-ray diffraction of the major diastereomer of adduct **350** (R^1 = Ph, olefine = **348a**).

The reaction tolerated different patterns of alkyne substitution. On the other hand, regarding the alkene component and having in mind that norbornene exhibits a large strain energy, other strained olefins such as (*E*)-cyclooctene were also tested. However, the reaction of carbene complex **3a** (R^1 = Ph) with (*E*)-cyclooctene following method A conditions resulted in the direct cyclopropanation of the double bond, while a 10% of the four-component cycloadduct **352** was obtained under method B reaction conditions (Scheme 63). These results



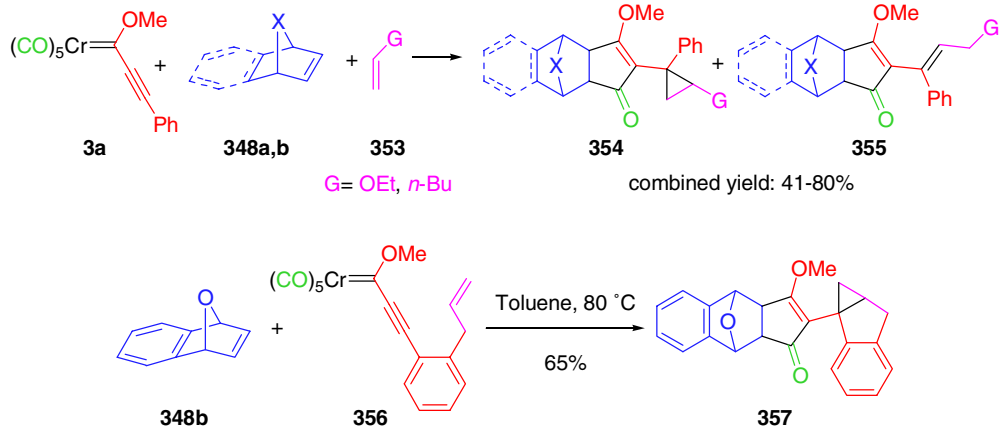
Scheme 62. Reactions of metallahexatrienes generated by [2 + 2] cycloaddtion to alkynyl FCCs **3e**.



Scheme 63. [2 + 2 + 1]/[2 + 1] Cycloaddition reactions of FCCs **3a** with bicyclic olefins.

pointed out that, in addition to the ring strain, steric hindrance seemed to play an important role and may be required for the reaction to proceed in acceptable yields. In fact, the reaction also takes place with bicyclic alkenes **348b,c** which, as norbornene, are strained and sterically hindered.

As two units of norbornene derivative were incorporated into the final product, we decided to check if the carbene moiety was able to selectively discriminate between two different olefins. To explore this option, carbene **3a** (R^1 = Ph) was treated with bicyclic olefins **348a** or **348b** in the presence of an excess of electron-rich or non-activated terminal olefins **353**; cyclopropanes **354** and conjugated dienes **355** were isolated in moderate to good combined yields (Scheme 64). Compounds **354** are the result of the cyclopropanation of **353** with a non-stabilized carbene complex and were obtained as a mixture of diastereomers, while only one, arising from a cyclopropane rearrangement of **354**, was detected for **355**. These results proved that carbene complex **3a** (R^1 = Ph) can effectively discriminate between two olefins: a strained bicyclic alkene **348** which forms a cyclo-



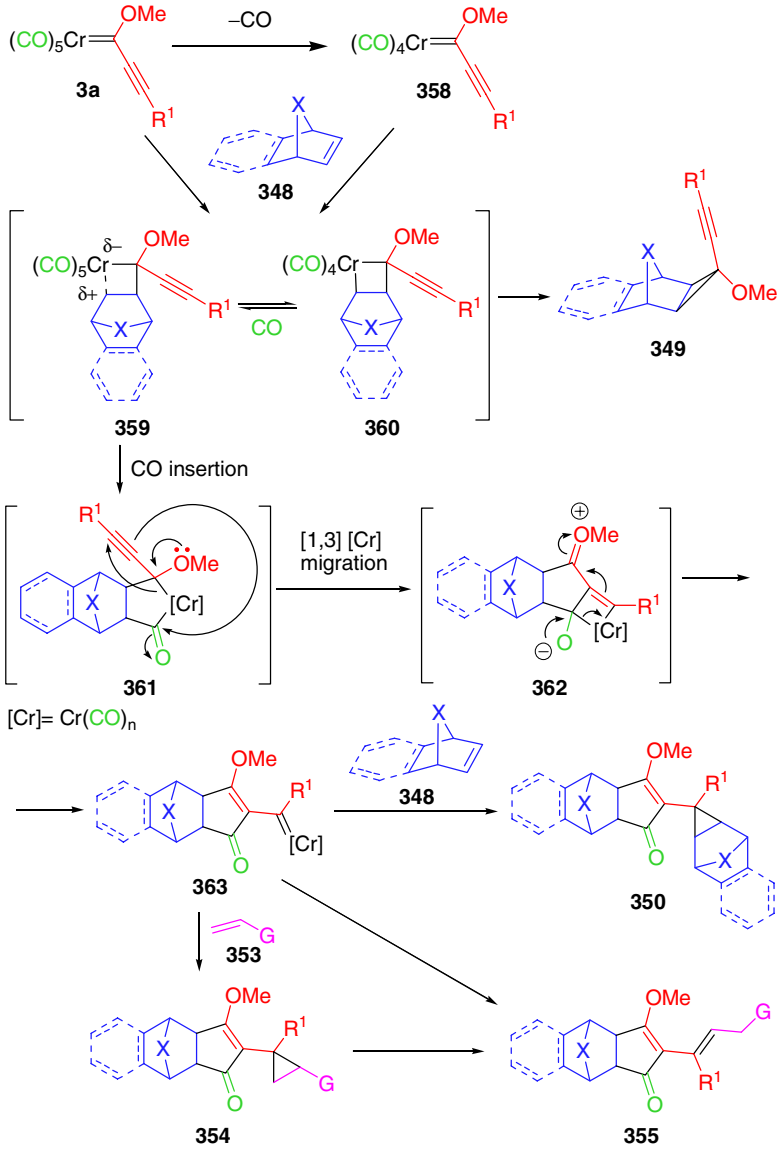
Scheme 64. Selective olefine discrimination and intramolecular version of the [2 + 2 + 1]/[2 + 1] cycloaddition reaction.

pentenone ring and a terminal alkene **353** that is cyclopropanated.

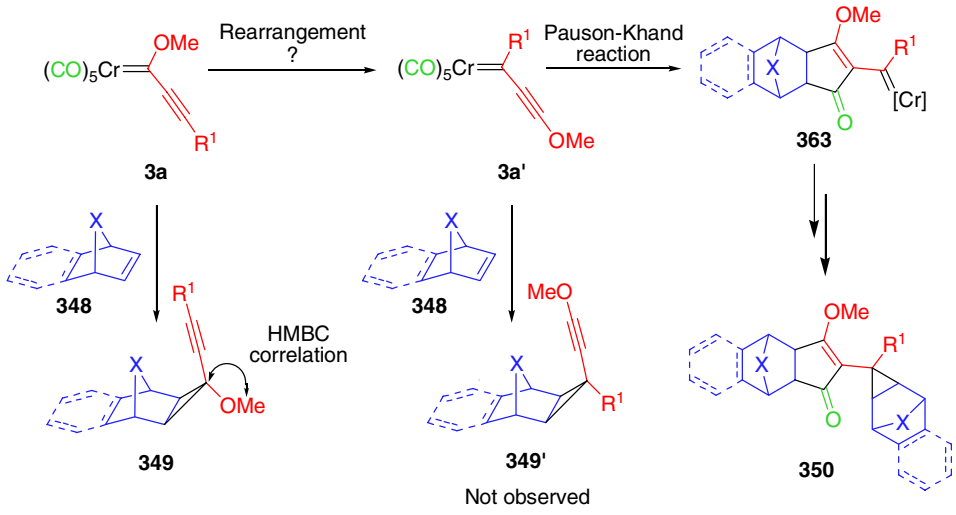
An intramolecular version of this reaction could be achieved by treating bicyclic olefin **348b** with alkynyl carbene **356**, bearing an allylic moiety. Cycloadduct **357**, was isolated in a 65% yield as a 1.5:1 diastereomeric mixture (Scheme 64).

The proposed mechanism is initiated by a CO ligand removal from carbene complexes **3a**, thus generating a tetracarbonyl species **358**; bicyclic olefins **348** will probably add to **3a** or **358** in a 1,2-fashion or by a [2 + 2]-cycloaddition leading, respectively, to the dipolar addition product **359** or metallacyclobutane **360**, which may be in equilibrium (Scheme 65). Intermediate **360** may evolve to the formation of cyclopropanes **349**, being this pathway enhanced in the absence of CO (method A); however, when the reaction is carried out in the presence of CO (method B), an alternative route is highly preferred. Then, a CO insertion should take place in metallacyclobutane **360**, or most probably in **359** for steric reasons, that should be followed by a 1,3-metal migration [109] promoted by the electron pair of the methoxy group of **361**. The resulting metallacyclobutane **362** evolves by forming a non-stabilized carbene species **363**, which in fact bears a captodative moiety and would account for the formation of compounds **350**, **354** and **355** in the final steps. Therefore, the complete sequence can be labeled as a tandem [2 + 2 + 1]/[2 + 1] cyclization.

An alternative mechanism based on the initial rearrangement of carbene complexes **3a** followed by a Pauson–Khand-type [2 + 2 + 1] cyclization might also



Scheme 65. Proposed mechanism for the [2 + 2 + 1]/[2 + 1] cycloaddition reaction of FCCs **3a** with bicyclic olefins.



Scheme 66. Alternative pathway for the [2 + 2 + 1]/[2 + 1] cycloaddition reaction with bicyclic olefins.

explain the formation of intermediate **363** (Scheme 66). However, the participation of the rearranged carbene **3a′** in the reaction may be discarded as cyclopropanes **349′**, which should have been formed from rearranged carbenes **3a′**, have not been detected. Moreover, a very clear signal in the HMBC spectra between the methoxy group and the quaternary carbon of the cyclopropane ring corroborates the proposed structure for cyclopropanes **349** and appears to rule out this alternative mechanism.

8. Summary and outlook

The versatility of Fischer carbene complexes in synthetic organic chemistry as well as their ability to participate in multi-component reactions have been disclosed along these lines. Examples where up to five components react in a multi-component sequence to create up to nine carbon–carbon bonds or to lead to the formation of up to seven stereogenic centers have been pointed out, what shows the undisputable synthetic potential of FCCs.

It is also clear that, even though it is not in its infancy and many transformations have been perfectly rationalized, the chemistry of FCCs still astonishes its practitioners. One of the main reasons to such often unexpected behavior relies on the possibility of a dual evolution of the reaction intermediates: the incorporation or not of carbonyl ligands along the reaction pathway, which opens the door to the selective formation of different kinds of compounds.

However, many goals still remain unreached, such as for example, the development of asymmetric versions of some of the processes displayed in the review, which could be achieved using chiral ligands or an external source of chirality. There is also a real need to perform those transformations by involving just a catalytic role of the metal, because the employment of stoichiometric amounts of metal constitutes, for sure, the major drawback of FCCs chemistry. But, besides that, group 6 Fischer carbene complexes allow the synthetic chemist the creation of organic or organometallic skeletons which are not accessible by other routes, and thus will undoubtedly remain as valuable reagents for a long time.

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