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

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Received 2nd July 2010, Accepted 10th August 2010
DOI: 10.1039/c0cc02337j

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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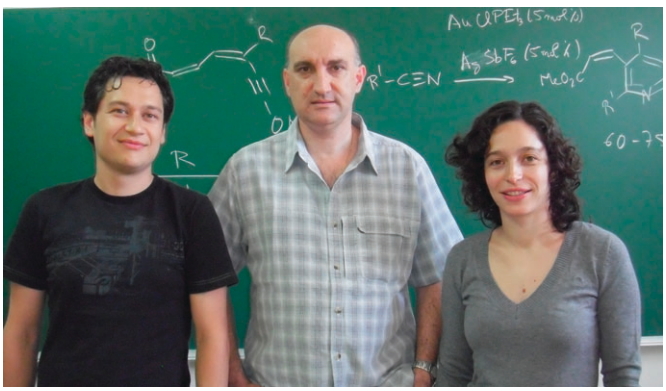
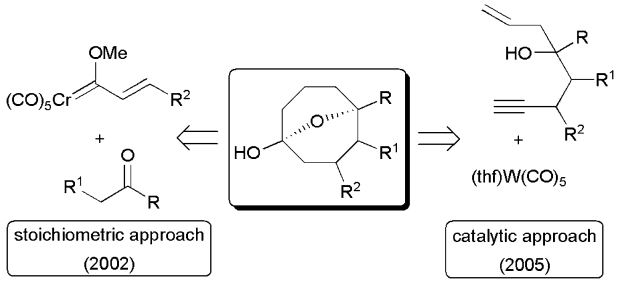


From left to right: Manuel Ángel Fernández-Rodríguez, Enrique Aguilar and Patricia García-García

Manuel Ángel Fernández-Rodríguez is a Ramón y Cajal researcher at the Universidad de Burgos. His current investigation is focused on organometallic chemistry and homogeneous catalysis. He obtained his PhD degree at the Universidad de Oviedo in 2003 under the supervision of Prof. J. Barluenga and Prof. E. Aguilar developing new processes involving Fischer carbene complexes. In 2004 he moved to Yale University, where he stayed two years for a postdoctoral position as a MEC/Fullbrigth fellow, working on cross-coupling reactions with Prof. J. F. Hartwig. He worked as a Juan de la Cierva researcher in the CSIC during the period 2006–2008 and joined the Universidad de Burgos in 2009.

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. Sanz, 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.

Enrique Aguilar received his PhD in Organic Chemistry from the Universidad de Oviedo (under the guidance of Prof. José Barluenga and Prof. Santos Fustero) in 1991. After postdoctoral research with the late Prof. A. I. Meyers at Colorado State University (1991–1994) working in natural product synthesis, he became a Researcher at Universidad de Oviedo and was promoted to Assistant Professor in 1996, and to Associate Professor in 2002. He has been a Visiting Scientist at the University of Colorado (1996, with Prof. Gary Molander). His research work is centered in the development of synthetic organic methodology, new asymmetric reactions, homogeneous catalysis and organometallic chemistry.



Scheme 1 Stoichiometric and catalytic approaches to eight-membered rings.

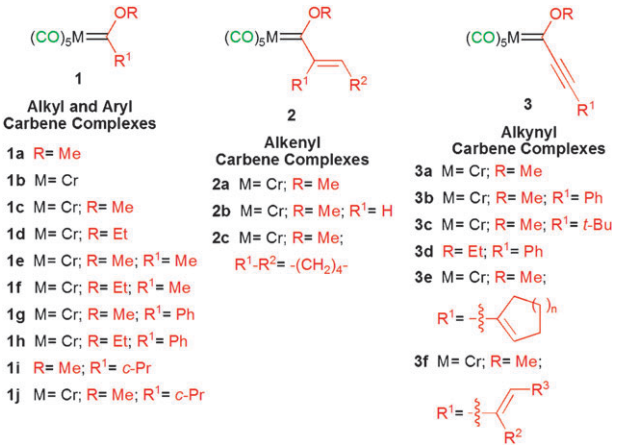


Fig. 1 Principal carbene complexes treated along the review.

evolution is depicted in Scheme 1. The synthesis of eight-membered rings was initially achieved by Barluenga *et al.* in a stoichiometric approach from alkenyl FCCs and ketone enolates;[4] a few years later, the same group developed an alternative tandem tungsten-catalyzed cycloisomerization–cyclopropanation reaction.[5] This process is one of very few examples of a catalytic reaction in which a heteroatom stabilized FCC is implied. Therefore, the door to the development of new catalytic methods based on the chemistry of FCCs (avoiding the use of large quantities of metallic species, and thus overcoming one of the main limitations of FCCs) has been opened.

In 2005 we wrote a review[2] covering the developments of group 6 FCCs as building blocks in multi-component reactions (MCRs), 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*. MCRs have received great attention not only because of their higher atom economy and their applications in combinatorial chemistry and diversity-oriented synthesis but also because they usually involve cascade reactions, which have an important role in the efficient and rapid generation of complex architectures.

This feature article has been conceived as an update to the previously mentioned review, and therefore, the same considerations and limitations will apply. For instance, reactions involving the addition of dielectrophiles or dinucleophiles to the appropriate FCC will not be discussed.[6] On the other hand, it should be remarked that FCCs very often act as 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 both 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.

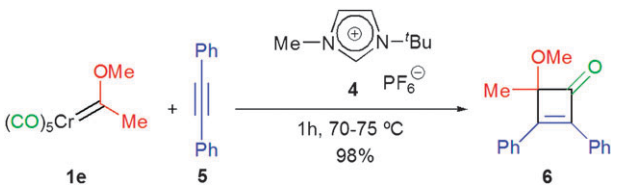
For a better understanding of the connectivity of each reaction and the origin of each fragment, we have decided to use colour schemes as we did in our previous review. This colour code will also apply to the intramolecular versions to state each component of the MCR. Along the article we will cover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

2. Reactions initiated by alkyne insertion

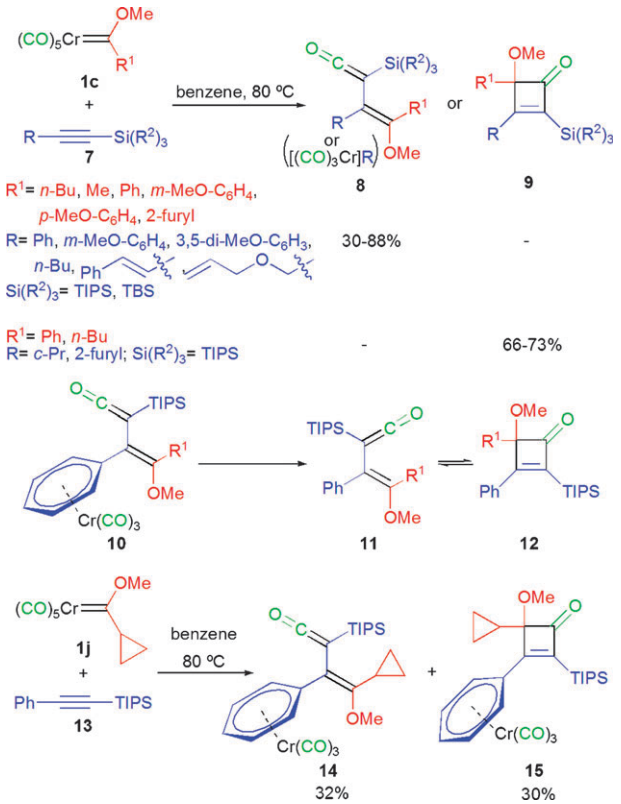
2.1. Reactions involving single alkyne insertion

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 **6** is obtained in 98% yield in the reaction of **1e** with tolane **5** in ionic liquid **4**, while only a 27% yield of the cyclobutenone chromium tricarbonyl complex is isolated when the reaction is performed in di-*n*-butyl ether under similar reaction conditions[8] (Scheme 2).

Silyl-substituted internal acetylenes **7** react thermally with chromium FCCs **1c** leading to highly stable silyl vinylketenes **8** (Scheme 3). Vinyl ketenes have been proposed as intermediates in the Dötz benzannulation reaction and, for compounds **8**, the ability of the silyl group to electronically stabilize ketenes as well as the steric congestion introduced by the bulky silyl group have been suggested as the key factors impeding the final electrocyclic ring closure. The evolution of the reaction depends on the nature of the alkyne and the FCCs. Generally, when aryl-substituted alkynes are employed the chromium moiety remains linked to the aryl group, as in **10**; its photolytic removal affords quantitatively (*E*)-silyl vinyl ketene **11**, which slowly converts to an equilibrium mixture of (*E*)-**11** and cyclobutenone **12**. Silyl vinyl ketenes may cyclise to form the



Scheme 2 MCR carried out in ionic liquid.

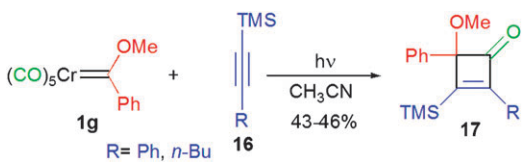


Scheme 3 Thermal reaction with silyl acetylenes.

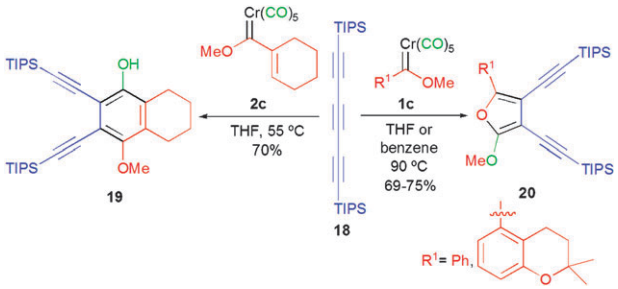
corresponding Dötz adducts or provide cyclopentenones by a [4 + 1] reaction with diazo compounds.[9] Interestingly, an almost 1 : 1 mixture of silyl-ketene **14** and cyclobutenone **15** has been obtained for the reaction of cyclopropyl FCC **1j** and TIPS-substituted phenyl acetylene **13**; however, cyclobutenones **9** have been isolated as sole reaction products when TIPS-substituted furan-2-yl or cyclopropyl acetylenes were employed[10] (Scheme 3).

On the other hand, the photochemical [2 + 2] reaction of FCC **1g** with TMS-substituted alkynes **16** affords regioisomeric 3-TMS-substituted cyclobutenones **17** in moderate yields[10] (Scheme 4).

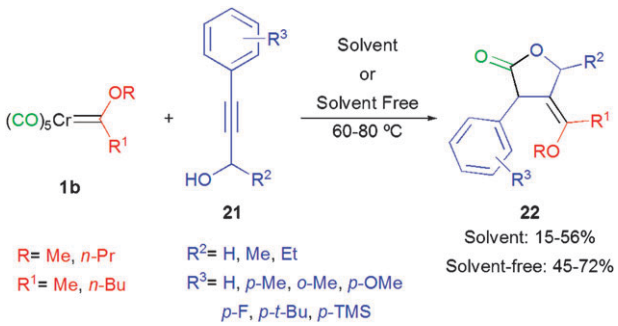
1,3,5-Hexatriynes react with alkoxy alkenyl FCCs through one or two of the end triple bonds of the triyne, when they bear phenyl- or adamantyl-substituents, to yield a mixture of Dötz adducts. However, the reaction with bis(triisopropylsilyl)triyne **18** takes place at the central alkyne unit; thus, the treatment of **18** with FCC **2c** leads to mono-benzannulated Dötz-product **19**, while, against phenyl or dihydrochromenyl chromium FCCs **1c**, furans **20** 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[11] (Scheme 5).



Scheme 4 Photochemical reaction with silyl acetylenes.



Scheme 5 Reaction of FCCs with conjugated triyne **18**.

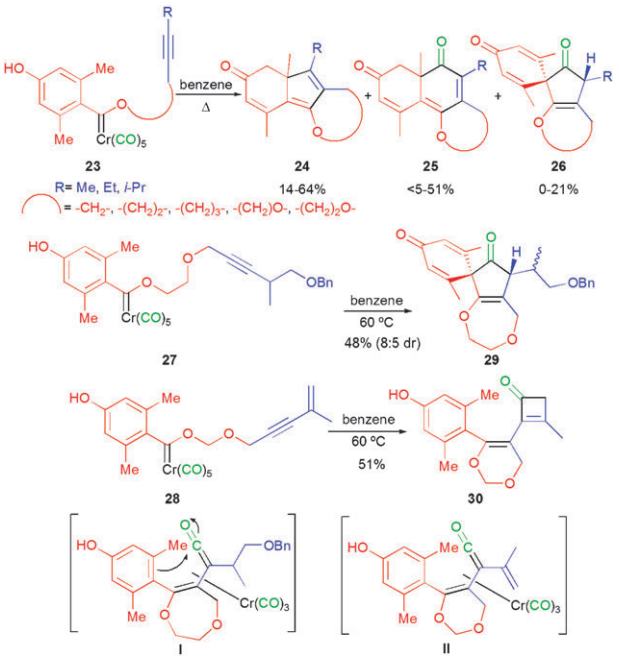


Scheme 6 Reaction of FCCs with propargylic alcohols **21**.

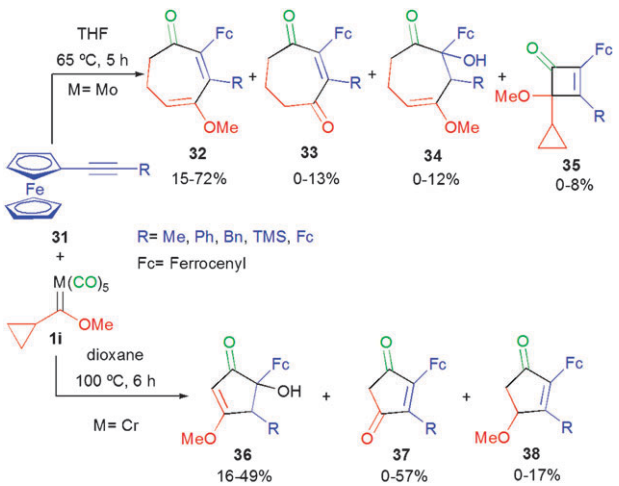
2.1.2 Reactions with propargylic alcohols. Recently reported solvent-free conditions have allowed to reduce the reaction time and to increase the yields of γ-butyrolactones **22**, formed in the reaction between alkoxy FCCs **1b** and propargylic alcohols **21**.[12] This reaction was simultaneously 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[2] (Scheme 6).

2.1.3 Reactions of 2,6-disubstituted aryl carbene complexes. The intramolecular reaction of 2,6-disubstituted 4-hydroxyaryl carbene complexes **23** with alkynes may lead to hydrindenones **24**, naphthalenediones **25** or spirocyclohexadienones **26** (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 hydrindenone when a six-membered ring is formed; on the other hand, increased amounts of naphthalenedione product **25** have been observed when five- or seven-membered heterocyclic rings are formed.[13] 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 **27** and **28** which produce spiro compound **29** and cyclobutenone **30** due to a different evolution of ketene intermediates **I** and **II** (Scheme 7).

2.1.4 Reactions of cyclopropyl carbene complexes. The behaviour of cyclopropyl FCCs **1i** towards alkynes, leading to five- or seven-membered carbocycles, is strongly dependant on the nature of the metal moiety, as pointed out previously.[2]



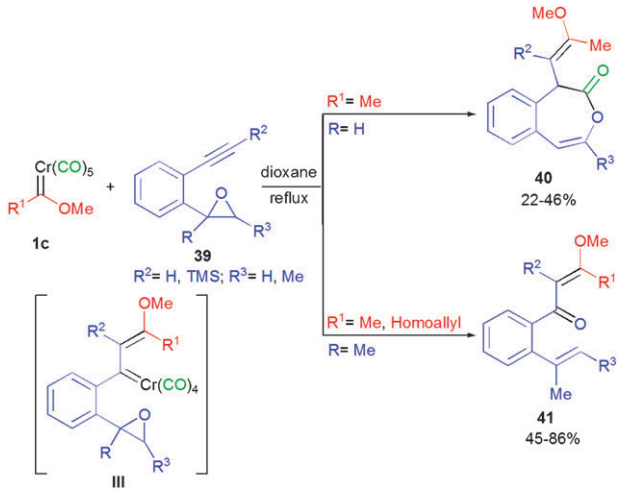
Scheme 7 Reaction of 2,6-disubstituted aryl carbene complexes.



Scheme 8 Reactions of cyclopropyl carbene complexes.

Particularly, towards ferrocenyl alkynes **31**, ferrocenyl-substituted 2,4-cycloheptadienones **32** are the major products of the reaction of molybdenum cyclopropyl carbene complexes (minor amounts of 2-cycloheptene-1,4-diones **33**, hydroxy-substituted cycloheptenones **34** and/or 2-cyclobutenones **35** are also isolated);[14] on the other hand, ferrocenyl-substituted 5-hydroxy-2-cyclopentenones **36** or 4-cyclopentene-1,3-diones **37** are the main products when chromium cyclopropyl FCCs are employed instead (minor amounts of cyclopentenones **38** and other compounds have also been isolated)[15] (Scheme 8).

2.1.5 Reactions with *ortho*-alkynylstyrene oxides. The coupling of FCC **1c** with *o*-alkynylstyrene epoxides **39** affords benzoxepinones **40** *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



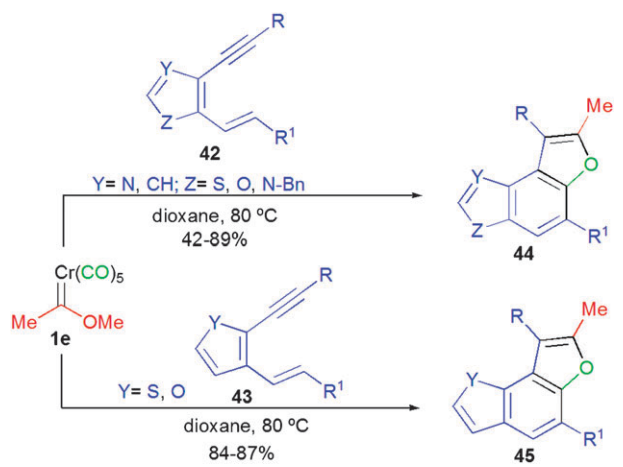
Scheme 9 Reaction of FCCs with *o*-alkynylstyrene oxides.

R = Me it affords dienone derivative **41** through intramolecular oxygen atom transfer[16] (Scheme 9).

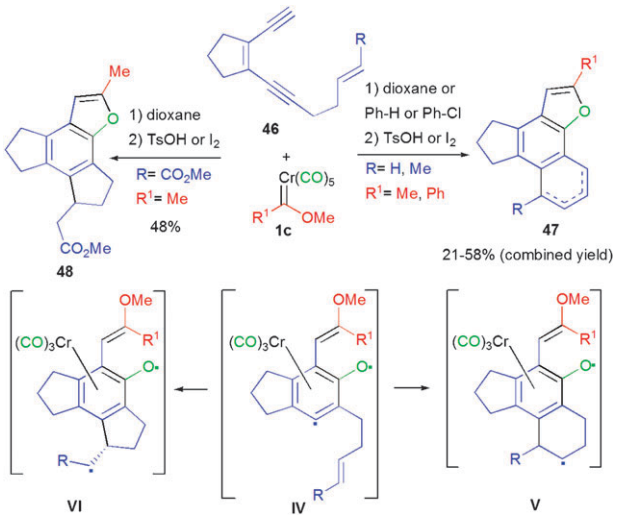
2.2 Reactions with enynes

2.2.1 Reactions with dienylacetylenes. Benzofuran 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 **42** or 3-alkenyl-2-alkynylheteroaromatic systems **43**.[17] Heteropolycycles **44** or **45** are thus formed in good yields (Scheme 10).

2.2.2 Reactions with enediynes. The reaction of FCCs **1c** with conjugated enediynes **46** 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.[18] 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 **47**. However, if R is a radical-stabilizing group a 5-exo cyclization happens leading to di-radical **VI**, which finally forms adduct **48** (Scheme 11).



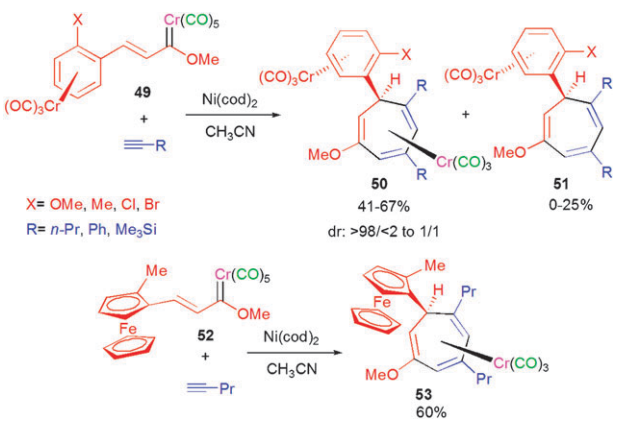
Scheme 10 Reactions of **1e** with dienylacetylenes.



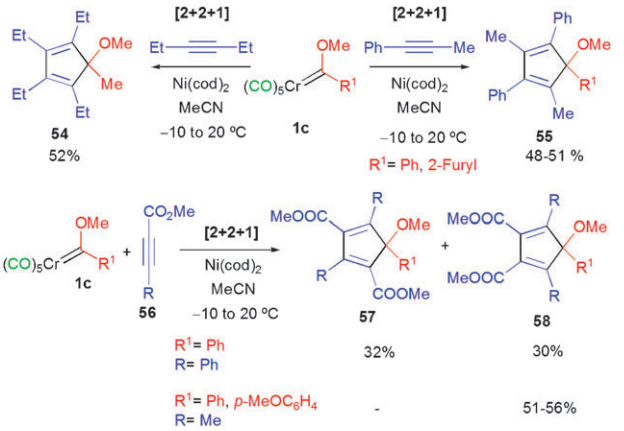
Scheme 11 Reactions of **1c** with diene–diynes.

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.[19] 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.[20] Taking advantage of this fact, Kamikawa has prepared optically pure planar chiral cycloheptatriene chromium complexes **50** and **51** by the diastereoselective [3 + 2 + 2] cycloaddition, employing binuclear α,β-unsaturated FCCs **49** (Scheme 12).[21] 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 **52** also has partaken in this reaction leading to the corresponding adduct **53** as a single diastereomer in 60% yield.



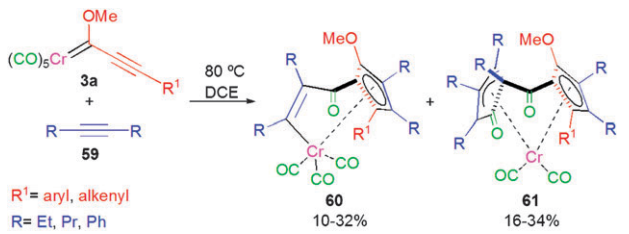
Scheme 12 Nickel-catalyzed reaction of planar chiral FCCs with terminal alkynes.



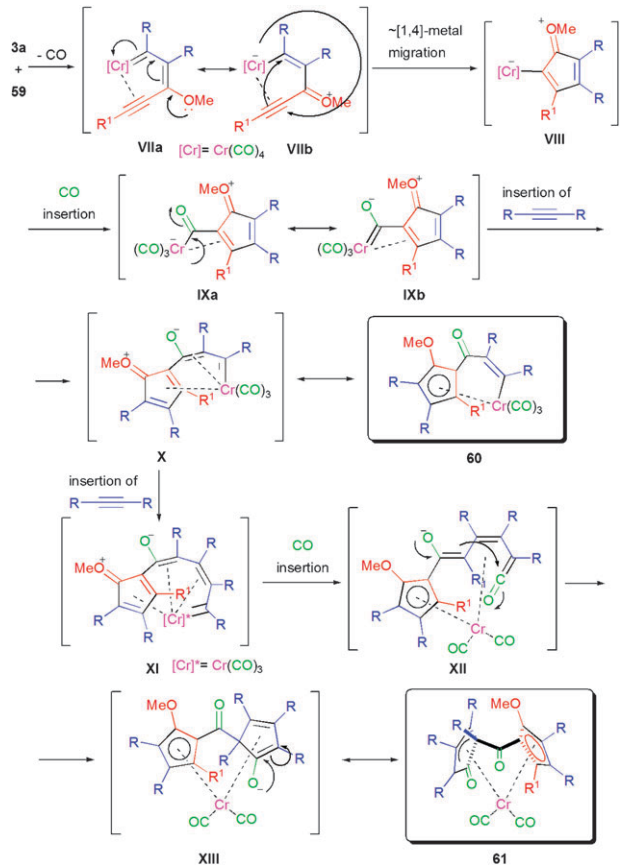
Scheme 13 Nickel-catalyzed reaction of FCCs **1c** with internal alkynes.

On the other hand, a different pathway has been observed in the reaction of chromium carbene complexes with internal acetylenes in the presence of $[Ni(cod)]_2$.[22] 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 **55** 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 **3a** 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.[23] 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(sp^2) bond and a cyclopentadienyl moiety in



Scheme 14 Multiple alkyne insertion on FCCs **3a**.

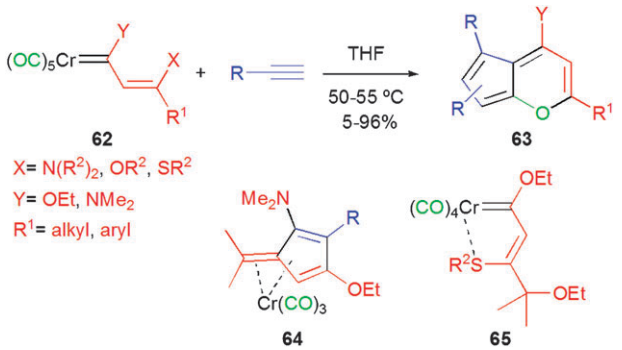


Scheme 15 Proposed mechanism for the multiple alkyne insertion on FCCs **3a**.

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 alkyne.



Scheme 16 Reactivity of β-donor substituted alkenyl FCCs **62** with alkynes.

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

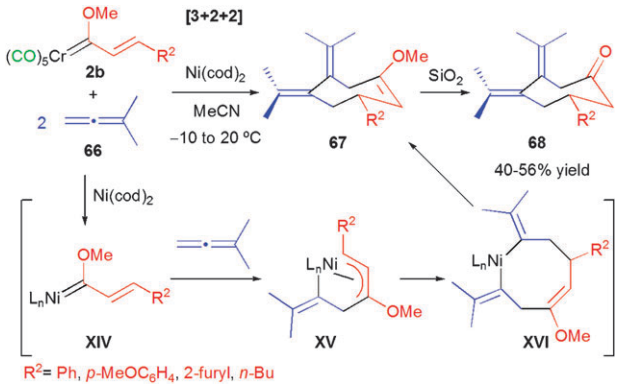
β-Donor substituted alkoxy alkenyl carbenes of chromium[24] **62** (Y = OEt) undergo the consecutive incorporation of two molecules of a terminal alkyne and a carbonyl ligand, with elimination of a small molecule (secondary amine, alcohol, or thiol), to form cyclopenta[*b*]pyrans **63** in yields up to 96%. The final product is a bicyclic system, which results from a formal [3 + 2 + 2 + 2] cyclization.[25] The regiochemistry in the incorporation on the second alkyne unit depends on the nature of both the alkyne 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 = NBn_2, Y = NMe_2) with phenylethyne (R = Ph) affords the corresponding 4-dimethylaminocyclopenta[*b*]pyrans (**63**, R = Ph, Y = NMe_2) 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 = SR^2, R^1 = $Me_2(EtO)C$–) (Scheme 16).

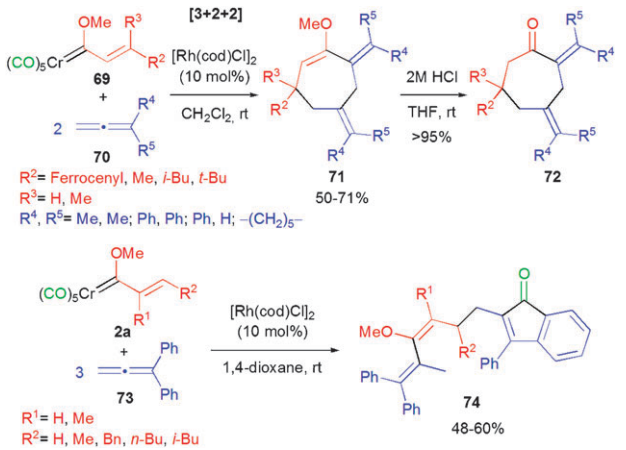
3. Reactions with allenes

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



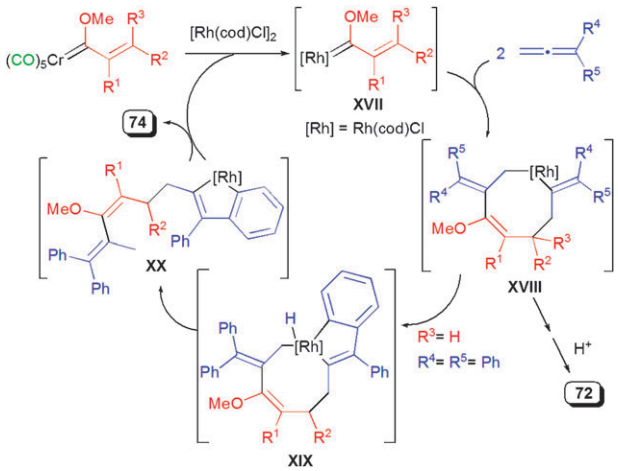
Scheme 17 Synthesis of seven-membered carbocycles **68** by reaction of FCCs **2b** with 1,1-dimethylallene in the presence of $Ni(cod)_2$ in MeCN.



Scheme 18 MCRs of alkenyl FCCs and allenes in the presence of $[Rh(cod)Cl]_2$.

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 regioselectivity 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 **73** 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 **XVII** 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



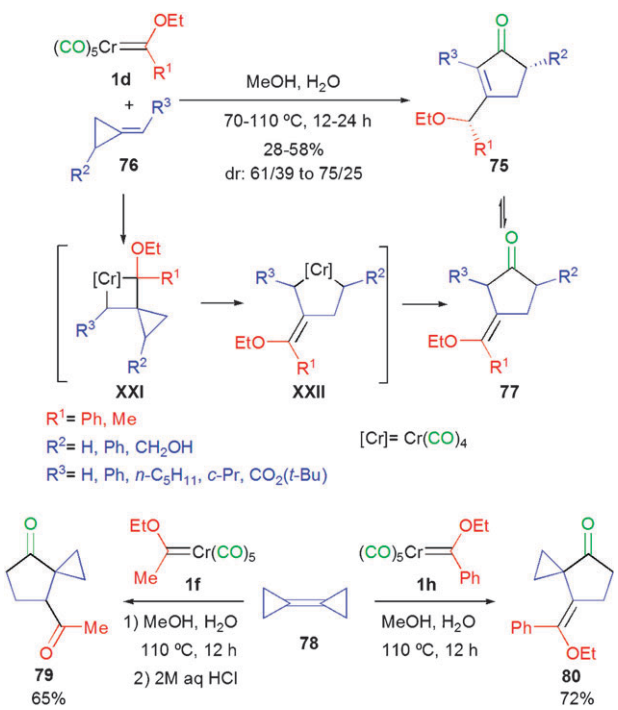
Scheme 19 Proposed mechanism for MCRs of alkenyl FCCs and allenes involving transmetallation to rhodium.

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



Scheme 20 Reactions of chromium FCCs and methylenecyclopropanes.

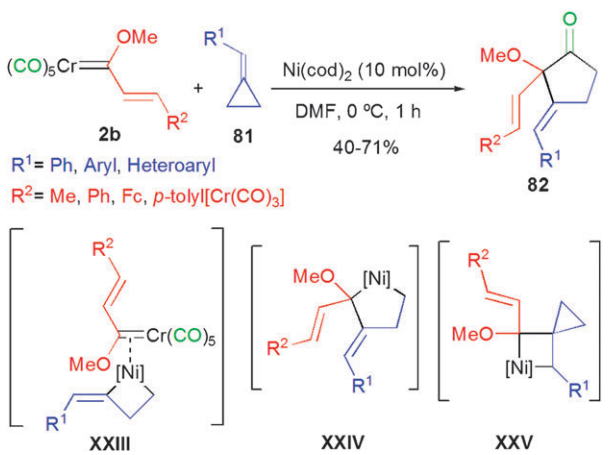
cyclopentenones **75** can be rationalized as arising from a [2 + 2]-cycloaddition of the methylenecyclopropane **76** to FCC **1d**, after initial dissociation of a CO ligand, to form 5-chromaspiro[2.3]hexane **XXI**. With its spirocyclopropane unit in the β-position with respect to the metal, **XXI** can undergo a facile cyclopropylmethylmetal 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, bicyclopropylidene **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 + 1−2]-cocyclization of Fischer (cyclopropylcarbene)chromium complexes and acetylenes, the Pauson–Khand reaction, and the template-assisted [2 + 3]-cocyclization of β-dialkylamino-substituted α,β-unsaturated FCCs.[2]

On the other hand, alkenyl FCCs **2b** react with methylene-cyclopropanes **81** in the presence of $Ni(cod)_2$ leading to alkenylidene cyclopentanones **82** through a [3 + 1 + 1] cycloaddition[30] (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] cyclo-addition with direct proximal C–C bond cleavage of the cyclo-propane 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**.

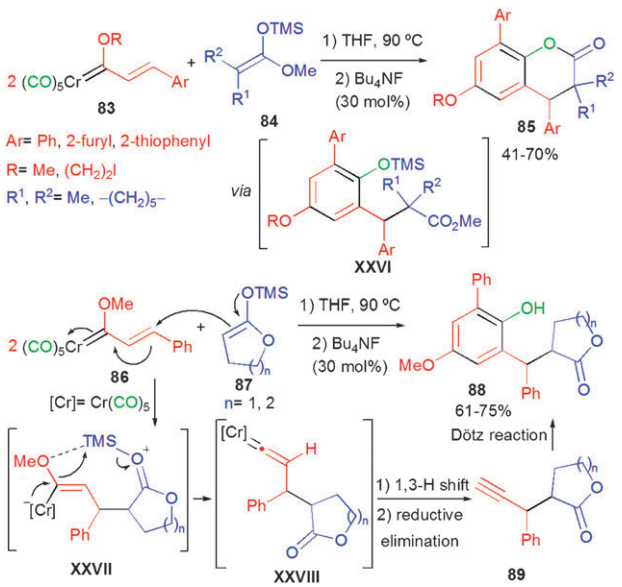


Scheme 21 Reactions of chromium alkenyl FCCs **2b** and methylene-cyclopropanes **81**.

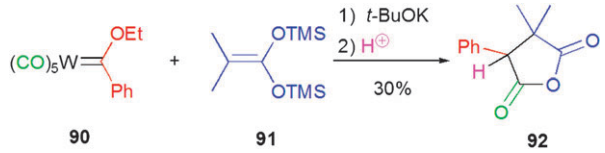
In any case, subsequent CO insertion and reductive elimination would lead to the final products.

4.2 Reactions with ketene acetals

The reaction of ketene acetals with Fischer alkynyl 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 acetals when FCCs derived from secondary alcohols are employed.[32] More recently, the corresponding reaction of disubstituted ketene acetals **84** with alkoxy alkenyl 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 tube[33] (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 alkenyl carbene, one equivalent of acetal and one CO ligand in an unprecedented four-component reaction. Moreover, when this procedure is applied to ketene acetals **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). First, a 1,4-addition of the substituted ketene acetal to the FCC would give a metallate specie **XXVII** that would evolve to form vinylidenechromium(0) complex **XXVIII**. A 1,3-hydrogen shift to generate a metal hydride specie followed by a reductive elimination would lead to alkyne intermediates **89**.[34] Finally, alkynes **89** would react with a second molecule of the alkoxy alkenyl carbene complex in a Dötz reaction to furnish the observed phenols or



Scheme 22 Reactions of chromium alkenyl FCCs and ketene acetals.



Scheme 23 Synthesis of anhydride **92** by a MCR between FCC **90** and silyl ketene acetal **91**.

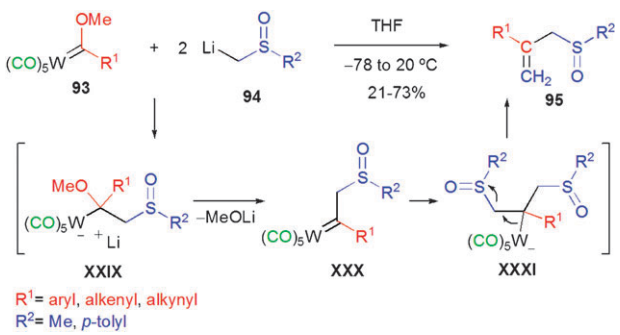
dihydrocumarines, after subsequent lactonization when possible. Indeed, when the reaction is conducted at room temperature alkynes **89** are isolated as a 5 : 1 mixture of isomers; they can be converted to the observed phenols **88** upon heating in the presence of the alkenyl carbene complex, thus demonstrating the role of alkynes **89** as intermediates in the process.

On the other hand, FCC **90** reacts with silyl ketene acetal **91** in the presence of *t*-BuOK to give anhydride **92** upon cleavage of both oxygen–silicon atoms, elimination of the ethoxy group, insertion of CO and elimination of $W(CO)_4$[35] (Scheme 23).

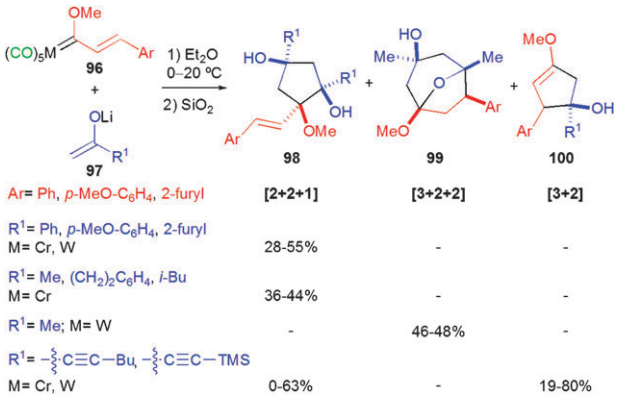
5. MCRs by insertions in metallates

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 **94** to tungsten alkoxy aryl, alkenyl or alkynyl carbene complexes **93** provide allyl sulfoxides **95** in moderate yields.[36] The process would be initiated by the formation of tungstate intermediates **XXIX** by nucleophilic addition of the first unit of carbanion to the carbene carbon. These species would evolve to non-stabilized carbene complexes **XXX** that may react with a second molecule of carbanion to produce a new metallate intermediate **XXXI**. A final β-elimination would afford the observed allyl sulfoxides **95** (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 **97** to β-substituted methoxy alkenyl carbene complexes **96**.[37] 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



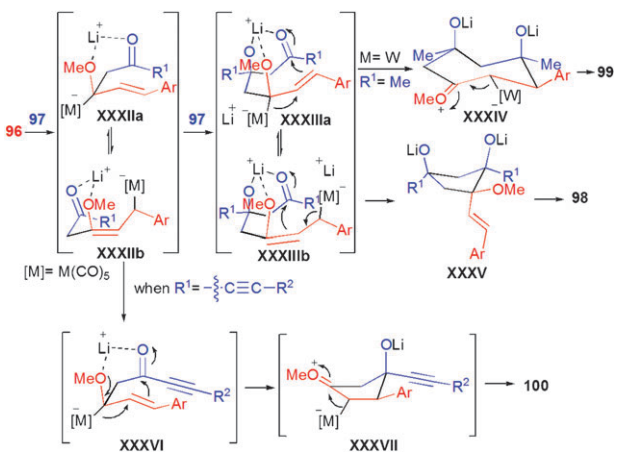
Scheme 24 Reaction of tungsten FCCs **93** with lithiosulfinyl carbanions.



Scheme 25 Lithium methylketone enolate addition to alkenyl FCCs.

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 **97** with the above mentioned chromium and tungsten complexes **96** in diethyl ether afford 1,3-cyclopentanediol derivatives **98** in a formal [2 + 2 + 1] three-component process (Scheme 25). Particularly, in the case of enolates derived from alkynyl methyl ketones, a competitive formal [3 + 2] two-component reaction occurs to give 3-cyclopentenols **100** in variable extensions. On the other hand, seven-membered carbocycles **99** are exclusively obtained in reactions of β-substituted methoxy alkenyl tungsten complexes with the lithium enolate of acetone as a result of a formal [3 + 2 + 2] cycloaddition. 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).

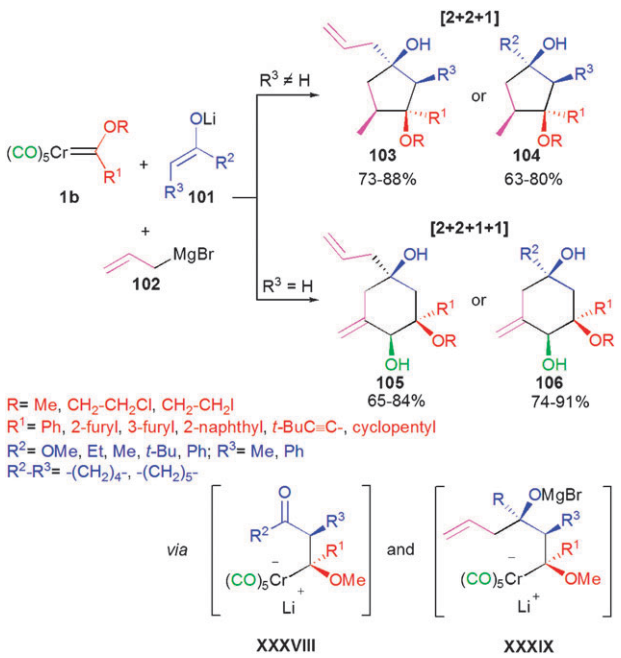
Tentative mechanistic proposals for all the cyclization pathways were reported by the authors and are illustrated in Scheme 26. A 1,2-addition of the lithium enolate **97** to the methoxy alkenyl carbene complex **96** would occur to form metallate intermediates **XXXIIa** that could be in equilibrium with **XXXIIb** coming from a 1,3-migration of the metal moiety. In the presence of coordinating solvents or additives, intermediates **XXXII** may directly evolve to cyclopentenol



Scheme 26 Proposed mechanism for the lithium methylketone enolate addition to alkenyl FCCs.

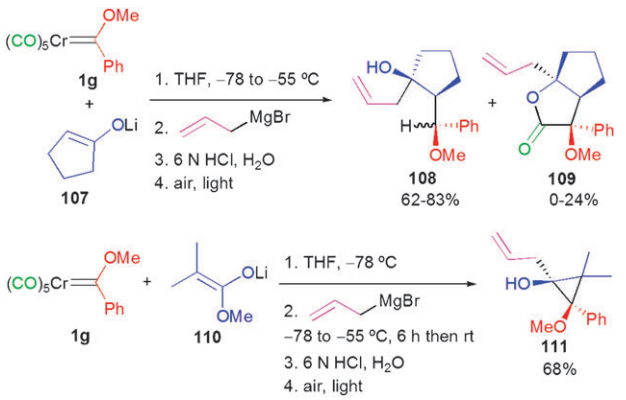
derivatives **100**. However, when the reactions were conducted in diethyl ether, the lithium ion could coordinate to the oxygen atoms of the intermediates thus increasing their rigidity and the electrophilic character of the carbonyl group and, therefore, favoring the addition of a second molecule of lithium enolate **97** to give the intermediates **XXXIIIa** or **XXXIIIb**. Then a nucleophilic intramolecular attack of the allyl metallate on species **XXXIIIb** would lead to five-membered cycloadducts **XXXV** that after hydrolysis would produce the observed adducts **98**. Alternatively, in reactions with enolates derived from methyl alkynyl ketones, intermediates **XXXVI** could undergo a cyclization reaction induced by a 1,2-metal migration to give, after elimination, decoordination of the metal and subsequent hydrolysis, 3-cyclopentenol derivatives **100**. On the other hand, in the case of reactions of tungsten carbenes with the enolate derived from acetone the evolution would be from intermediates **XXXIIIa** through a cyclization triggered by a 1,2-tungsten migration to furnish seven-membered carbocycles **XXXIV**. Further elimination and decoordination of the metal moiety followed by hydrolysis would render the observed cycloheptenediols **99**. The authors claim that the latter reactions evolve to seven-membered cycloadducts due to the greater steric hindrance of tungsten moiety that favors intermediates **XXXIIIa** over **XXXIIIb**.

Recently, a thorough study of a previously reported[38] 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).[39] 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.



103 73-88% 104 63-80%
105 65-84% 106 74-91%

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

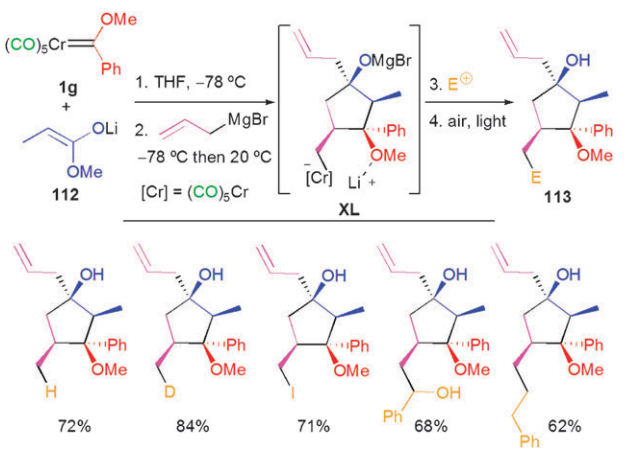


108 62-83% **109** 0-24%
111 68%

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

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 **101** and allyl magnesium bromide **102** 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.[40]

Besides the few exceptions above mentioned, new MCRs are observed when cyclopentanone lithium enolate **107** is used (Scheme 28). Thus, 1-alkylcyclopentanol **108** could be selectively obtained in good yield and as a single diastereoisomer when the enolate **107** 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 **108** and four-component butyrolactone **109** is formed when the reaction is performed by generating the enolate from 1-trimethylsilyloxycyclopentene and BuLi. On the other hand, the behaviour of β,β-disubstituted lithium enolates was found to be different. Thus, reaction of methoxy phenyl carbene **1g** with lithium methyl isobutyrate enolate **110** under optimized conditions provided cyclopropanol **111** 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



72% 84% 71% 68% 62%

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

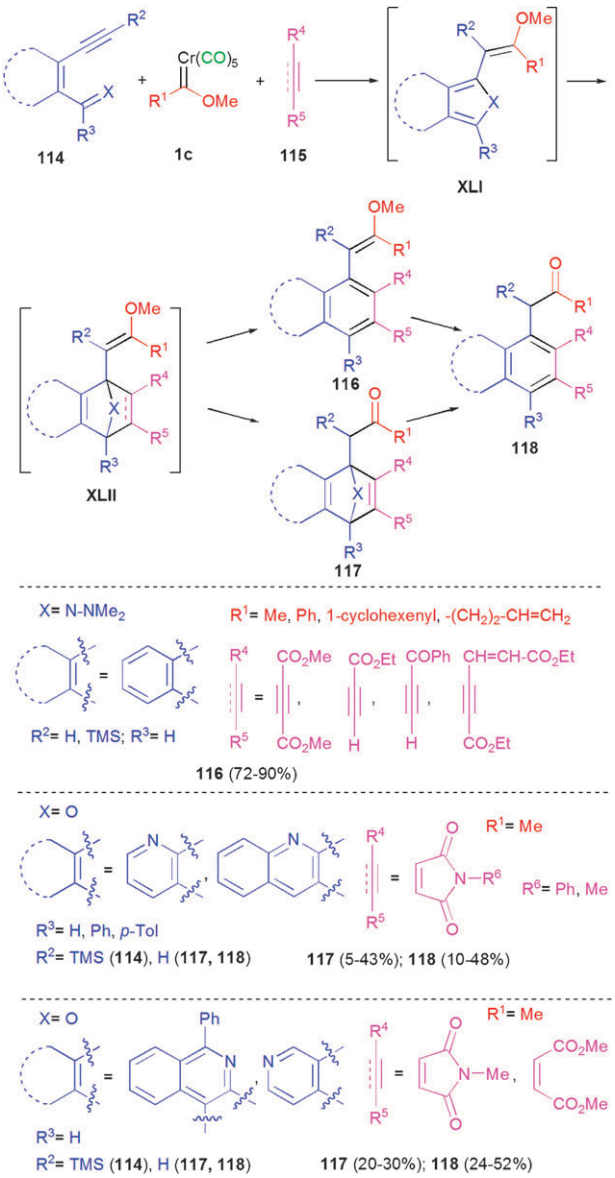
6.1 Isobenzofuran cyclization/Diels–Alder cycloaddition and related processes

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–NMe_2) employing benzaldehyde hydrazones **114** (X = N–NMe_2, R^3 = H) and alkynes as dienophiles **115**; the enol ether functionality is readily hydrolyzed to form ketones **118**.[42] Under the reaction conditions, the sequence does not stop at adducts **XLII**. 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 lignans,[43] phenanthridine ring systems[44] or isoquinoline derivatives[45] (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 yield[47] (Scheme 31).

Alkynes[42,48] and nitriles[49] 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

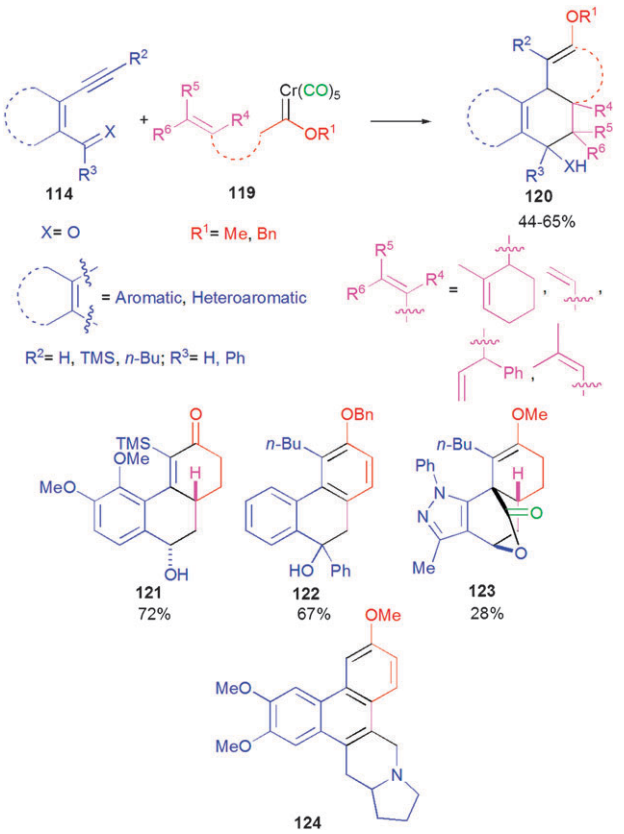


Scheme 30 Aromatic carbo- or heteropolycyclic compounds prepared by intermolecular isobenzofuran cyclization/Diels–Alder reaction sequence.

developed and the only examples are depicted in Scheme 33. Thus, the double bond may be tethered to the alkyne 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[50] 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

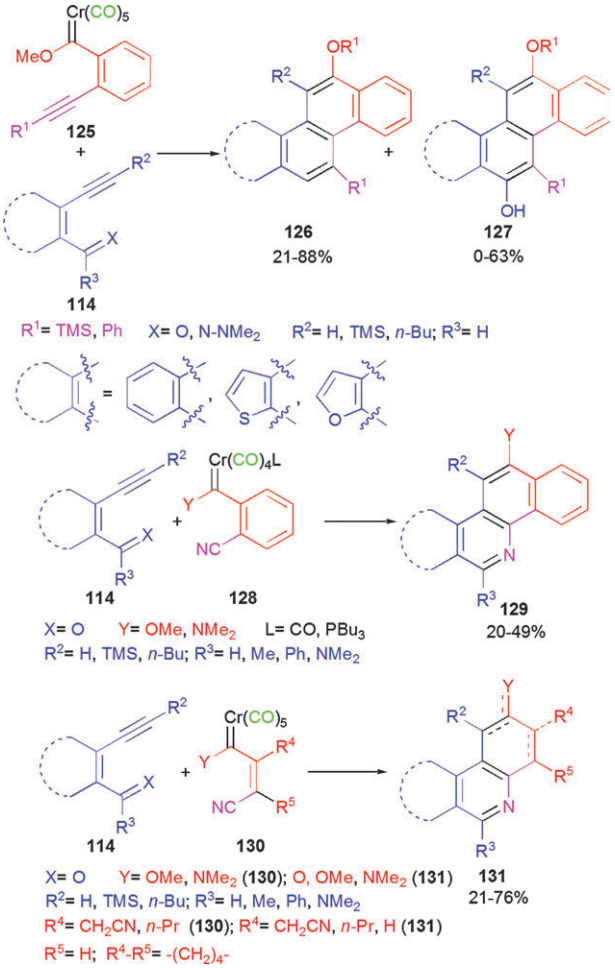
6.2.1 [2 + 2]/[2 + 1] and [3 + 2]/[2 + 1] tandem cycloaddition reactions of alkynyl FCCs. When alkynyl FCCs **3a** are heated in a sealed tube in THF at 90 °C in the presence of an excess of



Scheme 31 Alkenes as intramolecular dienophiles for the isobenzofuran cyclization/Diels–Alder reaction sequence.

2,3-dihydrofuran **138**, a [2 + 2]/[2 + 1] sequence takes place producing three-component adducts **139** in moderate yields.[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 alkynyl FCCs and related reactions. Conversely, the reaction of alkynyl 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 σ-C–C bonds.[52] A thorough study of the scope and limitations of this reaction has recently been published.[53] Thus, a series of multicomponent adducts **143** were selectively or exclusively obtained in moderate to good yields when bicyclic olefins **142** and alkynyl FCCs **3a** were mixed in refluxing toluene under a CO atmosphere (Scheme 35).

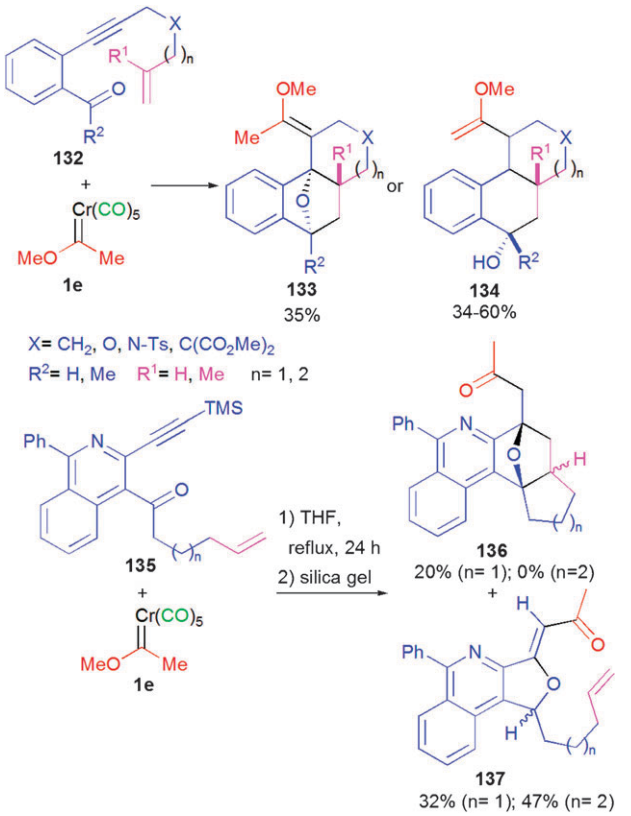


Scheme 32 Alkynes and nitriles as intramolecular dienophiles for the isobenzofuran cyclization/Diels–Alder reaction sequence.

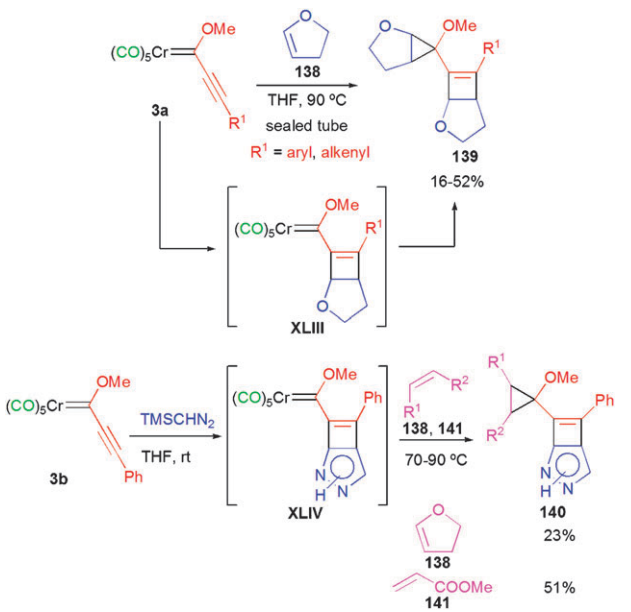
The reaction is proposed to occur through 2-cyclopentenone-derived FCC intermediate **XLV** (Scheme 35), which would cyclopropanate the second unit of olefin giving rise to the final products. This hypothesis opens the possibility to incorporate a different olefin as the fourth component. Notably, either 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 alkynyl 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

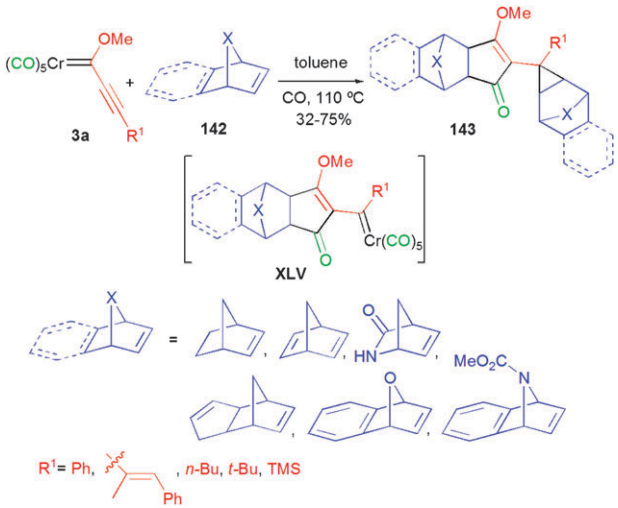


Scheme 33 Alkenes tethered to the alkynyl carbonyl moiety as intramolecular dienophiles for the isobenzofuran cyclization/Diels–Alder reaction sequence.

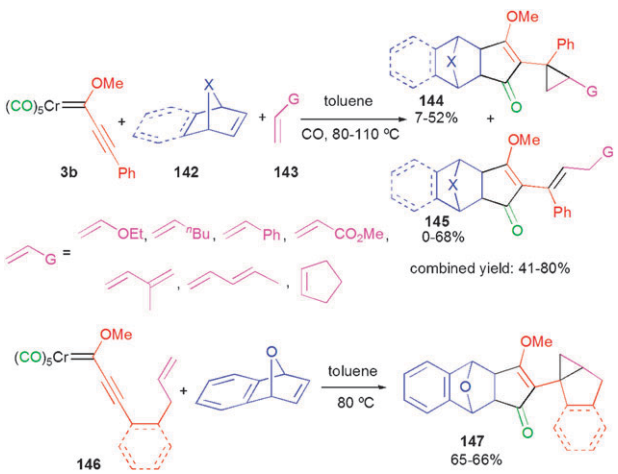


Scheme 34 [2 + 2]/[2 + 1] and [3 + 2]/[2 + 1] reactions of alkynyl FCCs.

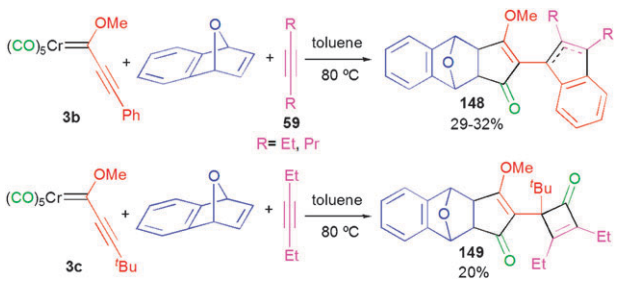
Diels–Alder/benzannulation/rearrangement reactions, yielding 5,10- and 5,6-naphthofurandione derivatives **152** and **153** in almost 1 : 1 ratio. Under the same reaction conditions, the analogous tungsten derivatives just undergo a Diels–Alder reaction with *anti* facial selectivity to **154**, but they do not evolve[54] (Scheme 38).



Scheme 35 [2 + 2 + 1]/[2 + 1] reactions of alkynyl FCCs.

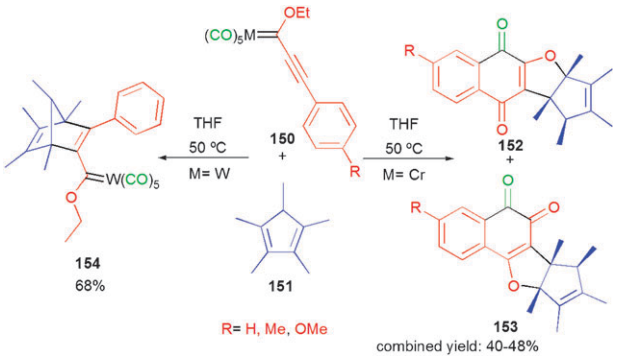


Scheme 36 Four different components [2 + 2 + 1]/[2 + 1] and intramolecular [2 + 2 + 1]/[2 + 1] reactions of alkynyl FCCs and olefins.

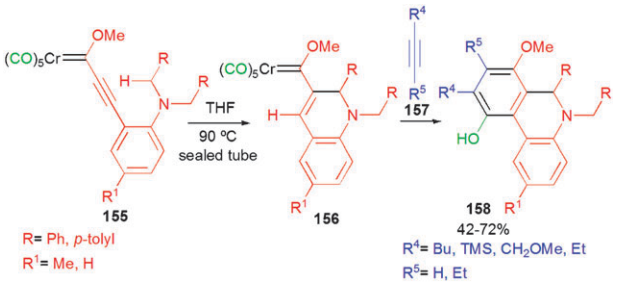


Scheme 37 Internal alkynes as fourth component in the tandem reaction.

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 *o*-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



Scheme 38 Diels–Alder cycloaddition/benzannulation/rearrangement reactions.



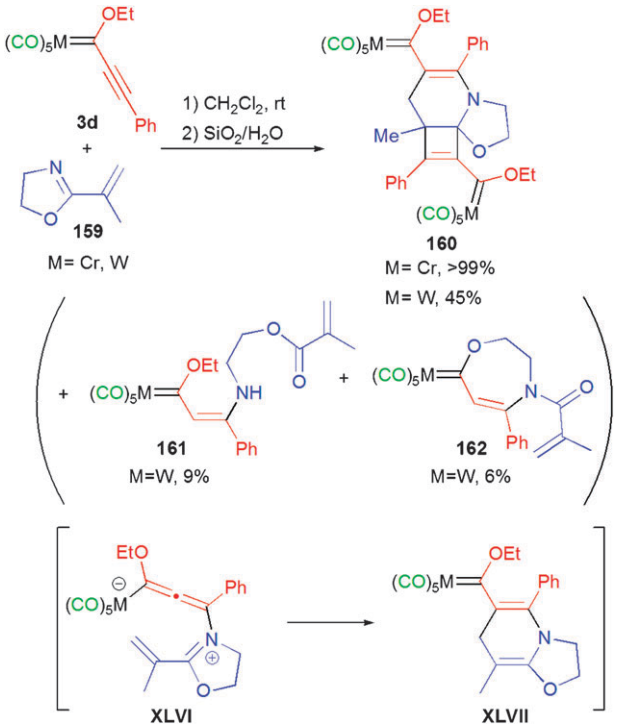
Scheme 39 Synthesis of 5,6-dihydrophenanthridines **158** by a hydride transfer/cyclization/Dötz benzannulation cascade process.

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).

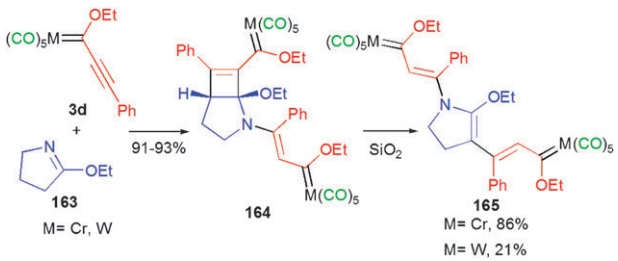
6.2.5 Tandem nucleophile addition/cyclization reactions. (1-Phenylpropynyl)carbene complexes **3d** react, under mild conditions, with 2-alkenyl-2-oxazoline **159** to afford unusually stable Fischer biscarbene complexes **160** containing a four-, five-, and six-membered tricyclic core.[56] As it happens when alkenyl imidates are employed as nucleophiles,[57] 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 biscarbenes **165**[58] (Scheme 41).

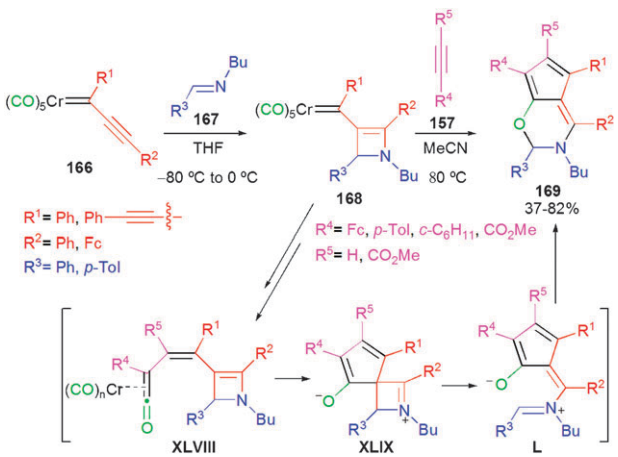
Non-heteroatom-stabilized alkynyl-substituted carbenes **166** readily react with imines **167** to furnish stable [2+2] cycloadducts **168** that can be isolated in good yields.[59] With this simple and efficient route to access *N*-alkyl-2-azetine derivatives **168** in hand, their reactivity towards alkynes **157** was explored and a multicomponent process leading to



Scheme 40 Nucleophilic addition of cyclic imidate **159** to FCC **3d**.



Scheme 41 Nucleophilic addition of imidate **163** to FCC **3d**.



Scheme 42 Three-component synthesis of bicyclic[1,3]oxazines **169**.

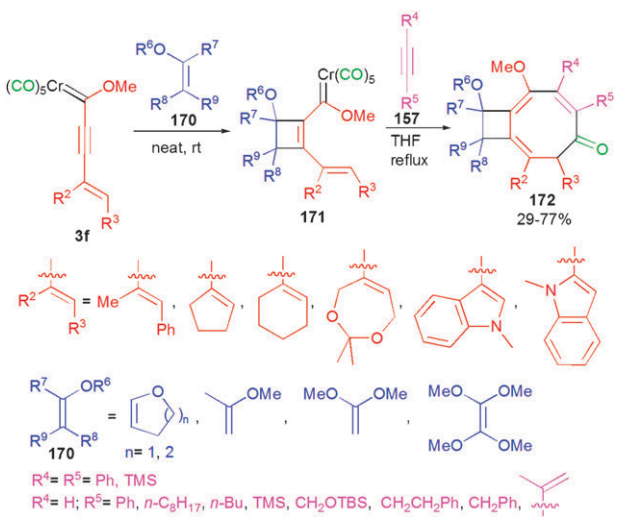
2,3-dihydrocyclopenta[*e*]oxazines **169** was found (Scheme 42).[59] The reaction sequence involves the formation of one C–O bond and three C–C bonds and gives rise to the highly substituted final products in moderate to good yields and as

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 **L** 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.

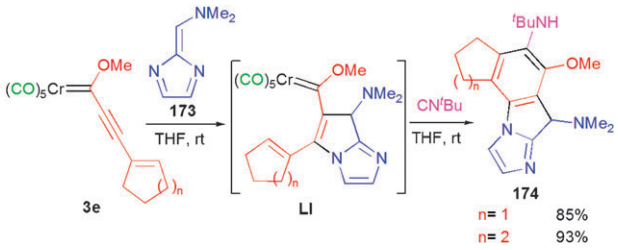
6.3 Domino reactions from alkenyl substituted alkynyl carbene complexes

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** (R^4 = 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.



Scheme 43 Synthesis of cyclooctatrienones **172** from FCCs **3f**.

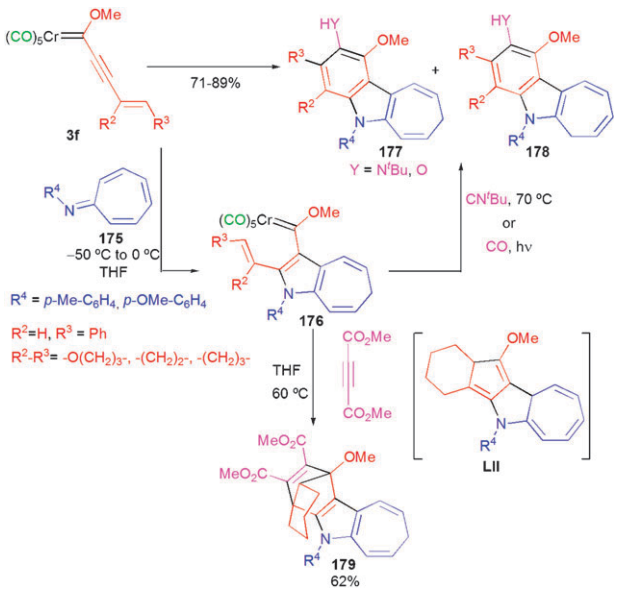


Scheme 44 Three-component synthesis of heteropolycycles **174**.

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[61] (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 cycloheptaindoles **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 casade sequences using relatively simple starting materials.

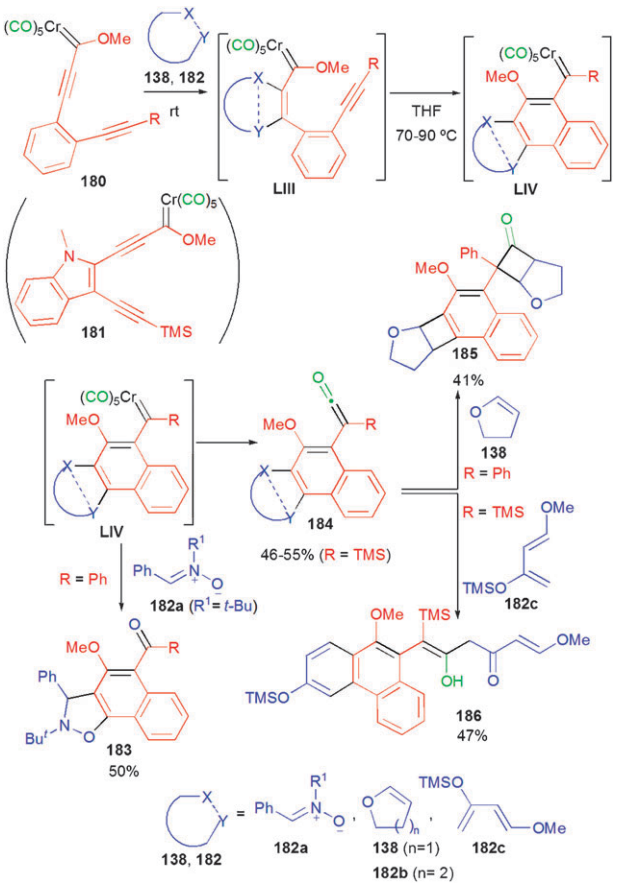
On the other hand, and in contrast to what is observed for 1-metallahexa-1,3,5-trienes **171** (Scheme 43), formation of eight-membered carbocycles does not take place for derivatives **176** when they are heated in the presence of dimethyl acetylenedicarboxylate. In this case cyclopentannulation occurs 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 maleinimide as dienophile for the trapping of the cyclopentannulation adduct has also been demonstrated (Scheme 45).



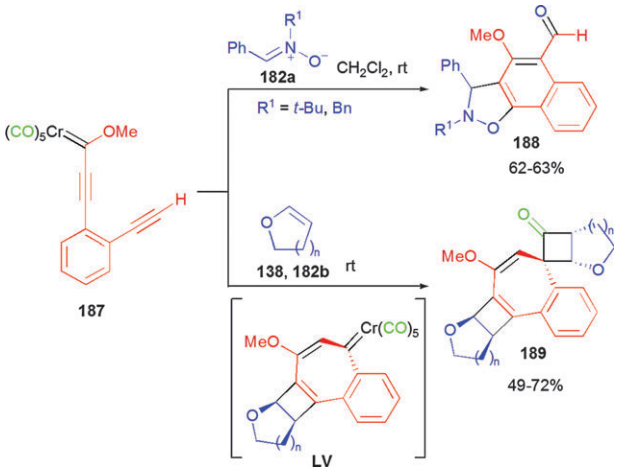
Scheme 45 MCRs involving 8-azaheptafulvenes **175**.

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-metallahexa-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 nitrone **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 nitrone, nor a second [2 + 2] cycloaddition takes place in the presence of excess 2,3-dihydrofuran. Only if Danishesfsky'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).



Scheme 46 Domino reactions from alkynyl substituted alkynyl carbene complexes **180** and **181**.



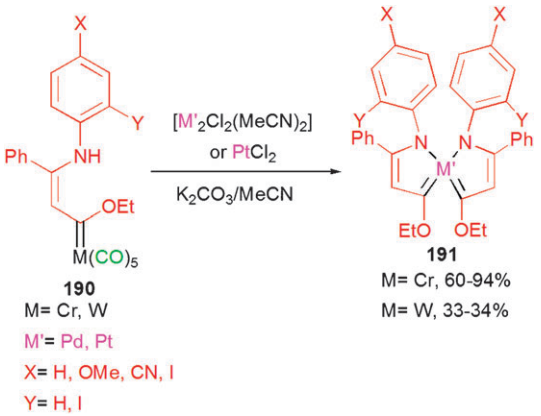
Scheme 47 Domino reactions from terminal alkyne-bearing alkynyl carbene complex **187**.

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 benzo[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 $[PdCl_2(MeCN)_2]$ or $[PtCl_2(MeCN)_2]$ (or $PtCl_2$) and excess of K_2CO_3 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]



Scheme 48 Synthesis of mononuclear alkoxy bis-carbene complexes **191**.

Conclusions

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 unreached, 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.

We are deeply grateful to Prof. Barluenga for his constant support and for the fruitful discussions maintained, particularly on this research field. We thank Dr B. K. Ghoray for providing us with a reprint of ref. 44. We also acknowledge the financial support received from the Ministerio de Ciencia y Tecnología (Spain) (grants CTQ2007-61048, CTQ2009-09949, Juan de la Cierva postdoctoral contract to P. G.-G., and Ramón y Cajal postdoctoral contract to M. A. F.-R.) and Principado de Asturias (project IB08-088).

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