

Metal-assisted cyclizations

Cascade and domino reactions

Armin de Meijere and Michael Schelper

Summary

Domino and cascade cyclizations provide one of the most elegant and economic accesses to complex carbon frameworks. In particular, transition metal-mediated and -catalyzed reactions offer an almost endless number of synthetic pathways from simple precursors to elaborate molecules. In the following overview emphasis is placed on some of the more impressive developments in this field within the last decade, spanning a circle from the very recent developments of rhodium-catalyzed cycloaddition reactions over the almost classical palladium-catalyzed oligocyclizations to the multifold reaction possibilities of Fischer carbene complexes.

Key-words Mots-clés

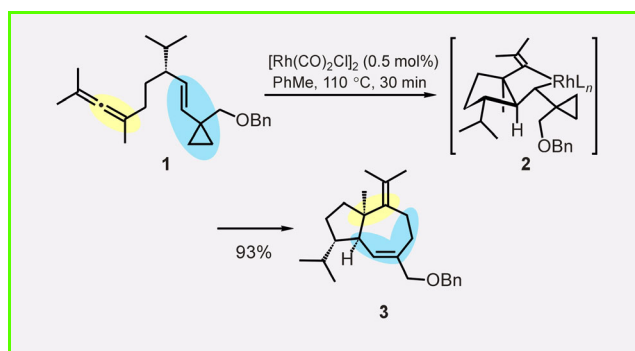
Transition metals, domino reactions, cascade cyclizations, catalysis, metal-template synthesis.
Métaux de transition, réactions en dominos, cyclisations en cascade, catalyse, synthèse assistée par les métaux.

During the last two decades, impressive new synthetic methodologies based on transition metal-mediated and -catalyzed transformations have surfaced. Among them, so-called domino or cascade reactions, in which substantially more than two new carbon-carbon or carbon-heteroatom bonds are formed in a single operation, provide the most elegant and efficient access to carbo- and heterooligocyclic systems with two or more annelated and/or spiroannelated rings. Although a variety of metals – such as aluminum, chromium, cobalt, indium, iron, manganese, magnesium, platinum, samarium, titanium, tungsten, zinc and zirconium – have been applied to mediate cascade cyclizations, the majority of metal-catalyzed cascade cyclizations have been reported for ruthenium, rhodium and in particular palladium catalysts.

In general, cascade reactions either start with the coordination of two carbon-carbon multiple bonds at the metal center or by oxidative addition of a carbon-heteroatom bond to the catalytically active metal species and subsequent carbometallation of a further multiple bond. In order to make multiple consecutive couplings possible, it is necessary to prevent premature separation of the catalyst from the substrate. The possibility to generate « living » metal intermediates by blocking β -hydride elimination or similar reductive elimination steps therefore is crucial for the success of these cascade reactions. The term « relais » has been introduced to describe a carbon-carbon multiple bond, that may undergo carbometallation to yield an intermediate which has no facile elimination process available and can thus carry the reaction cascade ahead. Most frequently, alkynes yielding kinetically stable alkenyl-palladium species, bicycloalkenes (like norbornene) giving bicycloalkylpalladium intermediates without syn-orientated β -hydrogens due to prevented internal rotation, and simple alkenes lacking β -hydrogens, are employed for this purpose. Eventually, all of such cascades are terminated by either a reductive elimination, a β -hydride elimination or by trapping of the intermediate metal complex by nucleophiles.

Ruthenium and rhodium catalysis

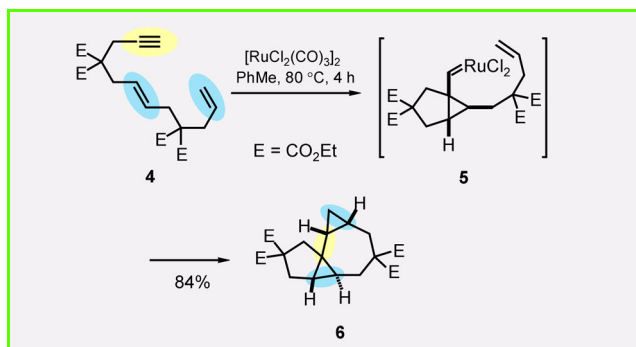
As far as the mechanisms are concerned, many organometallic transformations, the outcome of which looks like a straightforward cycloaddition, are actually cascade events. A particularly elegant example is the synthetically important rhodium(I)-catalyzed cocyclization of a vinylcyclopropane and an alkyne which has been conceived and developed by Wender et al. [1]. First executed in an intramolecular fashion, this formal [5+2] cycloaddition leading to ring-annelated and highly substituted seven-membered carbocycles, has subsequently also been developed for intermolecular cocyclizations with alkynes and also with alkenes and allenes. The latter variant was utilized as the key step to convert the allenylvinylcyclopropane **1** to the bicyclo[5.3.0]decene derivative **3** (93% yield) in the recently reported synthesis of (+)-aphanamol, which was obtained from **3** in three additional steps (*scheme 1*) [1c].



Scheme 1.

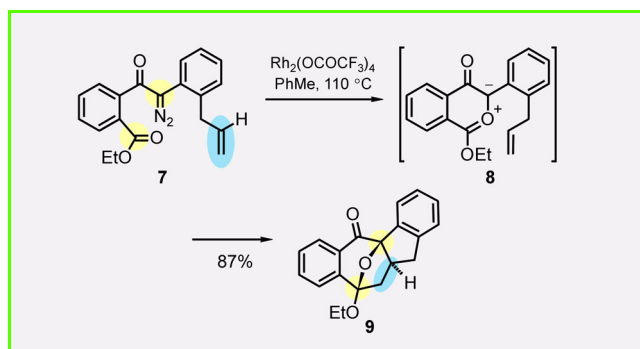
For many substrates, rhodium and ruthenium catalysts promote the same reactions and therefore in certain cases these catalysts may be exchanged for one another. A striking example is the highly efficient cascade cyclization of the acyclic dieneyne **4** to the interesting tetracycle **5** as

published by Murai et al. [2]. This overall cycloisomerization can be catalyzed by rhodium, platinum as well as ruthenium, and it presumably proceeds via a metalcarbene complex intermediate of type **5** which is held responsible for the generation of the second cyclopropane ring. Four new C,C bonds and four rings are formed in a single operation (scheme 2). Related cycloisomerizations catalyzed by ruthenium complexes and proceeding via rutheniumcarbene intermediates have been reported by Mori et al. [3].



Scheme 2.

The complexities of final products from cascade cyclizations are frequently also further enhanced by an additional inter- or intramolecular cycloaddition step, which may or may not be accelerated by the metal present in the reaction mixture. Padwa et al. utilized a rhodium(II) catalyst in their model studies towards the synthesis of (\pm)-ribasine [4]. By employing a domino cyclization-cycloaddition sequence starting from the rather simple diazo ketoester **7**, they were able to isolate the pentacyclic fused ring system **9** in an excellent 87% yield. Apparently, the rhodium catalyst first attacks the diazoketone moiety and the thus formed rhodiumcarbene complex subsequently inserts into the neighboring ester carbonyl group forming a carbonylylide, which then undergoes an intramolecular 1,3-dipolar cycloaddition onto the remaining double bond (scheme 3).



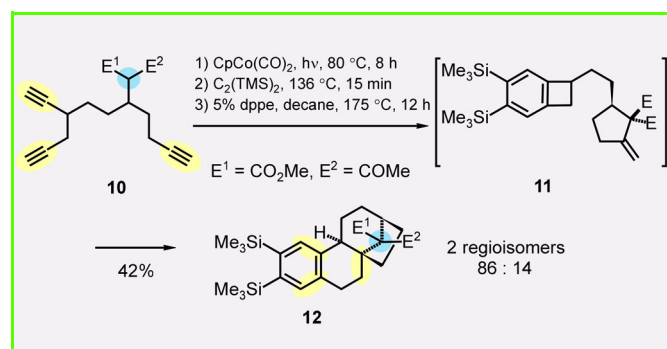
Scheme 3.

Cobalt and nickel mediation and catalysis

Most cobalt-mediated cascade cyclizations are of the formal [2+2+2] cycloaddition type of three multiple bond systems, as independently developed by Vollhardt et al. and Bönemann et al. [5]. The reaction sequence is generally accepted to proceed via cobaltacyclopentadienes, initially

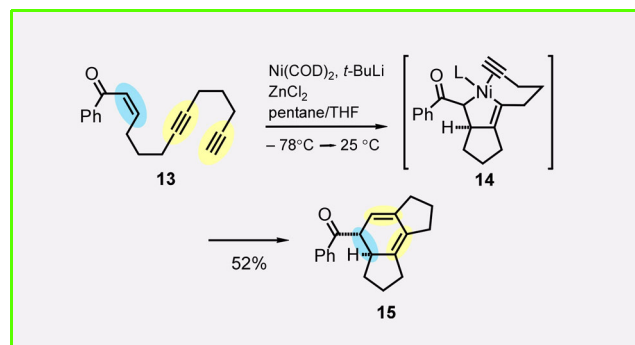
formed from two alkynes and the cobalt mediator, and the metallacyclopentadiene subsequently undergoes a [4+2] cycloaddition with another alkyne, a nitrile or an alkene. Reductive elimination of the metal finally yields the carbo- or heterocyclic six-membered ring. Much effort has been devoted to further develop cocyclizations of two alkynes with different multiple bond systems, and allenes have been found to favorably serve as the third multiple bond moiety as well.

Malacria et al. have tied-up an ene-type cycloisomerization with a subsequent cyclotrimerization, both mediated by cobalt, and an intramolecular [4+2] cycloaddition into a single cascade event. The initial Co(I)-mediated ene-type cycloisomerization of one acetylenic terminus in **10** with the β -keto ester moiety, as developed by the same group, forms the methylenecyclopentane moiety in the intermediate **11**. The two remaining triple bonds are then cocyclized with bis(trimethylsilyl)acetylene to give a cyclobutabenzene derivative which, after ring opening to an orthoquinodimethane, undergoes [4+2] cycloaddition with the initially formed methylene-cyclopentane at elevated temperatures. Thus, this remarkable one-pot operation very efficiently leads to the basic tetracyclic skeleton of the phyllocladane family of sesquiterpenes in a chemo-, regio- and stereoselective fashion (scheme 4) [6].



Scheme 4.

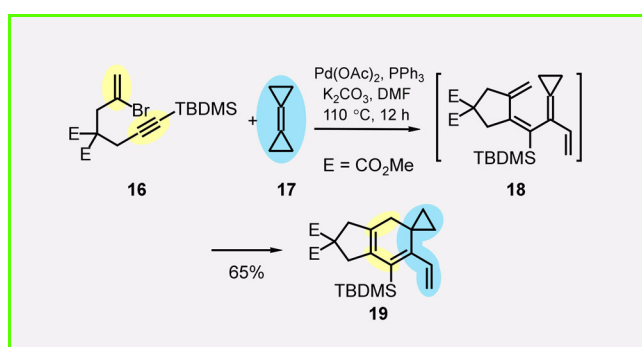
Quite similar in the underlying mechanism is the rarely utilized nickel-catalyzed cycloisomerization of enonediynes like **13** in the presence of organozincs (*in situ* generated from an alkyllithium and zinc chloride), developed by Montgomery et al. [7]. The acetylenic precursor **13** presumably first forms the nickellacyclopentene **14** which, by a subsequent alkyne insertion, and eventual reductive elimination yields the tricycle **15** (scheme 5).



Scheme 5.

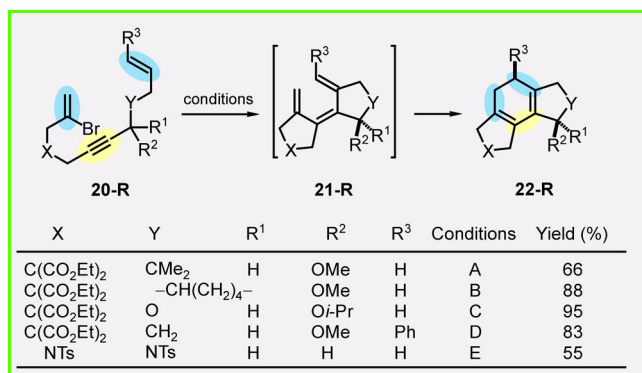
Palladium catalysis

Palladium-catalyzed cross-coupling reactions of the Stille, Suzuki and Heck type have – in recent years – been developed almost to perfection to approach bi-, tri-, tetra- and even higher oligocyclic carbon skeletons in single operation reaction cascades [8]. One of the most recent examples is that of de Meijere et al., in which an intramolecular Heck coupling of a 2-bromo-1,6-enediynes **16** is combined with a subsequent intermolecular trapping of the generated alkenylpalladium species by the highly reactive bicyclopopylidene (**17**) to yield the spiroannulated bicyclo[4.3.0]nonadiene **19**. After the intramolecular carbopalladation of the triple bond in **16** the reaction cascade proceeds with an intermolecular carbopalladation of **17**, followed by cyclopropylmethyl to homoallyl rearrangement, β -dehydropalladation and subsequent 6π -electrocyclization of **18**. At lower reaction temperatures (e.g. 80 °C in MeCN), the tetraene intermediate **18** can actually be isolated (scheme 6) [9].



Scheme 6.

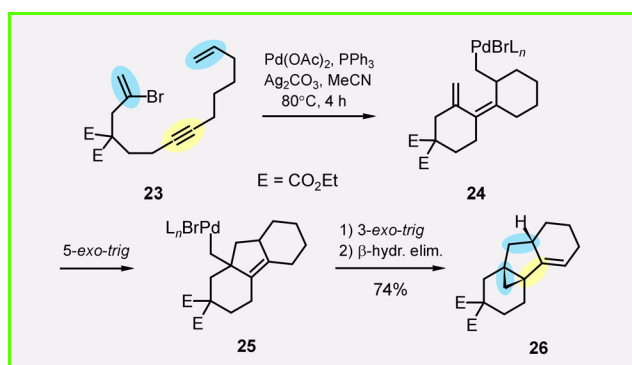
Three- and even four-step all-intramolecular cascade reactions have been designed and successfully executed as well. One concept relies on the generation of conjugated 1,3,5-hexatrienes which subsequently undergo a thermal 6π -electrocyclization to form an additional ring. This strategy has been developed into a quite general route to substituted carbo- as well as heterotri- and tetracyclic skeletons [10]. A large variety of acyclic 2-bromodieneynes **20-R** have been shown to cleanly undergo a twofold intramolecular Heck-type cross coupling to bicyclic trienes **21-R** which, at the elevated temperatures in the reaction medium (60-110 °C), smoothly undergo 6π -electrocyclization to give the tri- or tetracycles **22-R** in good yields (scheme 7) [11].



Scheme 7.

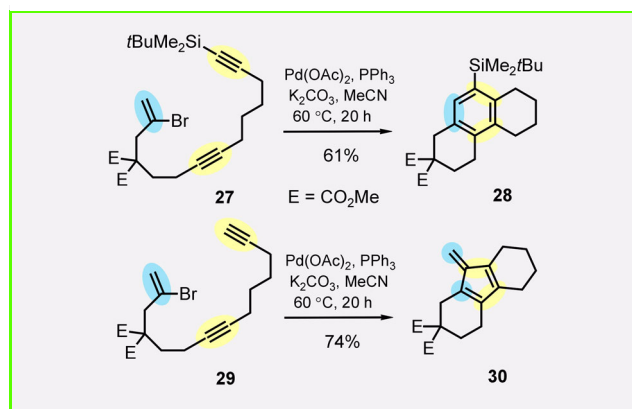
Conditions: A: Pd(OAc)₂, PPh₃, Ag₂CO₃, MeCN, 80 °C, 36 h; B: As in A, but 3 h; C: As in A, but 60 °C, 4 h; D: Pd(OAc)₂, PPh₃, K₂CO₃, MeCN, 110 °C, 3 d; E: Palladacycle (generated from Pd(OAc)₂ and P(*o*-Tol)₃), PPh₃, K₂CO₃, MeCN, 80 °C, 48 h.

The main limitation of this methodology is that of the achievable ring-size combinations. While the formation of 5-6-5 tricycles works best, and those of 6-6-5 combinations can be achieved with reasonable yields, any acyclic precursor with four atoms in both tethers between the bromoene, the alkyne relais and the ene moiety such as in **23**, did not yield the expected decahydrophenanthrene skeleton (6-6-6 ring size combination), but a tetracycle of type **26** with a cyclopropane bridging the A-B ring juncture. Apparently, the intermediate alkylpalladium bromide **24**, rather than suffering β -hydride elimination, undergoes intramolecular carbopalladation of the exomethylene group in a 5-*exo-trig* cyclization mode (scheme 8) [12]. It is noteworthy that this 3-*exo-trig* cyclization mode of forming a cyclopropane moiety, which corresponds to the reversal of a cyclopropyl to homoallyl rearrangement (see above, scheme 6) is frequently observed in this kind of cascade cyclizations [13].



Scheme 8.

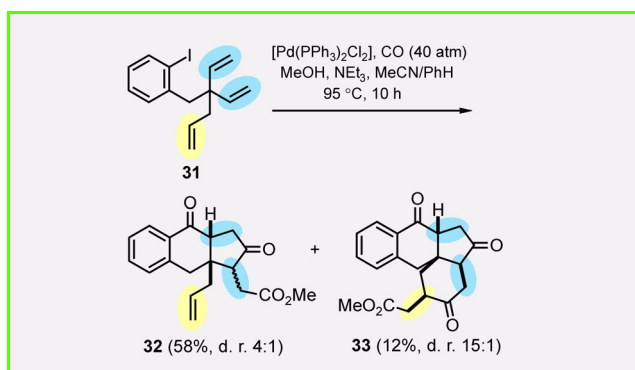
Although all of these oligocyclizations can be rationalized with nowadays mechanistic understanding, the real outcome of such cascade reactions is not always predictable as shown by the above example. Slight structural changes in the cyclization precursor may lead to dramatic changes in the final product. When the 2-bromo-enediynes **27** with a trialkylsilyl group at the acetylenic terminus was treated with a common palladium catalyst, it yielded the (desired) bisannulated benzene derivative **28**. However, the completely analogous 2-bromoenediynes **29** with an unsubstituted alkyne terminus, obtained by protodesilylation of **27**, upon treatment with the same catalyst cocktail, gave the fulvene **30** in good yield (scheme 9) [14]. The dichotomy between



Scheme 9.

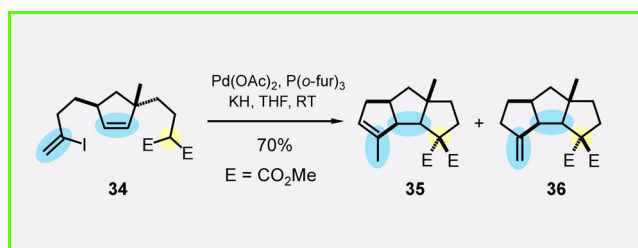
benzene and fulvene formation is intriguing, since both modes of cyclization can be rationalized and are found in multicomponent cocyclizations as well [15].

Additional complexity of the final products can be achieved by carbon monoxide insertion which may occur between consecutive carbopalladations within a cascade. Since carbon monoxide serves as a weakly bound ligand on palladium – being able to insert reversibly into carbon-palladium bonds – aryl-, alkenyl- and alkynylpalladium species undergo carbonylation reactions quite easily. Dependencies on the catalyst cocktail and the applied pressure (and therefore the concentration) of carbon monoxide have been studied to a great extent, and often the number of carbon monoxide insertions during the reaction cascade correlates with the latter. Negishi et al. reported quite striking examples of multiple CO insertions including one, in which seven new carbon-carbon bonds were formed in one single operation (*scheme 10*) [16].



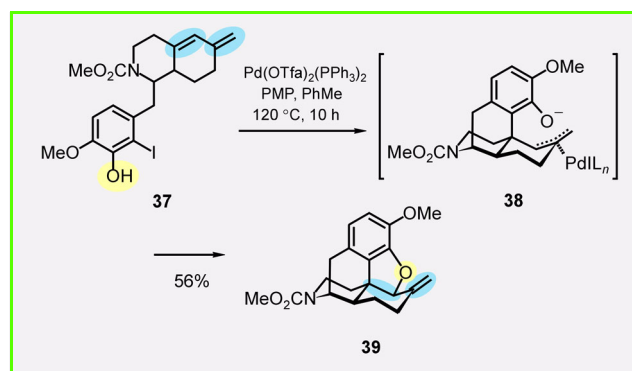
Scheme 10.

Other reaction modes result, when carbopalladation intermediates are trapped by internal or external nucleophilic components, since the metal-bearing carbon center of an organypalladium species is electrophilic. Carbon nucleophiles are the most commonly used partners, and one of the most remarkable examples of an all-intramolecular cascade involves the nucleophilic trapping of a homoallylpalladium intermediate by a malonic ester enolate moiety in **34** to yield the triquinanes **35** and **36** in a key step for the synthesis of capnellene by Balme et al. (*scheme 11*) [17].



Scheme 11.

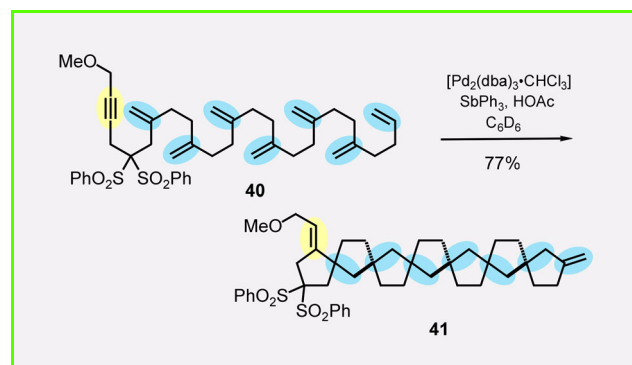
Heteroatom nucleophiles may also serve to capture organypalladium intermediates. Amines are employed most frequently, but trapping by oxygen and even sulfur nucleophiles have also been reported [18]. A convincing example of a cascade cyclization in which a hydroxy group is involved as the nucleophile has been developed into a key step for an elegant synthesis of morphine by Overman et al. The precursor **37** undergoes an intramolecular carbopalladation



Scheme 12.

PMP = 1,2,2,6,6-pentamethylpiperidine.

forming a σ -allyl/ π -allyl complex which is intramolecularly trapped by the phenolate ion (*scheme 12*) [19]. Directed syntheses of larger oligocycles become more difficult with an increasing number of fused rings, because side reactions within the oligo-unsaturated precursor may occur. The best results are obtained by zipper type reactions, that may be initiated by an intramolecular carbopalladation as in a conventional Heck cross coupling or as in an enyne cycloisomerization as developed by Trost et al. [20]. In one of the most impressive examples of a cascade reaction, seven new rings are generated in one operational step. In this case, a 1,1-disubstituted alkenyl unit serves as the relais for each consecutive step, since carbopalladation of such a moiety yields a neopentylpalladium species which is unable to undergo a terminating β -dehydropalladation. Therefore, cycloisomerization of heptaeneyne **40** yields the hexaspiro compound **41** in 77% yield (*scheme 13*) [21].



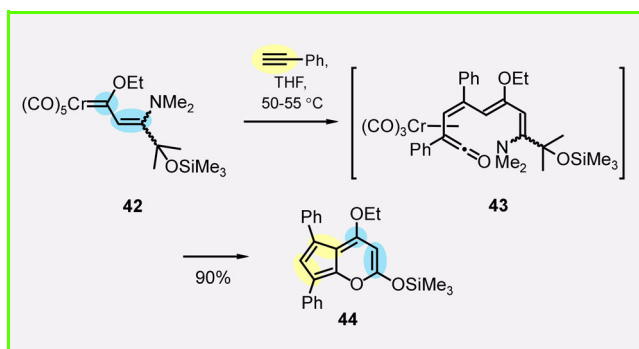
Scheme 13.

Chromium mediation

The advent of chromium being applied in organic synthesis has come about with the discovery by Fischer and Dötz, that certain types of the so-called Fischer carbene complexes [22], namely the aryl-substituted and α,β -unsaturated ones, undergo [3+2+1] cocyclizations with acetylenes under carbon monoxide insertion [23]. Hundreds of applications of this so-called Dötz reaction have meanwhile been published. Yet, α,β -unsaturated Fischer carbenes have also been found to undergo a multitude of other reactions, and by careful choice of the substrate structure as well as the reaction conditions, most of these reaction modes can be addressed selectively, so that α,β -unsaturated Fischer

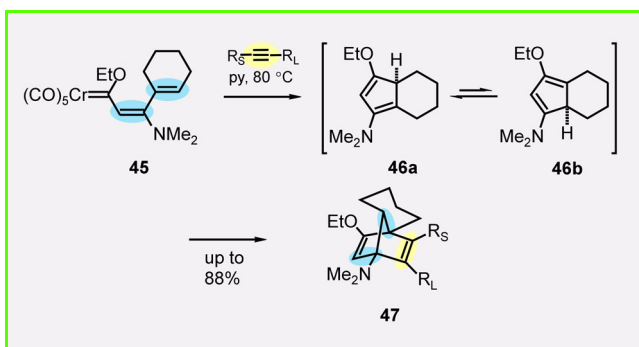
carbene complexes have rightly been termed « chemical multit talents » [24].

A cascade reaction which, in analogy to the Dötz reaction, starts with the insertion of an alkyne into the chromium-carbon double bond, has been discovered by de Meijere et al. for certain β -amino-substituted Fischer carbene complexes to lead to cyclopenta[*b*]pyrans [25]. The cascade continues with a second alkyne as well as CO insertion to yield **43**, which subsequently undergoes an intramolecular [4+2] cycloaddition, and it is terminated by 1,4-elimination of dimethylamine to give **44**. Overall this reaction corresponds to a [3+2+2+1] cocyclization (scheme 14).



Scheme 14.

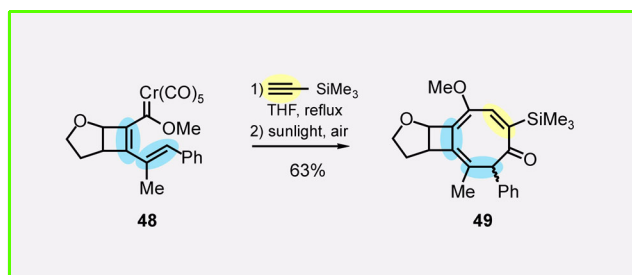
With an additional double bond in conjugation to the α,β -unsaturated chromiumcarbene moiety such as in **45**, these complexes constitute 1-metalla-1,3,5-hexatrienes that can undergo thermal 6π -electrocyclization and reductive elimination. The resulting ring-annulated cyclopentadiene **46a** equilibrates by rapid 1,5-hydride shift with **46b**, which can undergo intermolecular [4+2] cycloaddition with an added alkyne to yield tricyclic compounds of type **47** (scheme 15) [26].



Scheme 15.

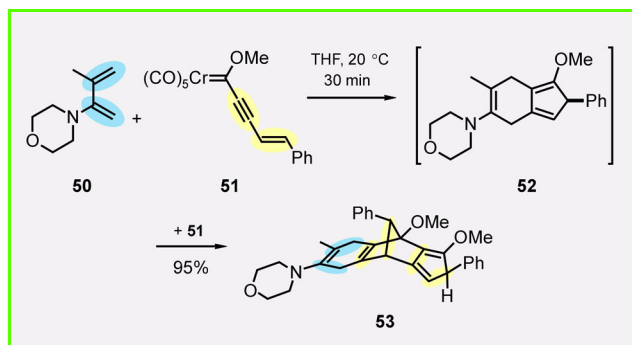
Barluenga et al. have recently found that 1-metalla-1,3,5-hexatrienes of type **48** can also insert an alkyne and one molecule of carbon monoxide, and then – instead of the usual 6π -electrocyclization – undergo 8π -cyclization to an eight-membered ring **49** with participation of the additional double bond present in the starting material **48** (scheme 16) [27].

As shown above for various examples, reaction cascades may consist of any number of metal-mediated and non-metal-mediated steps. Although frequently the metal-mediated process sets the scene for a subsequent thermal



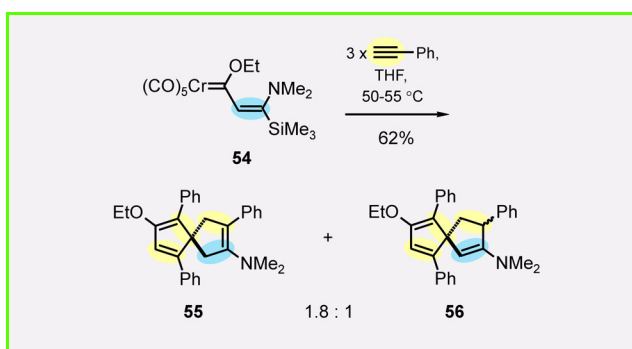
Scheme 16.

reaction, e.g. an electrocyclization or a cycloaddition, the sequential events can also occur the other way around. Barluenga et al. reported a striking example of a reaction cascade involving two thermal [4+2] cycloadditions, each immediately followed by a chromium-mediated cyclization [28]. The cascade commences with the Diels-Alder reaction of the morpholinyl-substituted diene **50** onto the α,β -unsaturated carbene complex **51** with subsequent electrocyclization and reductive elimination to give the ring-annulated cyclopentadiene **52**, and this smoothly undergoes a second [4+2] cycloaddition with another molecule of the carbene complex **51**, to be followed by a second electrocyclization and reductive elimination to eventually give the tetracycle **53** in 95% yield (scheme 17).



Scheme 17.

Finally, one of the mechanistically most puzzling cascade reactions is that involving one molecule of the β -dimethylamino- β -trimethylsilyl substituted α,β -unsaturated Fischer carbene **54** and three molecules of an aryethyne (e.g. phenylacetylene) leading to isomeric spiro[4.4]nonatrienes **55** and **56** in up to 62% yield (scheme 18) [29].



Scheme 18.

Outlook

This account is not meant to be a comprehensive review of metal-assisted cascade or domino reactions, as this would actually far exceed this complete issue. It is rather intended to point out some of the most important and striking examples picked from the literature of the last 12 years, demonstrating the tremendous variety of possibilities for metal-catalyzed and mediated reactions each leading from small building blocks to complex molecules in a single operational step. Considering the myriads of possible mechanisms and types of products, cascade and domino reactions surely offer a wide-open field of challenging research for the next decade to come.

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A. de Meijere

Armin de Meijere¹

is professor of the Faculty of Chemistry at the University of Göttingen*.

Michael Schelper²

is doctoral student in the research group of Prof. A. de Meijere.



M. Schelper

* Institut für Organische Chemie, Georg-August-Universität Göttingen, Tammannstr. 2, D-37077 Göttingen, Germany.

¹ Tel. : +49 (551) 393231. Fax : +49 (551) 399475. E-mail: ameijer1@gwdg.de

Homepage: <http://www.gwdg.de/~ucoc/adm>

² Tel. : +49 (551) 393296. Fax : +49 (551) 399475. E-mail: mschelp1@gwdg.de