Multi-component reactions involving group 6 Fischer carbene complexes: a source of inspiration for future catalytic transformations

Manuel Ángel Fernández-Rodríguez,*, Patricia García-García and Enrique Aguilar

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The ability of heteroatom stabilized Fischer carbene complexes (FCCs) to participate in multicomponent reactions (MCRs) has become a characteristic of such organometallics, particularly of chromium carbenes. This feature article updates the main results in this field during the last lustrum, highlighting the ability of FCCs for the construction of densely functionalized frameworks, mainly through the successive incorporation of unsaturated moieties (alkynes, CO ligands,…) in a sequential manner. Examples where up to seven components are coupled will be presented.

1. Introduction, scope and limitations of this feature article

The considerable improvement achieved in the areas of bio-, organo- and metal-catalysis over the last decade leads to consider that the state of the art of organic synthesis is deeply submerged in an age of catalysis.1 Even though, the role of heteroatom stabilized Fischer carbene complexes (FCCs) as stoichiometric synthetic intermediates in organic chemistry remains as a valuable tool;2,3 this is mainly due to the fact that they provide a variety of reactivity patterns, usually not amenable (so far) for alternative catalytic processes, that allow the construction of highly functionalized structures in a regio- and stereoselective manner. On the other hand, metal carbene complexes take part as catalysts (for instance, as catalysts for olefin metathesis) in numerous synthetic reactions, although such participation is scarce for heteroatom stabilized carbene complexes. Taking into account these facts, it is expected that the chemistry of FCCs may also serve as a source of inspiration for future catalytic transformations. An example of such an

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Patricia García-García gained a PhD from the Universidad de Oviedo in 2007 under the supervision of Prof. J. Barluenga and Prof. E. Aguilar working on new reactions of Fischer carbene complexes and the development of catalytic processes. Then she moved to Germany as a postdoctoral researcher where she worked in the field of organocatalysis with Prof. B. List in the Max-Planck Institut für Kohlenforschung (2007–2009). In September 2009 she joined the group of Prof. R. Sarz, where she is currently a Juan de la Cierva fellow. Her current research interests focus on organometallic chemistry and catalysis, including transition metal catalysis and organocatalysis.

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strength, through backbonding. As a consequence, chromium counterparts has been attributed to the differences in metal–CO FCCs are more prone to carbonyl insertion than their tungsten insertion of a CO ligand; indeed, the fact that chromium chromium– and tungsten–carbene complexes towards the point it is worth to mention the different behaviour of a source of two or more components in those reactions: the other hand, it should be remarked that FCCs very often act as reactions involving the addition of dielectrophiles or dinucleophiles to the appropriate FCC will not be discussed. On the contrary, reactions with alkynes with the advantages of enhancing the activity, selectivity and yield, and leading to demetallated products. For instance, cyclobutenone obtained in 98% yield in the reaction of with tolane in an ionic liquid, while only a 27% yield of the cyclobutenone chromium tricarbonyl complex is isolated when the reaction is performed in di-<i>n</i>-butyl ether under similar reaction conditions.8 Silyl vinyl ketenes may cyclise to form the silyl group have been suggested as the key factors impeding the a source of two or more components in those reactions: the carbene ligand and one or several carbonyl ligands. In this point it is worth to mention the different behaviour of chromium– and tungsten–carbene complexes towards the insertion of a CO ligand; indeed, the fact that chromium FCCs are more prone to carbonyl insertion than their tungsten counterparts has been attributed to the differences in metal–CO strength, through backbonding.7 As a consequence, chromium and tungsten FCCs may offer either similar or complementary modes of reactivity, depending on their counterparts and on the reaction conditions.

As in our previous review, we will also present intramolecular reactions in which only one or two starting materials are used, provided that the corresponding intermolecular version, including three or more components, has also been developed.

For a better understanding of the connectivity of each reaction and the origin of each fragment, we have decided to use colour schemes as we did in our previous review. This colour code will also apply to the intramolecular versions to state each component of the MCR. Along the article we will cover the chemistry of FCCs represented in Fig. 1. Other specific carbene complexes will be numbered as they appear.

2. Reactions initiated by alkyne insertion

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2.1.1. Reactions with bulky acetylenes. Imidazolium ionic liquid 4 can serve as an interesting alternative solvent for performing reactions of FCCs with alkynes with the advantages of enhancing the activity, selectivity and yield, and leading to demetallated products. For instance, cyclobutenone obtained in 98% yield in the reaction of with tolane in an ionic liquid, while only a 27% yield of the cyclobutenone chromium tricarbonyl complex is isolated when the reaction is performed in di-<i>n</i>-butyl ether under similar reaction conditions.8 Silyl vinyl ketenes may cyclise to form the silyl group have been suggested as the key factors impeding the a source of two or more components in those reactions: the carbene ligand and one or several carbonyl ligands. In this point it is worth to mention the different behaviour of chromium– and tungsten–carbene complexes towards the insertion of a CO ligand; indeed, the fact that chromium FCCs are more prone to carbonyl insertion than their tungsten counterparts has been attributed to the differences in metal–CO strength, through backbonding.7 As a consequence, chromium and tungsten FCCs may offer either similar or complementary modes of reactivity, depending on their counterparts and on the reaction conditions.

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corresponding Dötz adducts or provide cyclopentenones by a [4+1] reaction with diazo compounds. Interestingly, an almost 1:1 mixture of silyl-ketene and cyclobutenone has been obtained for the reaction of cyclopropyl FCC and TIPS-substituted phenyl acetylene; however, cyclobutenones have been isolated as sole reaction products when TIPS-substituted furan-2-yl or cyclopropyl acetylenes were employed (Scheme 3).

On the other hand, the photochemical [2+2] reaction of FCC with TMS-substituted alkynes affords regioisomeric 3-TMS-substituted cyclobutenones in moderate yields (Scheme 4).

1,3,5-Hexatriynes react with alkoxy alkenyl FCCs through one or two of the end triple bonds of the triyne, when they bear phenyl- or adamantyl-substituents, to yield a mixture of Dötz adducts. However, the reaction with bis(trisopropylsilyl)triyne takes place at the central alkyne unit; thus, the treatment of 18 with FCC leads to mono-benzannulated Dötz-product 19, while, against phenyl or dihydrochromenyl chromium FCCs, furans are isolated in 69–75%. The formation of furan products had been previously reported for the reaction of FCCs with alkynes, but not as major products (Scheme 5).

2.1.2 Reactions with propargylic alcohols. Recently reported solvent-free conditions have allowed to reduce the reaction time and to increase the yields of γ-butyrolactones, formed in the reaction between alkoxy FCCs and propargylic alcohols. This reaction was simultaneously developed by Kerr and Mori in the late 1990s and extended, with other alcohols or silyl ethers, to the formation of four- to seven-membered lactones (Scheme 6).

2.1.3 Reactions of 2,6-disubstituted aryl carbene complexes. The intramolecular reaction of 2,6-disubstituted 4-hydroxyaryl carbene complexes with alkynes may lead to hydrindones, naphthalenediones or spirocyclohexadienones (Scheme 7). The latter two products result from CO insertion prior to cyclization; particularly, 26 arises from spirocyclization of a vinylketene intermediate, such as I, onto the para-position of a phenol. As part of a research towards the synthesis of richardianidin-1, Wulff et al. found that the partition between the two major products 24 and 25 is a function of size of the newly formed heterocyclic ring with the greatest amount of hydrindone when a six-membered ring is formed; on the other hand, increased amounts of naphthalenedione product have been observed when five- or seven-membered heterocyclic rings are formed. The presence of the para-hydroxy group on the phenyl ring of the carbene complex does not greatly affect the outcome. Occasionally, the reaction may lead just to one product, as exemplified for the reactions of carbenes which produce spiro compound 29 and cyclobutenone 30 due to a different evolution of ketene intermediates (Scheme 7).

2.1.4 Reactions of cyclopropyl carbene complexes. The behaviour of cyclopropyl FCCs towards alkynes, leading to five- or seven-membered carbocycles, is strongly dependent on the nature of the metal moiety, as pointed out previously.
Particularly, towards ferrocenyl alkynes, ferrocenyl-substituted 2,4-cycloheptadienones are the major products of the reaction of molybdenum cyclopropyl carbene complexes (minor amounts of 2-cycloheptene-1,4-diones, hydroxy-substituted cycloheptenones, and/or 2-cyclobutenones are also isolated); on the other hand, ferrocenyl-substituted 5-hydroxy-2-cyclopentenones or 4-cyclopentene-1,3-diones are the main products when chromium cyclopropyl FCCs are employed instead (minor amounts of cyclopentenones and other compounds have also been isolated) (Scheme 8).

2.1.5 Reactions with ortho-alkynylstyrene oxides. The coupling of FCC 1c with o-alkynylstyrene epoxides affords benzoxepinones via epoxyvinylcarbene complex III, which undergoes subsequent CO insertion and cyclization. The evolution of the epoxyvinyl carbene complex intermediate III depends on the substitution pattern of 39; thus, when R = Me it affords dienone derivative 41 through intramolecular oxygen atom transfer (Scheme 9).

2.2 Reactions with enynes

2.2.1 Reactions with dienylacetylenes. Benzo[1,3]dioxolen rings have been easily annulated onto furan, thiophene and imidazole ring systems in a reaction involving the coupling of FCC 1e with either 2-alkeny-3-alkynylheteroaromatic systems or 3-alkenyl-2-alkynylheteroaromatic systems. Heteropolycycles are thus formed in good yields (Scheme 10).

2.2.2 Reactions with enediynes. The reaction of FCCs with conjugated enediynes that feature a pendant alkene group may follow two distinct pathways depending on the electronic nature of the group bonded to the non-conjugated double bond. It initially proceeds through carbene–alkyne coupling to generate an enyne–ketene intermediate which undergoes Moore cyclization to form IV. This di-radical prefers to evolve by a 6-endo cyclization to V, leading to kinetically and thermodynamically favored products. However, if R is a radical-stabilizing group a 5-exo cyclization happens leading to di-radical VI, which finally forms adduct (Scheme 11).
2.3 Multiple insertion of alkynes

2.3.1 Reactions involving transmetallation to late transition metals. The transmetallation of chromium FCCs with [Ni(cod)₂] has proved to be a useful methodology for the in situ generation of nickel(0) alkoxycarbene complexes. Interestingly, the different nature of both metals has allowed the discovery of novel reactivity patterns for carbene complexes, particularly in their reaction with alkynes. Thus, new [3+2+2] and [2+2+2+1] cyclization reactions, yielding cycloheptatrienes, have been described between these complexes and terminal alkynes. Taking advantage of this fact, Kamikawa has prepared optically pure planar chiral cycloheptatriene chromium complexes and by the diastereoselective [3+2+2] cycloaddition, employing binuclear α,β-unsaturated FCCs (Scheme 12). Further functionalization of both chromium-coordinated rings at 50 could be stereo- and chemoselectively achieved by utilizing the distinct properties of the chromium complexes. Planar chiral ferrocenyl carbene complex also has partaken in this reaction leading to the corresponding adduct as a single diastereomer in 60% yield.

On the other hand, a different pathway has been observed in the reaction of chromium carbene complexes with internal acetylenes in the presence of [Ni(cod)]₂. In this case, highly substituted cyclopentadiene derivatives 54 are generally obtained through a [2+2+1] cyclization involving the carbene ligand and two units of alkyne (Scheme 13). When non-symmetrical acetylenes are used the regioselectivity of the final product depends mainly on the electronic properties of the alkyne. Thus, unsymmetrical cycloadducts were obtained as a sole isomer in moderate yields in reactions with 1-phenyl-1-propyne. However, the use of an acetylene with an electron-withdrawing substituent 56, such as methyl phenylpropynoate, led to an equimolecular mixture of unsymmetrical and symmetrical cyclopentadienes 57 and 58, whereas regioselective formation of the symmetrical adduct 58 was achieved for methyl 2-butynoate (Scheme 13).

2.3.2 Multiple insertions in alkynyl carbene complexes. Whereas the reactions of aryl and alkenyl Fischer carbene complexes with alkynes have been extensively studied, few couplings of acetylenes with alkynyl carbenes have been reported. In this regard, Barluenga et al. have recently described that chromium alkoxy alkynyl FCCs react with symmetrical internal alkynes 59 through a multicomponent reaction that implies consecutive insertions of several acetylene units and carbonyl groups into the metal–carbon bond. Five-component adducts 60 or seven-component adducts 61 can be selectively obtained as major reaction products by controlling the reaction conditions (Scheme 14). The isolated yields are generally low, but still remarkable considering the complexity of the transformation that involves the creation of four C–C bonds, a σ Cr–C(sp²) bond and a cyclopentadienyl moiety in

Scheme 11 Reactions of 1c with diene–diynes.

Scheme 12 Nickel-catalyzed reaction of planar chiral FCCs with terminal alkynes.

Scheme 13 Nickel-catalyzed reaction of FCCs 1c with internal alkynes.

Scheme 14 Multiple alkyne insertion on FCCs 3a.
the first case and seven C–C bonds and two five-membered carbocycles in the second one.

A mechanism that explains the formation of both adducts has been proposed (Scheme 15). An initial thermal dissociation of a CO ligand would facilitate the insertion of the first molecule of acetylene to generate enynyl–carbene intermediate VII, which is stabilized by intramolecular triple bond coordination. Then a 1,4-metal rearrangement, that can alternatively be considered as the result of two consecutive [1,2] and [1,3] metal migrations, should take place to form cyclopentadienyl intermediate VIII. The subsequent insertion of a carbonyl ligand leads to the formation of acyl metallate IXa, which presents zwitterionic oxy–carbene complex IXb as a resonance structure. The insertion of another equivalent of acetylene in the carbene carbon–metal bond forms species X which in fact is a resonance structure of 60. Likewise, the consecutive insertion of two equivalents of acetylene on IX, followed by the incorporation of another CO ligand and the evolution of the formed intermediate XII through an intramolecular cyclization reaction lead to the formation of seven-component adducts 61. The chromium atom is formally oxidized from Cr(0) to Cr(II) along the global sequence of events.

According to this mechanism five-component chromate 60 is an intermediate in the formation of 61, hypothesis that was proved by transforming 60 into 61 in the presence of excess alkylene.

2.4 Reactivity of β-donor substituted alkenyl carbene complexes with alkynes

β-Donor substituted alkoxy alkenyl carbene complexes 62 (Y = OEt) undergo the consecutive incorporation of two molecules of a terminal alkylene and a carbonyl ligand, with elimination of a small molecule (secondary amine, alcohol, or thiol), to form cyclopenta[5]pyrans 63 in yields up to 96%. The final product is a bicyclic system, which results from a formal [3 + 2 + 2] cyclization. 25 The regiochemistry in the incorporation on the second alkylene unit depends on the nature of both the alkylene and the bulky group of the carbene complex. Fulvene chromium carbonyl complexes 64 have been occasionally isolated as byproducts. This sequence is not exclusive for alkoxy FCCs as the reaction of dimethylamino(2-dibenzylaminoethenyl) FCCs (62, X = NBn2, Y = NMe2) with phenylethyne (R = Ph) affords the corresponding 4-dimethylaminocyclopenta[5]pyrans (63, R = Ph, Y = NMe2) in moderate yields (28–39%) (Scheme 16).

On the other hand, chelated complexes of type 65 are the major reaction products when thiolates are employed as donor substituents (X = SR2, R1 = Me2(EtO)C–) (Scheme 16).

3. Reactions with allenes

FCCs derived from late transition metals such as nickel and rhodium have been employed by Barluenga and colleagues in multicomponent reactions with allenes. Reactions of 1,1-dimethylallene 66 with in situ generated nickel(0) alkoxy alkenyl carbene complexes XIV in acetonitrile as solvent occur to afford 1,2-dialkylidenecycloheptene derivatives 68 in a chemo-, regio- and diastereoselective manner (Scheme 17). 26

The reaction is proposed to proceed through the formation of metallacycle species XV which, in the presence of acetonitrile and favored by a Ni–acetonitrile coordination, undergoes the insertion of a second molecule of allene to give, after hydrolysis, the observed formal [3 + 2 + 2] cycloadducts 67. In contrast, and accounting for the crucial role of the Ni–NCMe interaction, reactions in toluene afford cyclopentene derivatives in a two-component process as a result of a reductive nickel elimination in intermediate XV. 27

As described above for the reaction of alkynes with nickel and chromium FCCs, the nature of the metal played a decisive role in the reactions of allenes with these complexes. Thus, chromium alkoxy alkenyl carbene complexes 69 reacted with...
1,1-disubstituted allenes 70 in the presence of a cationic Rh(I) catalyst to form cyclopentenes as a consequence of a [3+2] cycloaddition.27 However, if [Rh(cod)Cl]₂ is employed as catalyst, 1,3-dialkylidenecycloheptene derivatives 71 are exclusively and regioselectively obtained in moderate yields (Scheme 18).26 The acid hydrolysis of these [3+2+2] cycloadducts quantitatively furnished the corresponding cycloheptanones 72. On the other hand, a four-component process occurs, leading to indenone 74, when FCCs 2a are treated with 1,1-diphenylallene in the presence of either cationic or neutral Rh(I) catalysts (Scheme 18).28

The authors proposed the mechanism depicted in Scheme 19 that accounts for the formation of both multicomponent compounds. First the transmetallation of the initial chromium complexes would generate the corresponding rhodium carbenes XVII. These complexes would react with two molecules of allene: first by a [4+2] cycloaddition through the less substituted carbon–carbon double bond of the allene followed by the insertion of the second allene unit to produce metallacyclooctene species XVIII. At this point two reaction pathways are possible depending on the substitution of the allene. Thus, for 1,1-dialkylallenes a reductive elimination would take place leading to the formation of three-component adducts 72. On the other hand, when 1,1-diphenylallene is employed an ortho-metallation process may occur to generate the Rh(v) alkyl-hydride intermediate XIX which upon reductive elimination would render metallacycle species XX. These intermediates would finally undergo a CO insertion and reductive elimination to furnish the observed four-component cycloadducts 74 and would regenerate the rhodium catalyst.

4. Reactions with activated alkenes

4.1 Reactions with methylenecyclopropanes

Functionally substituted cyclopentenones 75 are obtained by a [4+1]-cocyclization of a methylenecyclopropane 76 and carbon monoxide with incorporation of the carbene ligand of chromium FCC 1d (Scheme 20).29 The formation of...
cyclopentenones 75 can be rationalized as arising from a [2 + 2]-cycloaddition of the methylenecyclopropane 76 to FCC 1d, after initial dissociation of a CO ligand, to form 5-chromaspiro[2.3]hexane XXI. With its spirocyclopropane unit in the β-position with respect to the metal, XXI can undergo a facile cyclopropymethylmetal to homoallylmetal rearrangement to give the alkylidenemetallacyclopentane XXII, which, after CO insertion followed by reductive elimination of chromium, yields 77. Finally, 77 apparently undergoes isomerization to the thermodynamically more stable product 75, as proved by labeling experiments.

On the other hand, bicyclopentylidene 78 reacts with FCCs 1f and 1h to give the corresponding spirocyclopentanones 79 and 80 in good yields as single diastereomers.

This method provides cyclopentenones with a unique substitution pattern and thus complements the [3 + 2 + 1]-co cyclization of Fischer (cyclopropylcarbene)chromium complexes and acetylenes, the Pauson–Khand reaction, and the template-assisted [2 + 3]-co cyclization of β-dialkylamino-substituted α,β-unsaturated FCCs.2

On the other hand, alkanyl FCCs 2b react with methylenecyclopropanes 81 in the presence of Ni(cod)2 leading to alkanylidenecyclopentanones 82 through a [3 + 1 + 1] cycloaddition60 (Scheme 21).

It is unclear whether Ni(cod)2 reacts primarily with the methylenecyclopropane or with the chromium carbene complex. Therefore, three possible reaction mechanisms have been proposed: the first one involves the formation of nickelacyclobutane XXIII, which is generated by the oxidative addition of methylenecyclopropane to nickel(0), and would add regioselectively to the carbon–chromium double bond while avoiding steric repulsion between a methylene group and a chromium pentacarbonyl group. The other two mechanisms assume the formation of a nickel carbene complex XIV, generated via carbene transfer reaction (Cr to Ni, see Scheme 17), which may evolve by: (a) a formal [3 + 2] cycloaddition with direct proximal C–C bond cleavage of the cyclopropane leading to nickelacyclopentane intermediate XXIV; (b) a [2 + 2] cycloaddition reaction between the carbene and methylene groups to nickelacyclobutane intermediate XXV, followed by ring expansion to the same intermediate XXIV.

In any case, subsequent CO insertion and reductive elimination would lead to the final products.

4.2 Reactions with ketene acetal s

The reaction of ketene acetal s with Fischer alkanyl carbene complexes is a well-known procedure that leads to [2 + 2] cycloadducts. The analogous reactions with Fischer alkyl or aryl carbenes have been reported to proceed through a 1,2 nucleophilic addition to finally furnish butyrolactones,31 although the reaction can be directed to the formation of cyclopropanone acetal s when FCCs derived from secondary alcohols are employed.32 More recently, the corresponding reaction of disubstituted ketene acetal s 84 with alkox y alk enyl FCCs 83 has been studied. In this case, the formation of the lactones coming from the 1,2-addition is completely suppressed and, therefore, 4-aryl-3,4-dihydrocumarines 85 are obtained in moderate to good yields by performing the reaction in THF at 90 °C in a sealed tube33 (Scheme 22). A detailed investigation of the reaction conditions has allowed the development of a one-pot protocol via the formation of esters XXVI (see Scheme 22). The synthesis of dihydrocumarines 85 involves two equivalents of the alkynyl carbene, one equivalent of acet al and one CO ligand in an unprecedented four-component reaction. Moreover, when this procedure is applied to ketene acetal s 87 derived from five- and six-membered lactones, phenols 88 are selectively obtained as single diastereomers and do not evolve to the expected dihydrocumarines under any condition tested. Having in mind all these observations, the authors have proposed the following mechanism (Scheme 22).

Finally, alkynes 89 would react with a second molecule of the alkox y alk enyl carbene complex in a Dötz reaction to furnish the observed phenols or...
dihydrocumarines, after subsequent lactonization when possible. Indeed, when the reaction is conducted at room temperature alkynes are isolated as a 5:1 mixture of isomers; they can be converted to the observed phenols upon heating in the presence of the alkenyl carbene complex, thus demonstrating the role of alkynes as intermediates in the process.

On the other hand, FCC reacts with silyl ketene acetal in the presence of t-BuOK to give anhydride upon cleavage of both oxygen–silicon atoms, elimination of the ethoxy group, insertion of CO and elimination of W(CO) (Scheme 23).

5. MCRs by insertions in metallates

Several MCRs of FCCs are based on the formation of metallates, which are able to trigger additional inter- or intramolecular insertions. In this regard, the addition of two equivalents of α-unsubstituted lithiosulfinyl carbanions to tungsten alkoxy aryl, alkenyl or alkynyl carbene complexes provide allyl sulfoxides in moderate yields. The process would be initiated by the formation of tungstate intermediates by nucleophilic addition of the first unit of carbanion to the carbene carbon. These species would evolve to non-stabilized carbene complexes that may react with a second molecule of carbanion to produce a new metallate intermediate. A final β-elimination would afford the observed allyl sulfoxides (Scheme 24).

On the other hand, Barluenga et al. recently described two new three-component carbocyclization processes based on the different evolution of a common chromate intermediate initially formed by the addition of methyl ketone lithium enolates to β-substituted methoxy alkyl carbene complexes. In both MCRs two equivalents of the enolate and one equivalent of the carbene complex are involved. The outcome of the reaction depends on the metal of the FCC, on the structure of the enolate and on the presence or absence of a strong coordinating solvent in the reaction medium. Thus, reactions of aryl, alkyl or alkynyl methyl ketone lithium enolates with the above mentioned chromium and tungsten complexes in diethyl ether afford 1,3-cyclopentanediol derivatives in a formal [2+2+1] three-component process (Scheme 25). Notably, independently of the lithium enolate employed, the reactions selectively proceed to the formation of [3+2] cycloadducts in moderate yields and with total diastereoselection in a coordinating medium (by using PMDTA as additive).

Tentative mechanistic proposals for all the cyclization pathways were reported by the authors and are illustrated in Scheme 26. A 1,2-addition of the lithium enolate to the methoxy alkyl carbene complex would occur to form metallate intermediates that could be in equilibrium with coming from a 1,3-migration of the metal moiety. In the presence of coordinating solvents or additives, intermediates may directly evolve to cyclopentenol.
derivatives. However, when the reactions were conducted in diethyl ether, the lithium ion could coordinate to the oxygen atoms of the intermediates thus increasing their rigidity and the electrophilic character of the carbonyl group and, therefore, favoring the addition of a second molecule of lithium enolate to give the intermediates or XXXIIb. Then a nucleophilic intramolecular attack of the allyl metallate on species XXXIIb would lead to five-membered cycloadducts XXXV that after hydrolysis would produce the observed adducts. Alternatively, in reactions with enolates derived from methyl alkynyl ketones, intermediates XXXVI could undergo a cyclization reaction induced by a metal migration to give, after elimination, decoordination of the metal and subsequent hydrolysis, 3-cyclopentenol derivatives. On the other hand, in the case of reactions of tungsten carbenes with the enolate derived from acetone the evolution would be from intermediates XXXIIa through a cyclization triggered by a 1,2-metal migration to furnish seven-membered carbocycles XXXIV. Further elimination and decoordination of the metal moiety followed by hydrolysis would render the observed cycloheptenediols. The authors claim that the latter reactions evolve to seven-membered cycloadducts due to the greater steric hindrance of tungsten moiety that favors intermediates XXXIIa over XXXIIb.

Recently, a thorough study of a previously reported diastereoselective three-, four- or five-component formal [2+2+1] and [2+2+1+1] cycloadditions of FCCs 1b, lithium enolates 101 and allyl magnesium bromide 102 that lead to pentasubstituted cyclopentanols 103/104 or tetrasubstituted cyclohexane-1,4-diols 105/106 has been accomplished by Barluenga’s group (Scheme 27). The scope of the reactions has been found to be broad although a few exceptions leading to tetrasubstituted cyclopentanols and pentasubstituted cyclohexanols have been also reported.

All these processes involve the generation of acyl chromate species XXXVIII and XXXIX (see Scheme 27) through sequential addition of a ketone or ester lithium enolate and allyl magnesium bromide to chromium FCCs 1b. Lithium alkylpentacarbonylchromates XXXVIII and XXXIX act as key intermediates which further evolved through intramolecular reactions, such as addition to carbonyl groups and alkene or CO insertions.

Besides the few exceptions above mentioned, new MCRs are observed when cyclopentanone lithium enolate is used (Scheme 28). Thus, 1-alkylcyclopentanol could be selectively obtained in good yield and as a single diastereoisomer when the enolate is generated with cyclopentanone and LDA. The structure of this three component compound differs from the expected cycloadduct in that the final ring closing has not occurred. However, a mixture of the 1-alkylcyclopentanol and four-component butyrolactone is formed when the reaction is performed by generating the enolate from 1-trimethylsilyloxycyclopentene and BuLi. On the other hand, the behaviour of β-substituted lithium enolates was found to be different. Thus, reaction of methoxy phenyl carbene with lithium methyl isobutyrate enolate under optimized conditions provided cyclopropanol as single adduct (Scheme 28). In this regard, reactions of methoxy aryl FCCs with β-substituted ketone lithium enolates (such as 107), in the absence of allyl magnesium bromide, selectively afford...

**Scheme 27** MCRs of FCCs 1b, lithium enolates 101 and allyl magnesium bromide 102.

**Scheme 28** Different behavior of distinct lithium enolates vs. FCC 1b.

**Scheme 29** Four-component reaction leading to cyclopentanols 113.
cyclopropanol derivatives in good yields. This process is highly dependent on the reaction conditions and therefore, by varying temperatures and reaction times, CO ligand insertion may occur to furnish three-component cyclobutanone derivatives.41

Furthermore, cyclopentylchromate species XL, proposed to be intermediates in the formation of four-component cyclopentanols 113, could be trapped with several electrophiles thus proving their role as intermediates and, importantly, allowing the development of new intermolecular multicomponent processes (Scheme 29).

6. Domino reactions

6.1 Isobenzofuran cyclization/Diels–Alder cycloaddition and related processes

The scope of the three-component isobenzofuran cyclization/Diels Alder cascade sequence developed by Herndon has been extended along the last five years. Thus, chromium methoxy FCCs 1c have been coupled to enyne–aldehydes, enyne–ketones, or enyne–hydrazones in the presence of dienophiles 115 leading to aromatic carbo- or hetero-polycyclic compounds. For instance, naphthalene derivatives 116 have been formed via isoindole intermediates XLI (X = N–NMe2) employing benzaldehyde hydrazones 114 (X = N–NMe2, R3 = H) and alkynes as dienophiles 115; the enol ether functionality is readily hydrolyzed to form ketones 118.43 Under the reaction conditions, the sequence does not stop at adducts XLI. Similar tandem approaches, but using alkynyl heteroaromatic carbonyl compounds 114 (X = O), have led to the syntheses of compounds of types 117 and 118, such as nitrogen-containing heterocyclic analogues of 1-arylnaphthalene ligands,44 phenanthridine ring systems44 or isoquinoline derivatives45 (Scheme 30).

Two major strategies have been developed to carry out intramolecular versions of these reaction sequences. In one of them, the dienophile is linked to the carbene partner, as in 119. Alkenes have been used as dienophiles in most of the cases,43–46 leading to polycyclic structures such as 120 in reactions involving alkynyl carbonyl compounds 114 (X = O). Occasionally, enol ether hydrolysis, aromatization of the newly formed ring or carbonyl insertion in the oxygen bridge may take place leading to adducts such as 121, 122 or 123. Remarkably, this reaction has been the key step for a seven step total synthesis of anticancer agent antofine 124 in 23% overall yield47 (Scheme 31).

Alkenes42,48 and nitriles49 tethered to the FCC also have been employed as intramolecular dienophiles in this sequence. Thus the reaction of 114 with alkynylphenyl FCCs 125 leads to polycyclic aromatic frameworks 126 and 127 (Scheme 32). Surprisingly, the coupling of 2-alkynylbenzoyl derivatives 114 (X = O) with β-cyano chromium FCCs 128 and 130 follows the same reactivity pattern to form phenanthridine derivatives (129 and 131) although in mediocre yields, which is understandable due to the thermodynamic unfavorability of the key step. Unfortunately, phenanthridine derivatives 131 are usually obtained as mixture of compounds with different degree of unsaturation (Scheme 32).

The second strategy is based on linking the dienophile to the alkynyl carbonyl partner. This option has been scarcely developed and the only examples are depicted in Scheme 33. Thus, the double bond may be tethered to the alkynyl moiety as in 132 or to the carbonyl group as in 135. Fused ring structures with a high degree of stereoselectivity, such as 133 or 134, are isolated in the first case in yields comparable to that observed in systems where the dienophile is tethered to the FCC. On the other hand, the length of the linker has proved to be a determining factor for the intramolecular Diels–Alder reaction as it does not take place for FCCs 135 (n = 2), leading exclusively to 137, while a mixture of 136 and 137 is obtained for 135 (n = 1)44 (Scheme 33).

6.2 Domino reactions of “simple” alkynyl carbene complexes

6.2.1 [2 + 2]/[2 + 1] and [3 + 2]/[2 + 1] tandem cycloaddition reactions of alkynyl FCCs. When alkynyl FCCs 3a are heated in a sealed tube in THF at 90 °C in the presence of an excess of
2,3-dihydrofuran 138, a [2+2]/[2+1] sequence takes place producing three-component adducts 139 in moderate yields.\textsuperscript{51} The intermediacy of cyclobutenyl–carbene XLIII in the process was proved by carrying out the reaction in a stepwise fashion, with formation of XLIII at room temperature and its conversion into 139 by heating in the presence of the olefin. Interestingly, the second step of this cascade process implies the cyclopropanation of an electron-rich alkene without the use of high pressures of CO, typically required. Moreover, a related [3+2]/[2+1] tandem reaction to adducts 140 has been developed using trimethylsilyldiazomethane as 1,3-dipole and either an electron-rich or an electron-deficient olefin (138, 141) as the cyclopropanation counterpart (Scheme 34).

### 6.2.2 [2+2+1]/[2+1] tandem cycloaddition reactions of alkyln FCCs and related reactions.

Conversely, the reaction of alkyln FCCs 3a with strained and hindered olefins such as norbornene derivatives 142, follows a completely different pathway: a [2+2+1]/[2+1] sequence occurs giving rise to highly functionalized polycycles 143 that incorporate four components in an unprecedented process that implies the creation of two new rings and five $\sigma$-C–C bonds.\textsuperscript{52} A thorough study of the scope and limitations of this reaction has recently been published.\textsuperscript{53} Thus, a series of multicomponent adducts 143 were selectively or exclusively obtained in moderate to good yields when bicyclic olefins 142 and alkyln FCCs 3a were mixed in refluxing toluene under a CO atmosphere (Scheme 35).

The reaction is proposed to occur through 2-cyclopentenone-derived FCC intermediate XLV (Scheme 35), which would cyclopropane the second unit of olefin giving rise to the final products. This hypothesis opens the possibility to incorporate a different olefin as the fourth component. Notably, either electron-rich, neutral or electron-deficient olefins 143 may act as the fourth component in the reaction sequence (Scheme 36); this result also represents an evidence for the formation of XLV (Scheme 35) as reaction intermediate. The corresponding cyclopropanation products 144 are generally accompanied with variable amounts of related conjugated dienes 145. Furthermore, intramolecular trapping of the olefin moiety has also been achieved (146 to 147, Scheme 36).

Moreover, internal alkynes 59 are also suitable reagents to act as the fourth component in the reaction sequence. Therefore, indenes 148 are obtained via a [2+2+1]/[3+2] cascade when alkyln FCC 3b bearing a phenyl group in the triple bond is used, whereas cyclobutenone 149 is formed if tert-butyl substituted complex 3c is employed (Scheme 37).

### 6.2.3 Diels–Alder cycloaddition/benzannulation/rearrangement reactions.

The thermal reaction of chromium (arylethynyl)-ethoxycarbene complexes 150 with 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene 151 takes place through consecutive
Diels–Alder/benzannulation/rearrangement reactions, yielding 5,10- and 5,6-naphthofurandione derivatives \(152\) and \(153\) in almost 1:1 ratio. Under the same reaction conditions, the analogous tungsten derivatives just undergo a Diels–Alder reaction with \textit{anti} facial selectivity to \(154\), but they do not evolve\(^{54}\) (Scheme 38).

### 6.2.4 [1,5]-Hydride transfer/cyclization/Dötz benzannulation cascade process

Another possibility for initiating a cascade process in alkynyl FCCs, other than their reaction with olefins, is the intramolecular [1,5]-hydride transfer/cyclization that takes place in chromium \(\alpha\)-aminophenylalkynyl complexes \(155\) upon heating.\(^{55}\) This sequence leads to 1,2-dihydroquinolynyl carbene derivatives \(156\) that can be isolated if no other reagent is present in the reaction media. However, when the
isomerization is promoted in the presence of alkyne 157 a multicomponent cascade sequence occurs in which the initially formed carbene participates in a subsequent Dötz benzannulation with the acetylene providing 5,6-dihydrophenanthridines 158 in moderate to good yields (Scheme 39).

6.2.5 Tandem nucleophile addition/cyclization reactions. (1-Phenylpropynyl)carbene complexes 3d react, under mild conditions, with 2-alkenyl-2-oxazoline 159 to afford unusually stable Fischer biscarbene complexes 160 containing a four-, five-, and six-membered tricyclic core. As it happens when alkenyl imidates are employed as nucleophiles, the initially formed iminium carbonyl metalates XLVI undergo a cyclization to the dihydropyridyl carbene complexes XLVII. These compounds evolve to the final products by a [2+2] cycloaddition with another equivalent of 3d. Overall, the sequence can be termed as [4+2]/[2+2] cycloaddition, which is more efficient for the chromium complex; small amounts of nucleophile addition products 161 and 162 are isolated when the tungsten complex is employed (Scheme 40). Chemoselective stepwise demetalation of these complexes 160 can be efficiently carried out with pyridine N-oxide.

On the other hand, bimetallic derivatives 164, formed by reaction of 3d with five-membered cyclic imidate 163, rearrange over silica gel to form biscarbones 165 (Scheme 41).

Non-heteroatom-stabilized alkynyl-substituted carbones 166 readily react with imines 167 to furnish stable [2+2] cycloadducts 168 that can be isolated in good yields. With this simple and efficient route to access N-alkyl-2-azetine derivatives 168 in hand, their reactivity towards alkynes 157 was explored and a multicomponent process leading to 2,3-dihydropyridine oxazines 169 was found (Scheme 42). The reaction sequence involves the formation of one C–O bond and three C–C bonds and gives rise to the highly substituted final products in moderate to good yields and as
a single isomer. In the proposed mechanism the reaction is initiated by the regioselective insertion of the alkyne into the Cr—C bond, followed by CO insertion to generate metal-ketene complex XLVIII. Then, nucleophilic attack affords azetinium species XLIX, which experiences electrocyclic ring opening to I and subsequent cyclization to give product 169. Interestingly the C3—C4 bond of the azetine unit is cleaved in this reaction, which is in contrast with the C4—N cleavage-initiated usual reactivity pattern of simple azetines.

6.3 Domino reactions from alkenyl substituted alkynyl carbene complexes

1-Metallahexa-1,3,5-trienes 171 can be easily obtained from a [2 + 2] cycloaddition of alkynyl FCCs 3f with enol ethers 170. These cyclobutene-containing dienyl Fischer carbenes are stable at room temperature, but they exhibit a rich reactivity when heated and/or in the presence of other reagents. For example, phenols are obtained under refluxing THF, insertion of isocyanides to yield anilines takes place at room temperature and eight-membered carbocycles 172 are formed upon heating in the presence of acetylenes.2 This last process has been recently studied in detail and, as shown in Scheme 43, it can be performed with a variety of dienyl carbenes 171 and terminal alkynes 157 (R4 = H) to get a variety of cyclooctatrienones 172 with complete regioselectivity.60 Internal acetylenes can partake in the reaction as well, although longer times are required and lower yields are obtained. Moreover, metallabuta-1,3-trienes 171 with an indolyl substituent are also appropriate counterparts for the process. Interestingly, the whole synthetic sequence starting from vinyl-substituted alkynylchromium FCCs 3f can be performed in a one-pot fashion. This three-component process can be envisioned as an extended Dötz cyclization, as it involves the insertion of an acetylene and a CO ligand, and represents an interesting new methodology for the preparation of functionalized eight-membered carbocycles 172 (Scheme 43).

Moreover, a particular type of 1-metallahexa-1,3,5-trienes is formed upon reaction of alkynylcarbene complexes 3e with dimethylaminodiazafulvene 173 through a [6 + 2] cyclization. As it occurs for 1-metallahexa-1,3,5-trienes 171 (Scheme 43), the pyrrolo[1,2-a]imidazole derivatives LI obtained in this way react in situ with an isocyanide to furnish heteropolycycles 174 in high yields. This last process represents a cascade [6 + 2] cyclization/[5 + 1] cyclization (Scheme 44).

A similar behaviour is observed when 8-azaheptafulvenes 175 are used instead of dimethylaminodiazafulvene.62 In this case a [8 + 2] cyclization takes place initially, yielding cycloheptadiene-fused pyrrol derivatives 176 that, in a one-pot procedure, experiment isocyanide or CO insertion followed by ring closure giving rise to cycloheptaindolines 177 and 178 as an inseparable mixture of isomers (Scheme 45). It is noteworthy the high degree of substitution and functionalization of the heteropolycycles obtained in these cascade sequences using relatively simple starting materials.

On the other hand, and in contrast to what is observed for 1-metallahexa-1,3,5-trienes 171 (Scheme 43), formation of eight-membered carbocycles does not take place for derivatives 176 when they are heated in the presence of dimethyl acetylenedicarboxylate. In this case cyclopentannulation occurs prior to the insertion of the alkyne, and the intermediate cyclopentadiene LII formed in this way is then trapped as a [4 + 2] cycloadduct with the acetylene. The use of maleimide as dienophile for the trapping of the cyclopentannulation adduct has also been demonstrated (Scheme 45).
6.4 Domino reactions from alkynyl substituted alkynyl carbene complexes

Alkynyl carbene complexes 180 featuring an additional pendant triple bond partake in cascade reactions triggered by different types of cycloadditions ([4 + 2], [3 + 2], [2 + 2]) to the triple bond linked to the carbene carbon.63 As in the case of alkenyl substituted alkynyl FCCs 3f (Scheme 43), a 1-metalahexa-1,3,5-triene LIII is initially formed at room temperature upon reaction with one equivalent of alkynophile reagents 138, 182. However, a different outcome, involving the additional acetylene, is observed upon heating: an intramolecular exo alkyne insertion is proposed to give rise to polycyclic carbene complex LIV that can evolve by different ways depending on the substitution of the appended triple bond and the nature of the triggering cycloaddition. Thus, when a phenyl group is placed in the acetylene terminus of the starting dialkynyl carbene (R = Ph), oxidation of intermediate LIV to 183 takes place in the presence of an excess of nitrene 182a (R = t-Bu). Alternatively, in the presence of 2,3-dihydrofuran 138, a second [2 + 2] cycloaddition occurs after insertion of a CO ligand to furnish polycyclic compound 185. On the other hand, the use of TMS-substituted alkynes allows in most of the cases the isolation of the silylketenes 184 formed by insertion of a CO ligand in carbene complexes LIV. As pointed out before, these silyl ketenes are stable and neither its oxidation is observed in the presence of excess nitrene, nor a second [2 + 2] cycloaddition takes place in the presence of excess 2,3-dihydrofuran. Only if Danishefsky’s diene 182c is used as the cycloaddition counterpart, silylketene 184 reacts in situ with a second molecule of diene to provide phenanthrene derivative 186. A similar behaviour was observed for indolic Fischer carbene complex 181 (Scheme 46).

Conversely, the reaction with carbene complex 187, featuring a terminal alkyne, follows a different pathway when the process is initiated by the [2 + 2] cycloaddition of cyclic enol ethers 138, 182b: the carbene intermediate of type LIII (see Scheme 46) experiences in this case an endo cyclization into a seven-membered ring to intermediate carbene LV, which evolves forming benzol[7]annulene 189 after CO insertion and subsequent [2 + 2] cycloaddition (Scheme 47). However, an analogous behaviour to that of 180 is observed when the reaction is started by [3 + 2] cycloaddition with nitrones 182a, giving rise to naphthoisoxazole carboxaldehydes 188 (Scheme 47).

On the other hand, the analogous alkoxy alkynyl FCCs bearing a pendant alkene also undergo cascade processes triggered by [4 + 2], [3 + 2] or [2 + 2] cycloadditions to the triple bond to afford the corresponding 1-metalla-1,3,5-hexatriene intermediates. The subsequent evolution of these species by intramolecular cyclopropanation or olefin metathesis is controlled by the substitution of the olefin.64

7. Synthesis of mononuclear group 10 alkoxy-biscarbene complexes

A MCR leading to the synthesis of group 10 symmetrical organometallic species may be achieved by mixing two equivalents of α,β-unsaturated chromium FCCs 190 with one equivalent of [PdCl₂(MeCN)₂] or [PtCl₂(MeCN)₂] (or PtCl₂) and excess of K₂CO₃ in MeCN at rt, to provide stable mononuclear biscarbenes 191 [M = Pd, Pt] in good to excellent yields (Scheme 48). Transmetalation from an analogous tungsten(0) carbene complex occurred in lower yields under similar reaction conditions.65,66
Along this feature article, it has been shown that multi-component reactions have plentifully settled as characteristic for Fischer carbene complexes, forty years after these organometallics appeared for the first time. Among all the known roles of the metal carbonyl fragment, their ability to undergo successive insertion of unsaturated species (mainly alkynes and carbonyl ligands, but also allenes, alkenes, isocyanates...) by individual bond-forming steps acquires special relevance as it allows the one-pot synthesis of highly functionalized frameworks (such as the ones shown along this feature article), particularly for chromium carbene complexes. Since our earlier review, the scope of some processes has been completely established, new transformations and sequences (involving up to seven components) have been developed and novel synthetic techniques, such as solvent-free reactions, ionic liquids, solid support, or microwave irradiation, have been employed for the chemistry of FCCs. We then stated that “...many goals still remain unachieved, such as for example, the development of asymmetric versions of some of the processes...”. In the five years since we made such statement little has been done in that area; therefore, it still remains as a valuable reference, but nowadays FCCs also have to serve as a source of inspiration for the discovery and development of new reagents and reaction conditions capable of mimicking their behaviour although in a catalytic fashion; in this regard, their transfer to late transition metals (mainly Ni, Rh) appears undoubtedly as an opened-door but not as the only option.

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Notes and references


24 For the reaction of β-amino substituted alkylalkenyl carbene complexes with diynes, see: Y.-T. Wu, T. Labahn, A. Demeter,