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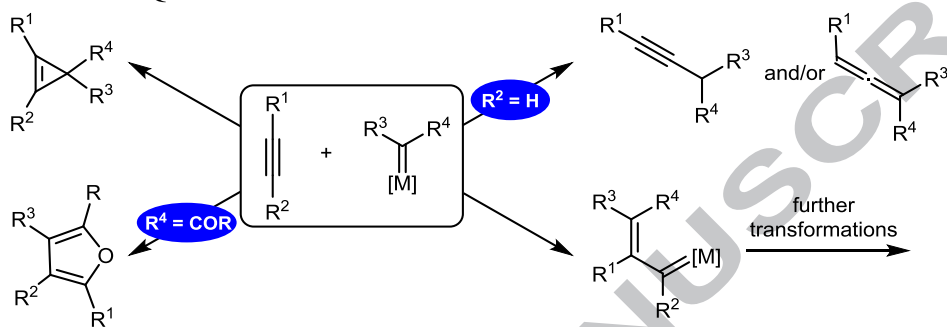


Graphical Abstract

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The rich reactivity of transition metal carbenes with alkynes

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ABSTRACT

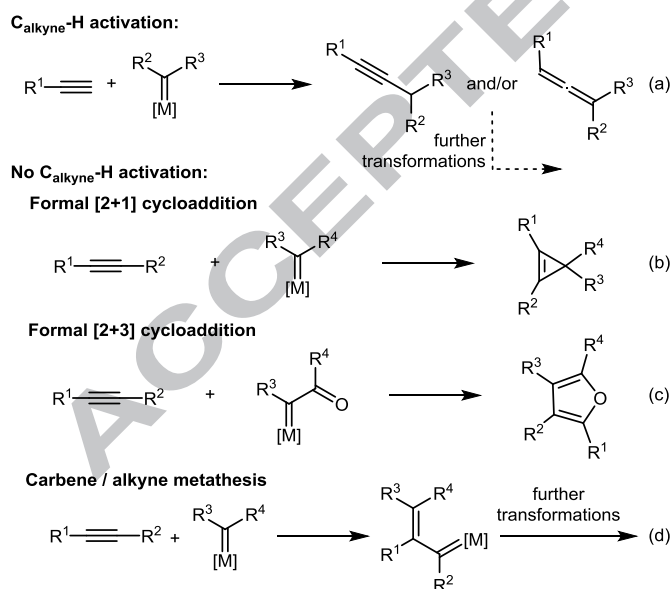
Transition metal carbenes are versatile intermediates that can mediate in many reactions. Among the different reactions they can participate in, their reactions with alkynes are especially diverse. The present digest describes the different reaction pathways that can take place when a transition metal carbene reacts with an alkyne, summarizes the most recent developments for each reactivity profile, and tries to shed light on the factors influencing the different reaction types.

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Transition metal carbenes are high energy intermediates with a particularly diverse reactivity profile that are extensively used in synthetic chemistry.¹ They can participate in various transformations, such as X-H insertions, cyclopropanations, ylide formations and 1,2-migrations. Transition metal carbenes can react with a large number of functional groups. Among these various functional groups, alkynes show a particularly diverse reactivity. In the present digest, we will revise the myriad of transformations that can take place when alkynes react with transition metal carbenes. The transformations have been classified by whether or not a C_{alkyne}-H activation of a terminal alkyne is involved (Scheme 1). Firstly, the reactions in which alkyne or allene compounds are formed in processes that involve a C_{alkyne}-H activation are described (Scheme 1, a). When either the alkyne or the diazo precursor are conveniently functionalized, further reactivity that generally leads to cyclic compounds is obtained, as will be discussed in a second section. Processes not involving C_{alkyne}-H activation are then presented, subdivided into three categories. The first two of these comprise processes that can, in general terms, be described as cycloaddition reactions (Scheme 1, b and c). The last contains the processes that are postulated as involving a carbene/alkyne metathesis as key step (Scheme 1, d).

This report will focus on the most recent advances in the area, and includes only the examples in which the transition metal carbene is generated from decomposition of diazo compounds, or related derivatives that are postulated to generate this type of compounds in situ, with different transition metals. Examples in which the transition metal carbene is obtained as a result of a previous reaction (i.e. cyclization of ene-yne-ketones, gold-catalysed oxidative diyne cyclizations, etc.) are not covered in the present digest.

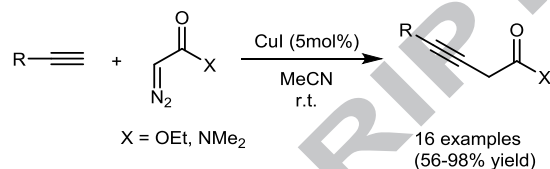


Scheme 1.

Processes involving C_{alkyne}-H activation

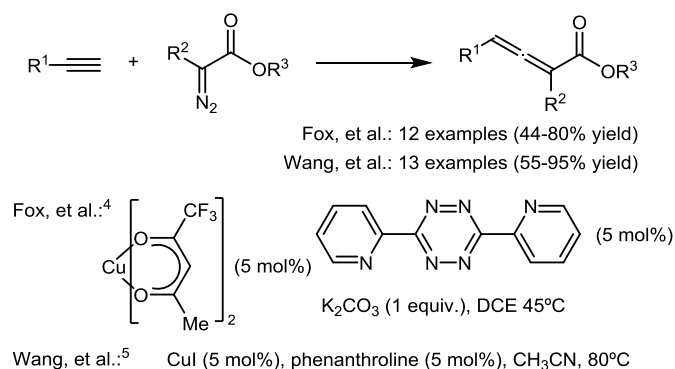
The copper-catalysed decomposition of diazo compounds in the presence of terminal acetylenes to produce allenes and alkynes (Scheme 1, a) was reported in seminal works although with generally moderate yields and harsh reaction conditions.² It

was not until 2004 that Fu *et al.* described a practical method for the synthesis of 3-alkynoates by coupling terminal alkynes with ethyl diazoacetate under CuI catalysis in non-basic conditions at room-temperature (Scheme 2).³ A small quantity of the allene isomer of the 3-alkynoate was observed as a by-product. The reaction was efficient with aryl, alkyl, and silyl-substituted alkynes and was also extended to a diazoamide.



Scheme 2.

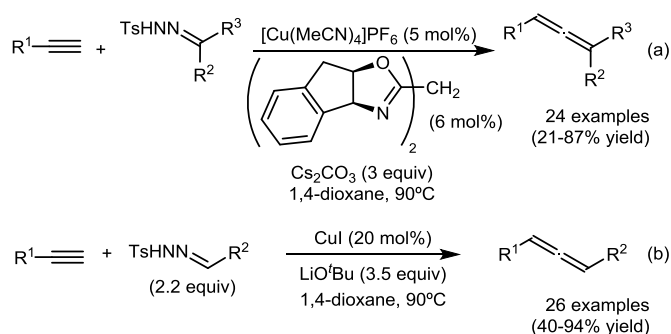
Some years later, Fox *et al.* reported the coupling of α -substituted- α -diazoesters with terminal alkynes with selectivity that was complementary to Fu's method.⁴ Allenates were obtained as main products with small traces of the alkynoates when Cu(II)(trifluoroacetylacetonate)₂ and 3,6-di(2-pyridyl)-s-tetrazine as the ligand were used as the catalytic system in DCE (Scheme 3). The authors found that the inclusion of potassium carbonate improved the selectivity for allenates products. Wang *et al.*, who have been particularly active in researching this topic, reported the same transformation as Fox *et al.* but using CuI and phenanthroline in acetonitrile at 80°C under base-free conditions (Scheme 3). However, it should be noted that this finding^{5a} was a later correction to the originally published paper,^{5b} which had described furans as being obtained.



Scheme 3.

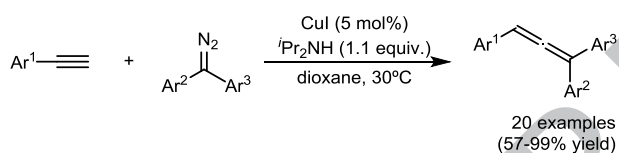
Wang *et al.* then introduced the use of *N*-tosylhydrazones as carbene sources for coupling to terminal alkynes. The combination of [Cu(MeCN)₄](PF₆)₂ with a racemic bis(benzoxazole) ligand provided an efficient catalytic system for the synthesis of trisubstituted allenes in basic conditions (Scheme 4, a).⁶ *N*-tosylhydrazone substrates derived from alkyl and aryl ketones reacted smoothly although in moderate yields. The reaction was not efficient with *N*-tosylhydrazones derived from aldehydes but the same authors later on reported a modification which was efficient for these substrates.⁷ By using CuI without a ligand, 1,3-disubstituted allenes were obtained in moderate to

good yields (Scheme 4, b). It was possible to scale up the synthesis to gram-scale.



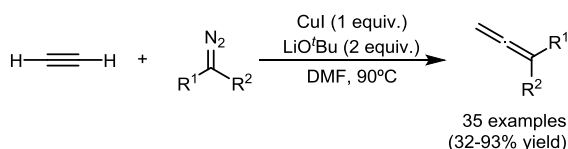
Scheme 4.

Wang *et al.* also reported the synthesis of tri-aryl-substituted allenes by using diaryldiazomethanes as substrates (Scheme 5).⁸ As an extension of their previous work, they succeed in developing a milder method which does not require the use of a ligand for the copper catalyst. In fact, by mixing the diaryldiazomethanes with the terminal alkyne under a nitrogen atmosphere with CuI, *i*Pr₂NH in 1,4-dioxane at 30°C, the trisubstituted allenes could be obtained in good yields.



Scheme 5.

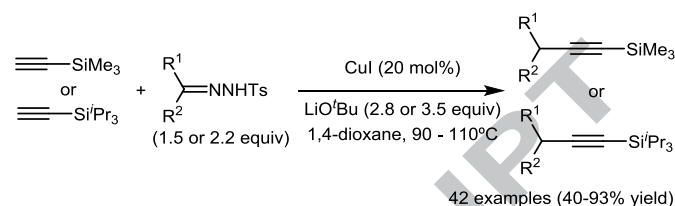
In order to synthesize terminal allenes, Wang *et al.* disclosed a reaction in which ethyne was used as a coupling partner (Scheme 6).⁹ The reaction, that needs one equivalent of copper, is operationally simple, since ethyne is reacted at atmospheric pressure conditions (with a balloon). Key to the success of this was the change of solvent to DMF. When aromatic *N*-tosylhydrazones bearing electron-donating substituents were reacted with three equivalents of base, 1-methyl-2-arylacetylene products were obtained in moderate yields. The authors attributed the formation of these products to the base-promoted rearrangement of the primary allene products. This reaction is amenable to metal carbenes generated both from *N*-tosylhydrazones and α -diazooacetates, although in this last case, one equivalent of 1,10-phenanthroline needs to be employed.



Scheme 6.

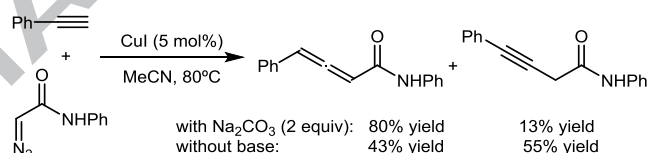
When the same authors tried to extend the terminal alkyne scope to trialkylsilylalkynes, they found that the selectivity of the reaction switched again to favour the formation of alkynes

(Scheme 7).¹⁰ The coupling proceeded efficiently with *N*-tosylhydrazones derived from aromatic and aliphatic aldehydes and ketones. Steric effects could not account for the alkyne/allene selectivity since the coupling with a *tert*-butyl substituted alkyne, with analogous steric hindrance, selectively gave the allene.



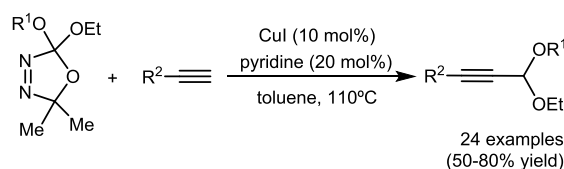
Scheme 7.

Sun *et al.* described the CuI catalysed reaction of diazoacetamides and alkynes to form mixtures of dienamides and 3-butynamides.¹¹ When sodium carbonate was added to the reaction mixture, the allenic compounds were obtained as main products. In base-free conditions, alkynes were the major product to be isolated (Scheme 8). In a test control, a couple of the alkynes were converted to the isomeric allenes under the optimized reaction conditions, but excluding the copper catalyst.



Scheme 8.

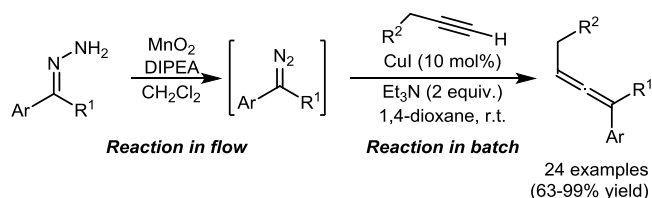
In 2014, Zhou *et al.* reported the synthesis of propargylic acetals through the CuI-catalysed coupling of terminal alkynes with dialkoxycarbenes, obtained from thermal cleavage of 2,2-dialkoxy-5,5-dimethyl- Δ^3 -1,3,4-oxadiazolines (Scheme 9).¹² Metal carbenes bearing electron-donating substituents, which are difficult to obtain from diazo compounds or *N*-tosylhydrazones, could easily be generated using this source of carbenes. The best yield was obtained when pyridine was used as a base in toluene. Various oxadiazolines and terminal carbenes were efficiently involved in the reaction.



Scheme 9.

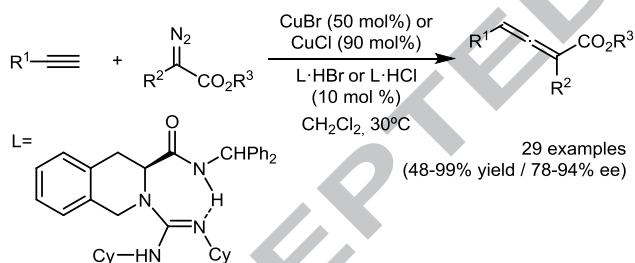
Ley *et al.* combined the formation of unstabilized diazo compounds in flow and the coupling to terminal alkynes in batch for the formation of di- and trisubstituted allenes.¹³ The diazo compounds were generated from their corresponding hydrazones by oxidation with activated MnO₂ in flow and directly added to the reaction mixture containing the base, the terminal alkyne and the CuI. Whereas disubstituted allenes could be obtained using

triethylamine in 1,4-dioxane at room temperature, in order for the method to be applicable to the synthesis of trisubstituted allenes, addition of a 20 mol % of 2,6-lutidine as an additive was necessary (Scheme 10). In order to highlight the great selectivity and functional-group tolerance of the methodology developed, the authors applied the reaction to norethindrone and propargylated quinine.



Scheme 10.

An asymmetric version for the synthesis of chiral trisubstituted allenoates was reported in 2015 by Liu et al., making use of a chiral guanidine amide that acts as a ligand for copper.¹⁴ Although most of the reactions reported so far have shown that CuI gave superior results to other copper(I) halides, Liu et al. used CuBr or CuCl in their optimized conditions with no additional base present (Scheme 11). Control experiments showed that the process did not consist of an enantioselective isomerization of an alkyne that might be formed. X-band EPR measurements suggest that the reaction begins with the formation of a ligand/copper carbene that suffers a mechanism that is more complex than the generally speculated, as the authors discuss in their paper.

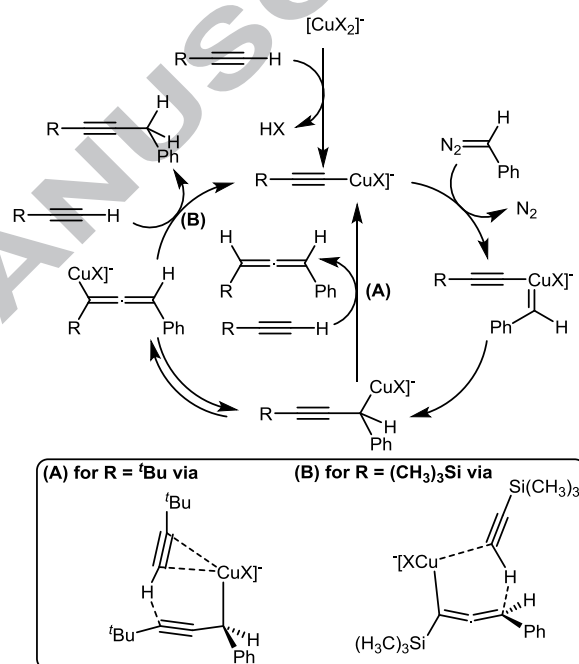


Scheme 11.

In order to shed light on the mechanism of these reactions, M. Wang and Liu reported in 2014 a DFT study¹⁵ into the mechanism of the Cu(I) catalysed coupling of *tert*-butylethyne or trimethylsilylethyne with (diazomethyl)benzene that were known to furnish an allene⁷ or a silylated alkyne¹⁰, respectively. Whereas almost all authors coincide with the fundamental steps involved in the catalytic cycle for such couplings, i.e. copper-acetylide and copper carbene formation, copper carbene migratory insertion and protonation, other details of the reaction mechanism are ambiguous. The aim of the paper was two-fold. Firstly, to determine the order in which the elemental steps take place in the catalytic cycle, i.e. if the catalytically active species reacts first with the terminal alkyne or with the diazo compound. Secondly, the authors aimed to gain insights into the effect of the alkyne's substituents on the product selectivity (Scheme 12).

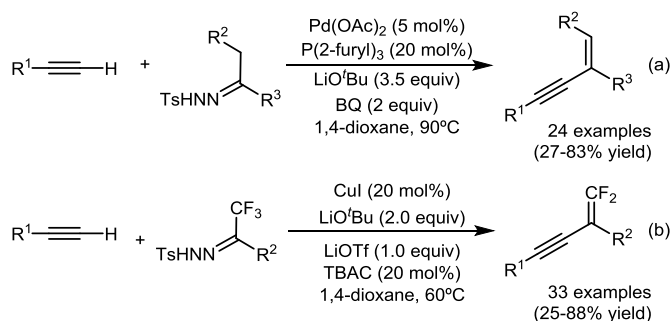
After the detailed mechanistic study which considered [^tBuO-Cu-O^tBu] as the catalytically active species, they were able to show that it is energetically more favourable to generate first the

copper acetylide, which subsequently reacts with the diazo compound to form the copper carbene. The second crucial point toward product selectivity in the catalytic cycle is protonation. After the migratory insertion of the alkynyl group into the Cu-carbene bond, which has a small energy barrier, equilibrium is established between the resulting alkynyl copper complex and its isomeric allenyl copper intermediate. Whereas trimethylsilylacetylene is proposed as the proton donor towards the formation of the trimethylsilylalkyne derivative, either the starting alkyne or *tert*-butanol competitively act as the proton donor when *tert*-butylethyne is reacted to give the allene (Scheme 12). What they propose as key factors for product selectivity are subtle structural variations such as the η^2 -coordination of the protonating alkyne to the copper-centre in the transition state leading to the allene or the back-donation from the π orbital of the triple bond to the σ^* orbital of Si-CH₃, which stabilizes the corresponding alkynyl anion and facilitates the proton exchange.



Scheme 12.

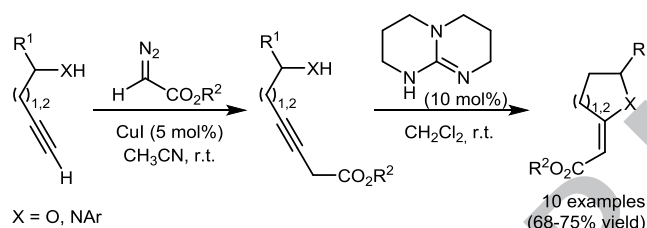
On the other hand, there are a couple of examples, both by Wang et al., in which conjugated enynes are obtained, as a result of a β -elimination process terminating the catalytic cycle (Scheme 13). In the first, the coupling of terminal alkynes with either *N*-tosylhydrazones or diazoesters was described although this time under palladium catalysis.¹⁶ The use of weak electron-rich phosphines as ligands for palladium(II) together with ^tBuOLi as a base and benzoquinone as the oxidant leads to the formation of conjugated (*Z*)-enynes (Scheme 13, a). When 2-diazopropanoates were reacted, the conjugated enyne that was initially formed suffered a subsequent palladium-catalysed cyclopropanation with the excess of diazo compound. In the second, trifluoromethyl ketone *N*-tosylhydrazones were used as substrates, again under CuI catalysis. 1,1-difluoro-1,3-enynes were accessed in a process that involved a rare β -F elimination (Scheme 13, b).¹⁷



Scheme 13.

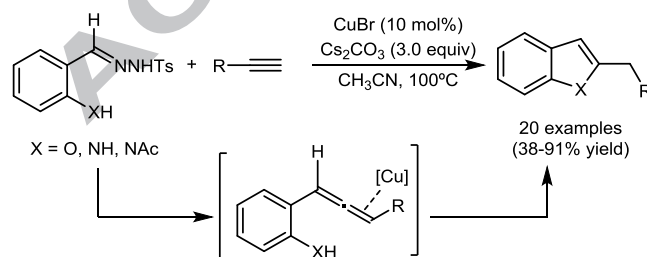
Several cases in which this reactivity is coupled to other reactions to obtain more elaborated, mostly cyclic, compounds complement this topic, as will be outlined below.

In 2010, Tan et al. reported the synthesis of oxacycles and azacycles through a Brønsted base-catalysed tandem isomerization-Michael reaction of alkynoates¹⁸ synthesized following Fu's method.³ This two-step protocol efficiently furnished 2-alkylidene tetrahydrofurans and piperidine, lactam and oxazolidinone derivatives (Scheme 14).



Scheme 14.

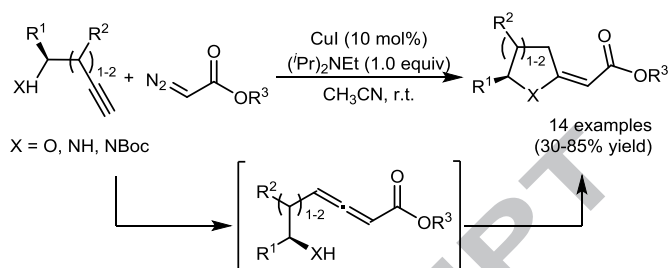
Several further examples achieved the cyclization step in the same reaction in which the coupling between the alkyne and the metal carbene took place. For instance Wang et al. realized that when *N*-tosylhydrazones derived from *o*-hydroxy- or *o*-aminobenzaldehydes were reacted, the hydroxyl or amino group functioned as an intramolecular nucleophile that attacked the initially formed allene to afford benzofurans or indoles (Scheme 15).¹⁹



Scheme 15.

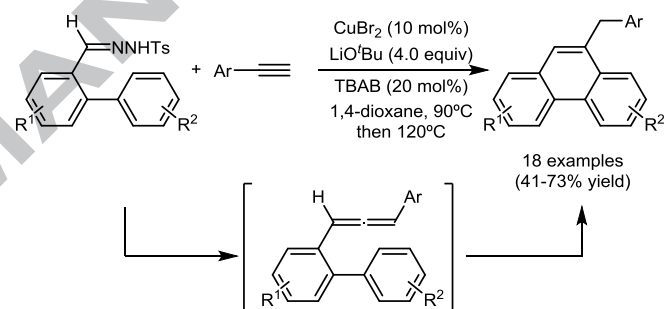
If an alkyne with a properly located nucleophile is reacted with a benzyldiazoester under Cu(I) catalysis, the allene which is initially formed suffers a cyclization reaction as a result of an oxa or aza-Michael reaction leading to either 5- and 6-membered oxa or azacycles, as reported by Kumaraswamy et al. (Scheme 16).²⁰

The methodology developed has been used for the synthesis of the piperidine alkaloid (+)-pinidione.



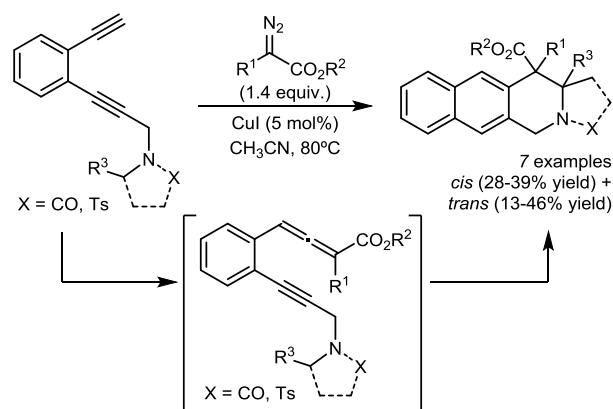
Scheme 16.

Wang et al. also developed a phenanthrene synthesis²¹ via CuBr₂-catalysed coupling of *N*-tosylhydrazones derived from *o*-formyl biphenyls with terminal alkynes. The allene product initially formed suffers a thermally triggered 6π cycloaddition and isomerization that affords the final phenanthrene product (Scheme 17).



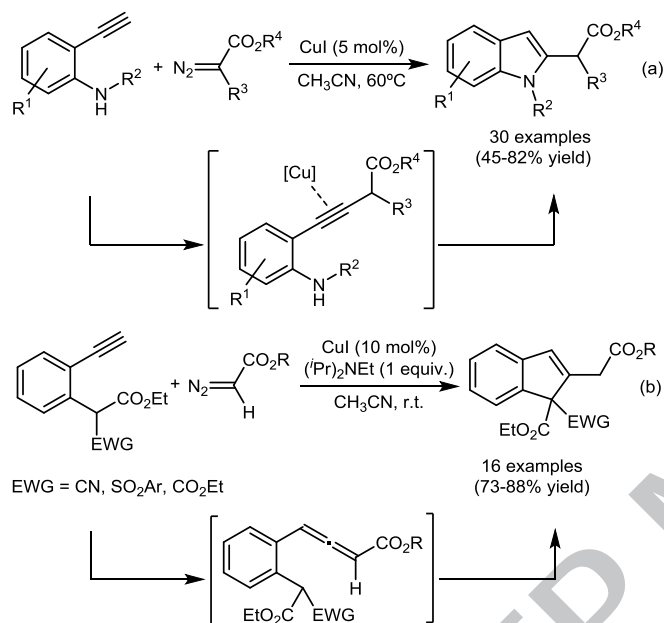
Scheme 17.

The reaction of diazoesters with diynes under CuI catalysis leads to the formation of tetracyclic esters through a Myers-Saito cyclization of the allenoate, which Nechab, Bertrand, et al. postulate as being formed in equilibrium with the alkynoate in a copper carbene mediated 1,3-proton migration, formed in the first coupling.²² The reaction delivers mixtures of the two possible diastereoisomers (Scheme 18). The products are isolated in high enantiomeric excesses when starting from enantiopure enediynes.



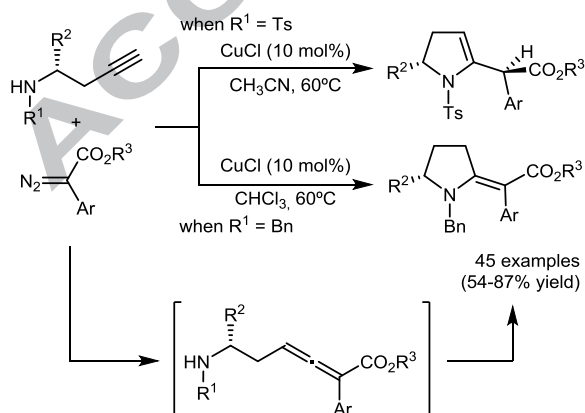
Scheme 18.

Sun et al. reported the direct synthesis of C2-(carboxylate methyl) substituted indoles by a copper-catalysed annulation of α -substituted diazoacetates with 2-ethynylanilines (Scheme 19, a).²³ The authors postulate a mechanism based on the Cu-catalysed coupling reaction providing an alkynoate, in which the copper still complexed to the alkyne catalyzes the annulation to form the indole ring. Kumaraswamy et al. used activated carbon nucleophiles in the cyclization reaction to achieve the efficient synthesis of indene and dihydronaphthalene derivatives (Scheme 19, b).²⁴ The intramolecular Michael addition of the carbon-based nucleophile to the allenolate explains the formation of the title compounds.



Scheme 19.

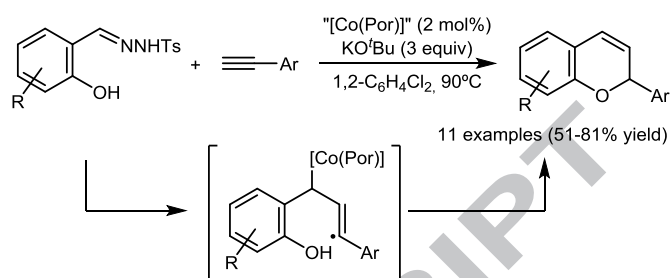
Sun et al. also reported the stereodivergent synthesis of dihydropyrroles and pyrrolidines through the copper catalysed reaction of diazo compounds and amino alkynes (Scheme 20).²⁵ After the copper-catalysed formation of the allenolate, an hydroamination reaction afforded the *N*-heterocycles.



Scheme 20.

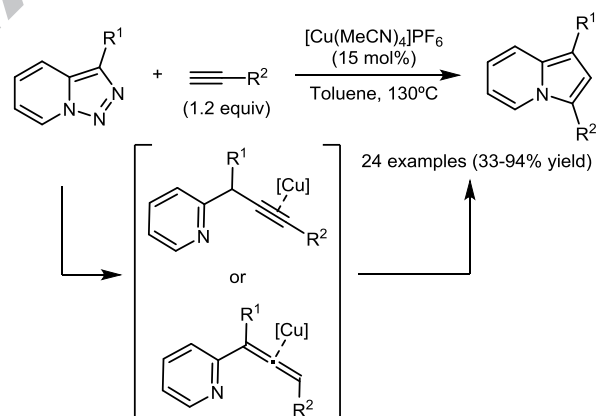
A cyclization reaction of *N*-tosylhydrazones and alkynes to deliver 2H-chromenes (Scheme 21) has been described by de

Bruin, et al.²⁶ The process is catalysed by a Co(II) complex of a porphyrin (“[Co(por)]”) and proceeds via a radical mechanism that involves a Co(III) carbene radical intermediate.



Scheme 21.

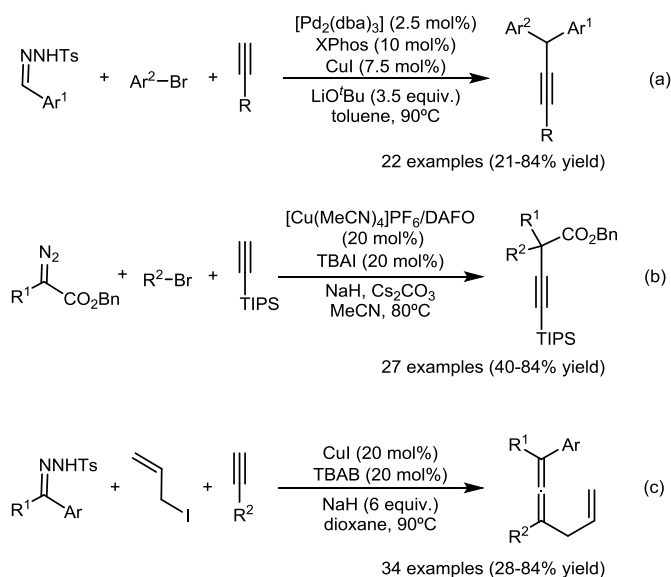
Gevorgyan et al. described the synthesis of indolizines through a coupling reaction involving a copper carbene generated by denitrogenation of pyridotriazoles (Scheme 22),²⁷ which are an interesting alternative for the generation of carbenes. Aryl, heteroaryl and aliphatic alkynes were all competent coupling partners in the reaction. The same authors had previously reported analogous processes under rhodium-catalysis but the postulated mechanism did not involve a C(*sp*)-H activation (*vide infra*).



Scheme 22.

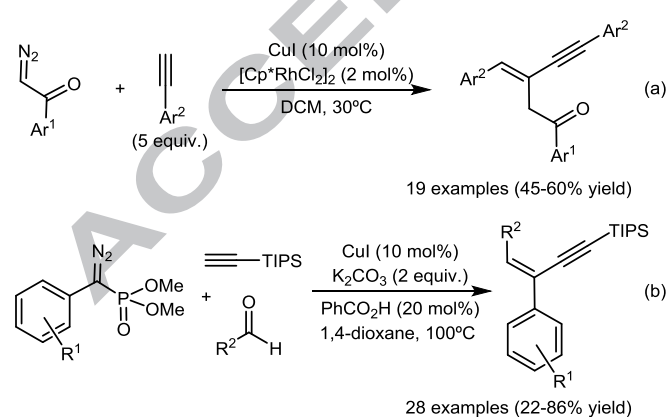
Finally, there are several examples in which three-component cross-couplings have been devised. Wang et al. reported two consecutive papers in which two new C-C bonds were constructed on the carbenic carbon. In the first, a Pd-catalysed sequence of migratory insertion-transmetalation-reductive elimination involving a *N*-tosylhydrazone, a copper acetylide (in situ generated from the alkyne) and an aryl halide was described. The method entails the consecutive construction of a C(*sp*)-C(*sp*³) and a C(*sp*²)-C(*sp*³) bond on to the former carbonic carbon (Scheme 23, a).²⁸ In the second, copper is used as the only catalyst to achieve the formation of both a C(*sp*)-C(*sp*³) and a C(*sp*³)-C(*sp*³) bond. In this case the carbene source is an α -diazo ester that reacts first with the alkyne to form the C(*sp*)-C(*sp*³) bond and then with either an alkyl halide or a Michael acceptor to construct the C(*sp*³)-C(*sp*³) bond furnishing an all-carbon quaternary centre (Scheme 23, b).²⁹ The same group reported another three-component reaction in which the allenyl copper intermediate, and not the propargyl copper one, formed after the first coupling reaction was trapped with an electrophile (Scheme

23, c).³⁰ *N*-tosylhydrazones derived from both aldehydes and ketones were competent substrates.



Scheme 23.

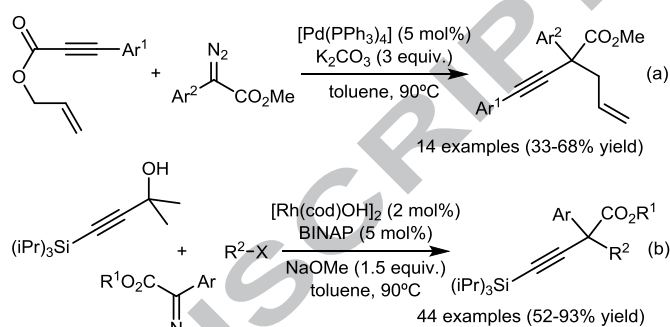
Hao, Tu, Jiang, et al. described the synthesis of 1,3-enynes through a three-component coupling reaction catalysed synergistically by rhodium and copper.³¹ An α -diazoketone was used as the carbene source to couple with an alkyne to generate an allene intermediate, which was nucleophilically attacked by the second alkyne equivalent (Scheme 24, a). Arylamines could also be used as nucleophiles to afford *N*-aryl enaminones. A novel synthesis of 1,3-enynes has also been recently described by Wang et al. using a three component strategy.³² The copper intermediate generated by reaction of α -diazophosphonates and triisopropylsilylacetylene was in situ reacted with an aldehyde in a Horner-Wadsworth-Emmons type reaction to provide access to conjugated enynes (Scheme 24, b).



Scheme 24.

Two other examples of three-component reactions are reported in the literature that have the particularity that acetylides are not directly generated from the terminal alkyne but are either obtained after the decarboxylation of an allylic carboxylate³³ or on β -carbon elimination from *tert*-propargyl alcohols.³⁴ In the first,³³ a propiolic acid derivative reacts under palladium

catalysis to afford a palladium allyl acetylide (with concomitant loss of CO_2) that then reacts with methylphenyldiazoacetate derivatives to generate enyne compounds with an all-carbon quaternary centre (Scheme 25, a). In the second, Wang et al.³⁴ make use of a rhodium(I) catalyst to generate an alkynyl Rh(I) species after acetone elimination through a β -carbon elimination from *tert*-propargyl alcohols. The intermediate thus formed reacts with the diazo compound and with either an aryl or alkyl halide to generate two new carbon-carbon bonds (Scheme 25, b).



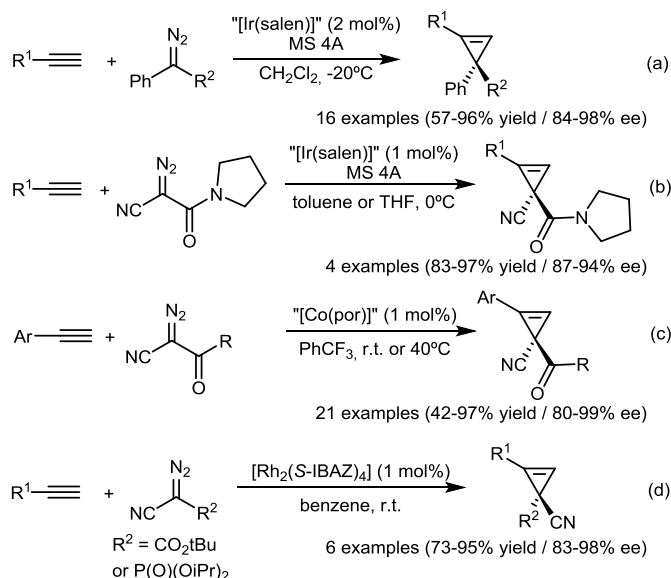
Scheme 25.

Processes NOT involving $\text{C}_{\text{alkyne}}\text{-H}$ activation

[2+1] Cycloaddition

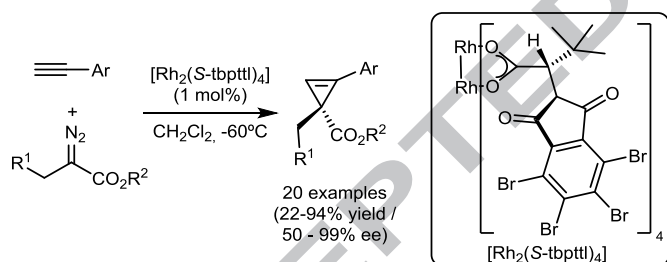
The preparation of cyclopropenes from a [2+1] cycloaddition reaction of diazo compounds and alkynes is a widely used, efficient methodology (Scheme 1, b). The reaction is catalysed by complexes of transition metals, mainly based on copper and rhodium, as has been described in previous review articles.³⁵ Here only a few general aspects will be recalled and complemented by more recent findings.

Katsuki et al. reported in 2011 the synthesis of enantioenriched cyclopropenes containing a quaternary asymmetric carbon by the reaction of 1-alkynes or arylacetylenes with diazo compounds.³⁶ The reaction was catalysed by an [Ir(salen)] complex that the same authors have also used in cyclopropanation and C-H reactions involving diazo compounds. Apart from the widely used ester and sulfonyl groups, phosphonate and trifluoromethyl groups were also engaged as the acceptor counterpart in the diazo precursor (Scheme 26, a). α -cyano- α -diazacetamides that are reluctant to participate in cyclopropanation reactions due to the acceptor nature of both substituents of the diazo compound were also used as substrates under the modified reaction conditions (Scheme 26, b). These acceptor/acceptor-substituted metal carbenes were generalized as substrates in enantioselective cyclopropanation reactions by Zhang et al (Scheme 26, c).³⁷ They use a chiral metalloradical porphyrin cobalt(II) complex that operates through a distinct radical mechanism. Two years later, Charette et al.³⁸ also contributed to the topic by developing a stereoselective Rh-catalysed cyclopropanation of alkynes with diaceptor diazo compounds (Scheme 26, d).



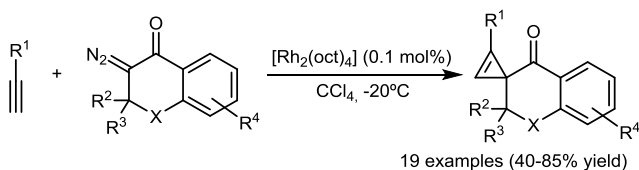
Scheme 26.

Hashimoto et al. prepared a new dirhodium(II) carboxylate complex that incorporates *N*-tetrabromophthaloyl-*(S)*-tert-leucinylate as chiral bridging ligands that proved capable of enantioselectively cyclopropanating terminal alkynes with α -alkyl- α -diazoacetates (Scheme 27).³⁹ The competing 1,2-hydride shift of α -alkyl- α -diazoacetates to form α,β -unsaturated esters could be at least partially avoided using the reported conditions.



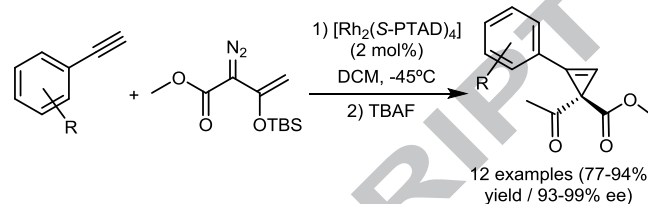
Scheme 27.

3-diazo chroman-4-one derivatives, an specific example of cyclic α -alkyldiazo carbonyl compounds, were also used in the cyclopropanation of phenylacetylene derivatives using a catalytical amount of $Rh_2(oct)_4$ (Scheme 28).⁴⁰ Ma et al. described the reaction and used the cyclopropene derivatives obtained in a cycloisomerization, either catalysed by BF_3 or $Cu(OTf)_2$, to assemble a new furan ring and form 4*H*-furo[3,2-*c*]chromene derivatives.



Scheme 28.

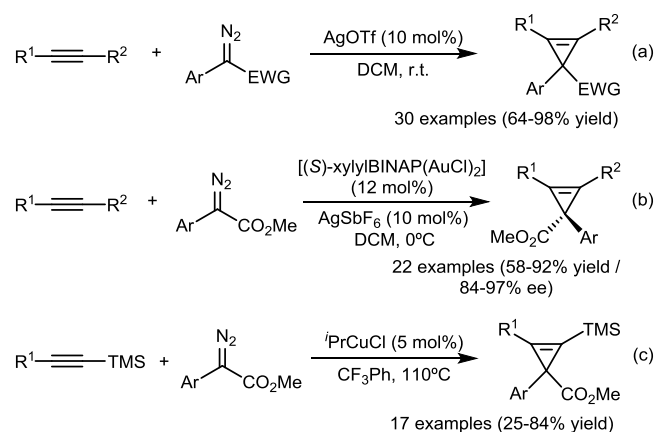
Asymmetric cyclopropenes bearing two carbonyl acceptor groups are not easily obtained due to the tendency of diazoacetates to form furan rings upon reaction with alkynes (*vide infra*). Davies et al. reported an indirect method to obtain such products that used siloxyvinyl diazoacetate, a donor/acceptor carbene precursor.⁴¹ In situ deprotection of the silyl group furnished the title compounds (Scheme 29).



Scheme 29.

Whereas cyclopropanation of internal alkynes is efficient with the highly reactive acceptor metal carbenes, it was not until 2011 that Davies et al. achieved its cyclopropanation starting from donor/acceptor diazo compounds. In a first paper, they described the use of silver triflate to afford tetrasubstituted cyclopropenes (Scheme 30, a).⁴² The asymmetric version was subsequently reported by the same authors switching from silver to gold catalysis.⁴³ Au(I) catalysts bearing BINAP ligands and activated with $AgSbF_6$, efficiently promoted the enantioselective cyclopropanation reaction (Scheme 30, b).

Coleman et al. also tackled the cyclopropanation of internal alkynes but using copper as the catalyst. After preliminary results showing that donor/acceptor diazo acetate reacted with 1-(*p*-methoxy)phenylprop-1-yne under CuI catalysis to afford tetrasubstituted cyclopropenes,⁴⁴ the authors applied the methodology to internal alkynylsilylanes to yield 1-silylcyclopropenes that are useful starting materials for various transition metal-catalysed transformations.⁴⁵ (1,3-Bis-(diisopropyl-phenyl)imidazole-2-ylidene) copper(I) chloride (*i*PrCuCl) was the catalyst of choice for the aforementioned transformation (Scheme 30, c).



Scheme 30.

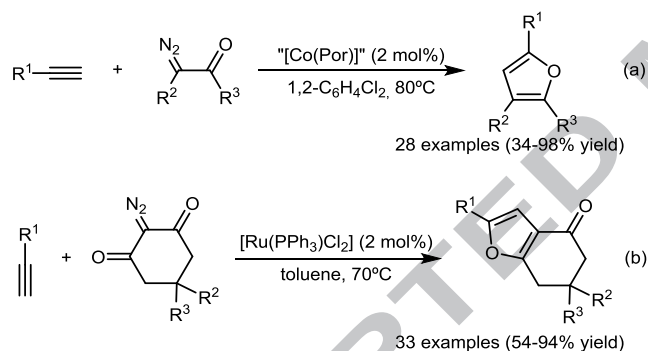
Finally, Rubin et al. reported an improved methodology for the use of trimethylsilylacetylene as an acetylene surrogate for the synthesis of 3-aryl-3-methoxycarbonyl cyclopropenes with an

unsubstituted double bond.⁴⁶ Since the alkyne was terminal, rhodium was efficiently used in this cyclopropanation reaction.

Formal [3+2] cycloaddition

Alkynes can also react with α -diazocarbonyl compounds under transition metal catalysis in a formal [3+2] cycloaddition to furnish furan derivatives (Scheme 1, c). This method is a highly convenient general protocol for the assembly of polysubstituted furans, as has been reviewed recently by Gevorgyan et al.⁴⁷ As in the case of cyclopropanation, here only a few general aspects will be mentioned, complemented by recent findings.

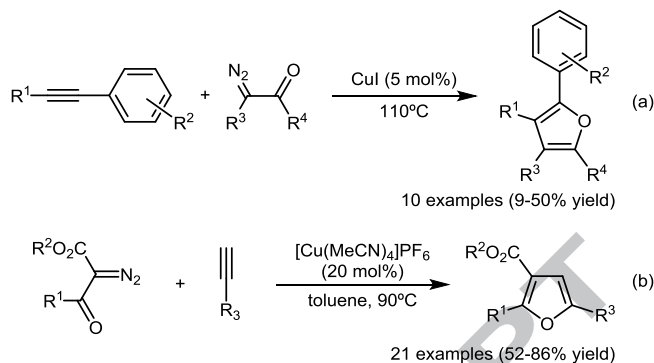
Although furan synthesis is generally catalysed by rhodium or copper complexes, other transition metals have also been used. Zhang et al. described the use of metalloradical Co(II)-porphyrin complexes [Co(Por)], which had already proved to be useful for the cyclopropanation reaction,³⁷ as catalysts for the formal [3+2] cyclization of alkynes with α -diazocarbonyl compounds (Scheme 31, a).⁴⁸ In cases where different carbonyl types were available for reaction, cyclization occurred preferentially on ketone or aldehyde carbonyl rather than the ester carbonyl. Both aromatic and aliphatic terminal alkynes were efficient substrates for the reaction. On the other hand, internal alkynes were inefficient for the transformation, which the authors take advantage of to develop an iterative synthesis toward oligofurans by reacting a bifunctional ketodiazooacetate bearing a TMS-protected internal alkyne.



Scheme 31.

Lee et al. reported the use of ruthenium for the reaction of terminal aryl alkynes and symmetrically substituted cyclic diazodicarbonyl compounds to afford fused bicyclic furan derivatives (Scheme 31, b).⁴⁹

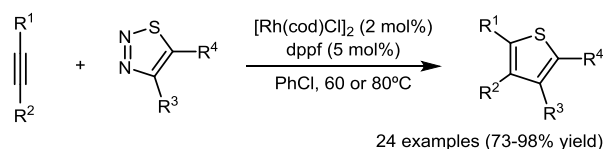
Coleman, et al. tackled the reaction with the less reactive internal alkynes.⁴⁴ Using CuI as the catalyst in neat conditions, tetrasubstituted furans were obtained in moderate yields (Scheme 32, a). Also using copper, Wang et al. reported the Cu(I)-catalysed reaction of terminal alkynes with β -keto- α -diazooesters as a straightforward synthesis of 2,3,5-trisubstituted furans (Scheme 32, b).⁵⁰



Scheme 32.

There is controversy as to which mechanism operates in the formal [3+2] cycloaddition of alkynes and α -diazocarbonyl compounds. Different possibilities have been proposed that involve ylide intermediates, by nucleophilic attack of the alkyne on to the metal carbene, or that the reaction starts with either a [2+1] or a [2+2] cycloaddition of the metal carbene and the alkyne involving cyclopropenes or metallacyclobutenes as intermediates, respectively.⁴⁷ The prevalence of one or other of this pathways is probably dependent on the catalyst used and the electronic and steric properties of the reagents.

The examples commented until now describe the cyclization of metallaovinyl carbenes for the formation of furans. Gevorgyan et al. have recently described the synthesis of multisubstituted thiophenes, via an analogous process that involved the intermediacy of a rhodium thiavinyl carbene rather than the metallaovinyl carbene.⁵¹ 1,2,3-thiadiazoles were used as an in situ source for the thiavinyl carbene that was trapped with rhodium and reacted with terminal alkynes, and even an internal one, to efficiently afford the desired polysubstituted thiophenes (Scheme 33). The use of a rhodium(I) catalyst was key to the success of the reaction.

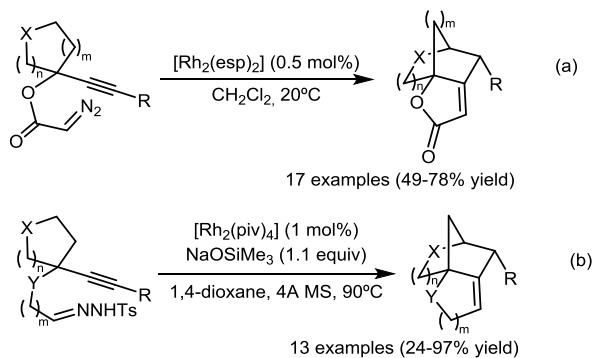


Scheme 33.

Carbene/alkyne metathesis

Carbene/alkyne metathesis refer to the processes where a metal carbene reacts with an alkyne, generating a new intermediate in which the carbene-like character is transferred to the β -carbon of the alkyne and a double bond is formed between the carbenic carbon and the α -carbon of the alkyne. The metal vinyl carbene thus formed may then be involved in typical metal carbene reactions such as cyclopropanation, C-H insertion or ylide generation, setting up cascade processes (Scheme 1, d). Since the seminal work of Padwa and Hoye, Padwa has worked intensively on the development of Rh(II) mediated carbene/alkyne metathesis on alkynyl-tethered diazocarbonyl compounds, providing a wide array of cyclopentenone derivatives.⁵² More recently, Doyle et al. addressed one of the limitations of the methodology – the synthesis of the substrates – by developing a general modular strategy for their preparation.⁵³

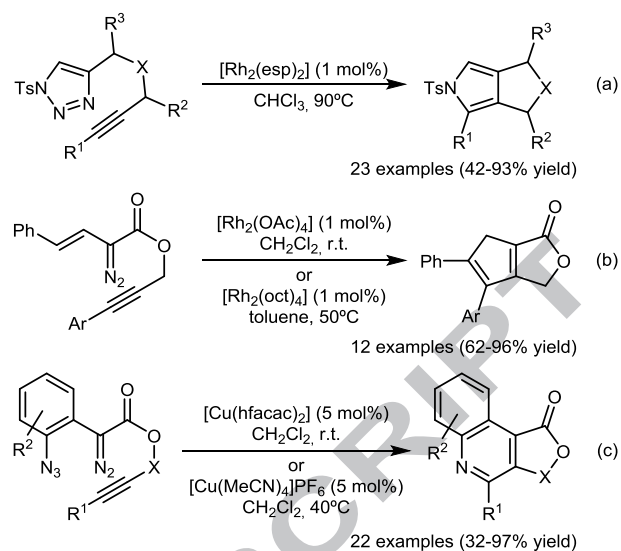
May et al. have used a carbene/alkyne metathesis followed by a C-H insertion to synthesize bridged polycyclic ring systems. Either by using an alkynyl diazoester⁵⁴ or an alkynyl tosylhydrazone,⁵⁵ bridged polycyclic ring systems of variable ring-sizes were obtained under Rh(II) catalysis, generally as diastereoisomeric mixtures (Scheme 34). NaOSiMe₃ was the ideal base to generate the diazocompound when tosylhydrazones were used as substrates, and in this case a ring-fused cyclopropene, could be identified as a key mechanistic intermediate.



Scheme 34.

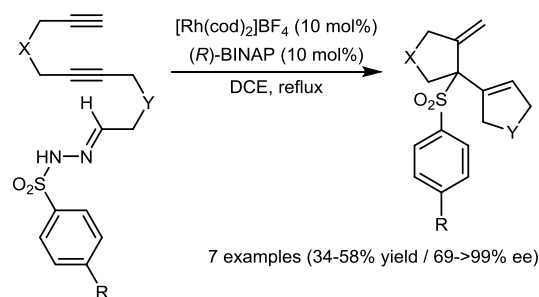
Gevorgyan et al. described the construction of 5,5-fused pyrrole units from alkynyl triazoles.⁵⁶ The rhodium-imino carbene generated from ring-opening of the *N*-sulfonyl-1,2,3-triazole, suffers a carbene/alkyne metathesis, followed by a nucleophilic attack of the imino N atom at the rhodium carbene to achieve the intramolecular transannulation reaction (Scheme 35, a).

Mao, Xu et al. reported a similar transformation that starting from alkynyl-tethered styryl diazoesters accomplished the construction of bicyclic cyclopentadiene scaffolds.⁵⁷ The transformation, which is only efficient for aryl alkynes, involved a carbene/alkyne metathesis followed by a formal [3+2] cycloaddition and a subsequent [1,5]-H shift (Scheme 35, b). The same group described the use of a transannular cyclization to obtain 4-carboxyl quinolines through a carbene/alkyne metathesis that terminated in the reaction of the vinyl carbene that was formed with the azide.⁵⁸ Whereas rhodium was only moderately efficient for quinoline formation, replacement by copper greatly improved the yield (Scheme 35, c).



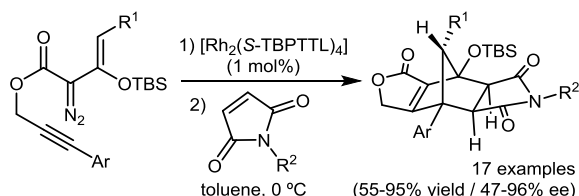
Scheme 35.

Our group has contributed to the topic by describing a two-fold carbene/alkyne metathesis on diyne arylsulfonyl hydrazone substrates.⁵⁹ The transformation is completed after an hydride migratory insertion followed by an intermolecular nucleophilic attack, furnishing sulfonated azacyclic frameworks. The reaction is highly enantioselective when using Rh(I) with atropisomeric BINAP ligands (Scheme 36) and constitutes the first example in which enantioselectivity has been achieved in cascades involving carbene/alkyne metathesis. Furthermore, the process is triggered by a base-free decomposition of the hydrazone. DFT calculations were used to postulate a mechanism of the reaction that was later supported by experimental evidence.



Scheme 36.

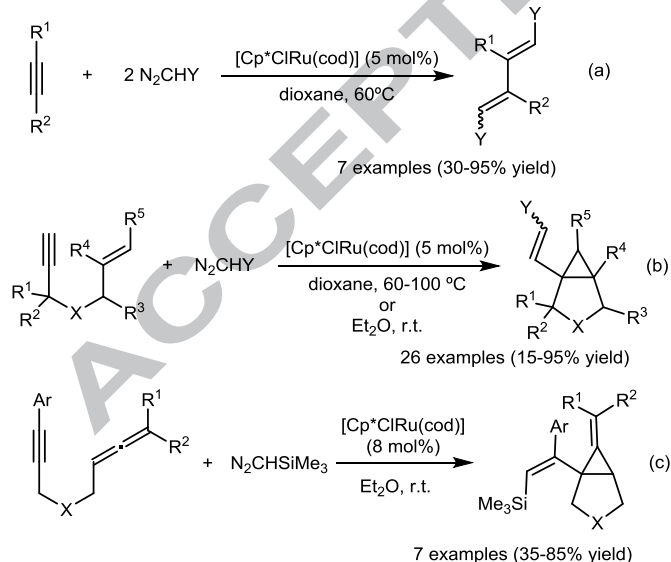
Bao, Xu, et al. have recently reported the enantioselective preparation of cyclopentadienes⁶⁰ by a cascade reaction of alkynyl-tethered enol diazoacetates. By introducing an enol functional group in the place of the styryl that they had used in an earlier study (Scheme 35 b),⁵⁷ chiral cyclopentadienes were obtained under Rh(II) catalysis, which were in situ trapped with *N*-phenylmaleimide to afford bridged polycyclic compounds (Scheme 37).



Scheme 37.

On the other hand, some groups have described intermolecular versions of the carbene/alkyne metathesis reaction. Dixneuf et al. studied the intermolecular formation of ruthenium vinyl carbenes and their subsequent transformations. One of the topics they explored was the formation of dienes.⁶¹ In a first paper, they reported their synthesis by a carbene/alkyne metathesis followed by the coupling of the ruthenium vinyl carbene formed with another equivalent of the diazoalkane (Scheme 38 a).^{61a} Two other papers followed that involved the reaction of propargylic carbonates and silyl diazo compounds.^{61b-c} Although a mechanism involving an initial Rautenstrauch rearrangement could not be unequivocally excluded, the authors propose a mechanism involving initial carbene/alkyne metathesis followed by acetate migration.

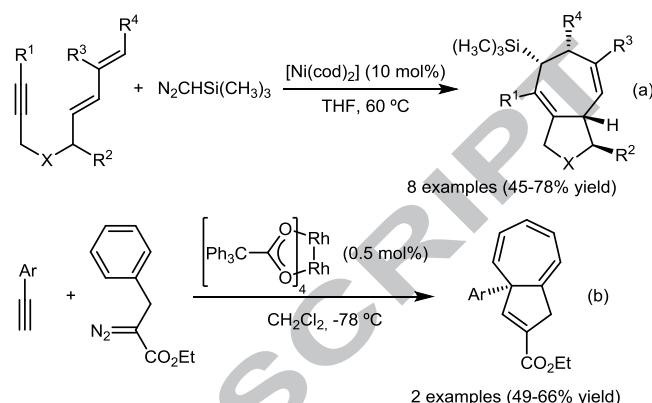
The same catalytic system, which inhibits the enyne metathesis, was efficient for the transformation of enynes into bicyclic vinylcyclopropanes.⁶² The diazoalkane intermolecularly reacts with the alkyne in the enyne to form the ruthenium vinyl carbene that intramolecularly cyclopropanates the tethered alkene (Scheme 38, b). This transformation has also been applied to the synthesis of bicyclic amino acid derivatives.^{62c} Later on, the same authors extended the methodology to the cyclization of allenynes into alkenyl alkylidene bicyclo[3.1.0]hexane derivatives (Scheme 38, c).⁶³



Scheme 38.

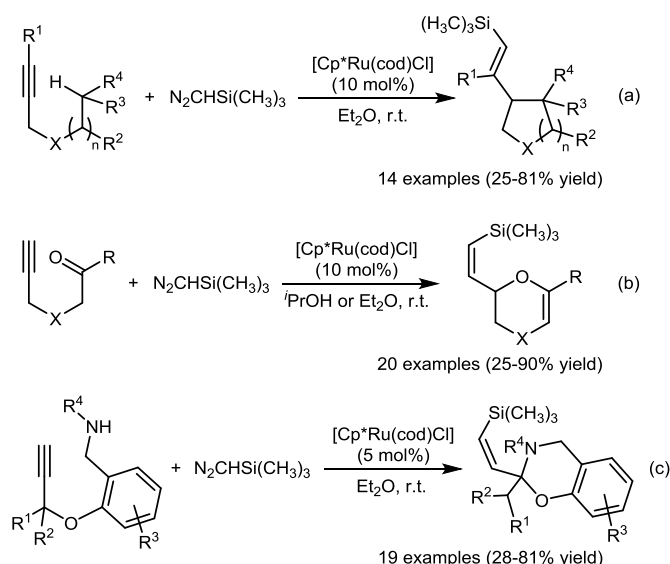
Montgomery et al. reacted a silyldiazo compound with a dienyne to develop a formal [4+2+1] cycloaddition.⁶⁴ Trimethyldisilyldiazomethane intermolecularly reacted under nickel catalysis with the diene-yne to initially afford divinylcyclopropanes that were transformed to bicycle-[3.5.0]-

decane derivatives upon [3,3] sigmatropic rearrangement (Scheme 39 a). Seven-membered rings could also be accessed by the Rh-catalysed cascade involving a carbene/alkyne metathesis followed by a Büchner ring expansion, as reported by Fox et al (Scheme 39 b).⁶⁵



Scheme 39.

Saá et al.⁶⁶ used the conditions established by Dixneuf et al.⁶¹ for the preparation of ruthenium vinyl carbenes to set up varied cascade processes (Scheme 40). In a first report,^{66a} they described a cascade that formed 5- or 6-membered rings through a C-H insertion onto activated positions (Scheme 40, a). In a second paper, they reported the synthesis in mild reaction conditions of 2-vinyldihydropyrans and dihydro-1,4-oxazines (Scheme 40, b) in a process in which the initially formed ruthenium vinyl carbene suffers a nucleophilic attack by the carbonyl group to afford a zwitterionic intermediate.^{66b} A final paper in the series, introduces the N-H insertion as a key step to the cascade to achieve the synthesis of 1,3-benzoxazines (Scheme 40, c).^{66c} The presence of an oxygenated tether is crucial for the rearrangement that follows the N-H insertion.



Scheme 40.

In summary, transition metal carbenes react with alkynes giving different products depending on various parameters. First

of all, the type of alkyne is crucial to determine whether or not a $C_{alkyne}-H$ activation is possible. Second, the structure of the metal carbene precursor is also a key factor in determining the reaction path, especially as to whether a [2+1] or a [3+2] formal cycloaddition operates. The catalytic system is the third crucial parameter. Although with notable exceptions, copper catalysts tend to favour processes involving $C_{alkyne}-H$ activation whereas rhodium and ruthenium better promote cycloaddition and metathesis-like reactivity. Therefore, this is an active research field that opens up the possibility of making a wide number of transformations for use in the synthesis of cyclic and polycyclic compounds. Notwithstanding, methodological studies still need to be carried out to better understand the different reaction pathways and the factors that might favour one particular pathway over another.

Acknowledgments

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Highlights for the paper:

The rich reactivity of transition metal carbenes with alkynes

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- Transition metal carbenes have a particularly diverse reactivity with alkynes
- Reactions can be classified depending on whether or not a Csp-H activation is involved
- Alkyne and metal carbene structure, and the catalyst used determine the reactivity