Metal-catalyzed annulations involving the activation and cleavage of C-H bonds

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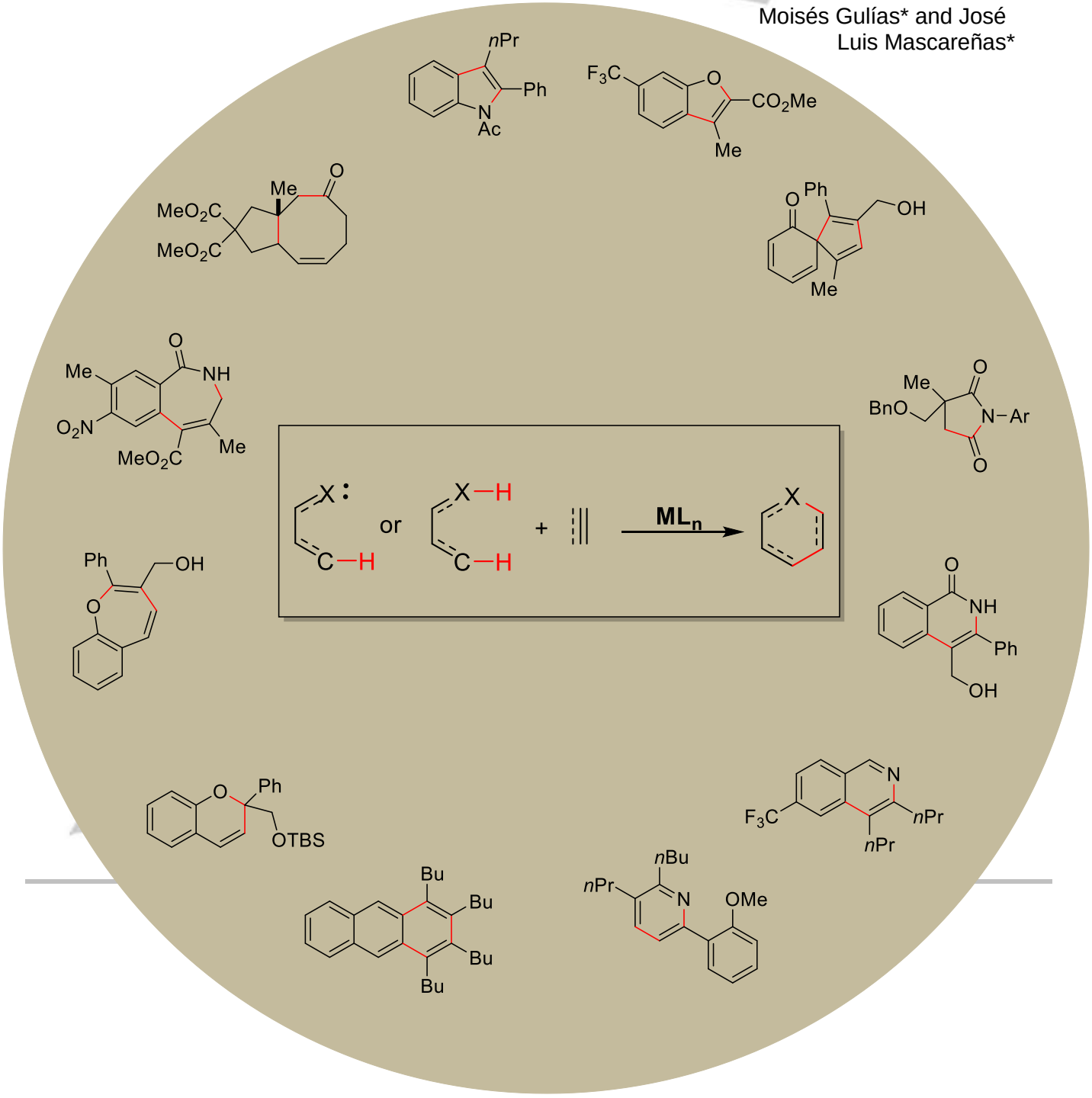


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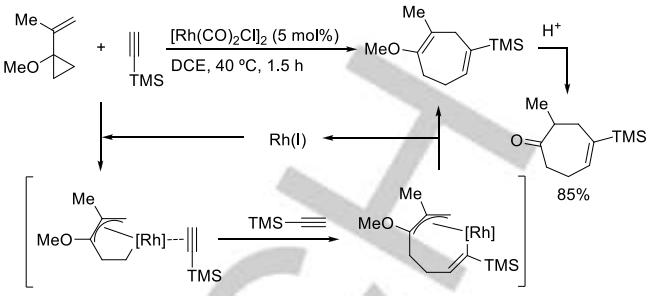
(18.5 cm in diameter)

Abstract: The exponential increase in the number of catalytic transformations that involve a metal-promoted activation of hitherto considered inert C-H bonds is promoting a paradigmatic change in the field of synthetic chemistry. While most reactions involving C-H activations consist of simple functionalizations or additions, recent years have witnessed a boost on related transformations that can be formally considered as cycloaddition processes. These transformations are particularly appealing from a synthetic perspective because they allow the conversion of readily available substrates into highly valuable cyclic products in a rapid and sustainable manner. In many cases, these annulations involve the formation of metallacyclic intermediates that resemble those proposed for standard metal-catalyzed cycloadditions of unsaturated precursors.

1. Introduction

A major goal in synthetic chemistry consists of the development of methods that allow transforming readily available precursors into target-relevant products in an atom and step-economical manner.[1] Especially challenging is the construction of products featuring relatively complex cyclic scaffolds from simpler, acyclic starting materials. In this context, cycloaddition reactions, by allowing the formation of two bonds and one cycle in a single step, are extremely appealing.[2] While classical cycloadditions like Diels-Alder, are restricted to substrates that are appropriately matched from the electronically point of view, it has been widely shown that by using metal catalysts it is possible to induce the annulation of substrates that otherwise are unreactive.[3] These metal-catalyzed reactions can be formally viewed as cycloaddition processes, albeit considering the iupac goldbook definitions,[4a] they might be better named as annulations.

Most of these metal-catalyzed cycloadditions involve the reaction of π-unsaturated substrates, ranging from simple alkynes or alkenes to more elaborated systems like alkylidenecyclopropanes or cyclobutenes, and usually require late transition metal reagents in a low oxidation state.[3] Generally, these cycloadditions take place through a mechanism based on an initial oxidative cyclometallation, in which the valence of the metal is increased, followed by migratory insertion of a second partner and final reductive elimination. This mechanistic path is exemplified in the Scheme 1 for a formal (5+2) cycloaddition developed by Wender and coworkers.[5]



Scheme 1. Rh-catalyzed formal (5+2) cycloaddition discovered by Wender and coworkers.

Recent years have witnessed a boost on the development of new catalytic transformations based on metal-catalyzed C-H activation processes.[6] Most of the work has been focused on functionalization, cross coupling or addition reactions, but more recently there has been an increasing number of reports dealing with formal catalytic cycloaddition processes.[7] While these annulations are mechanistically different to standard metal-catalyzed cycloadditions of unsaturated substrates, in many cases the key C-H activation/cleavage step leads to metallacyclic structures that resemble those resulting from classical oxidative cyclometallations.

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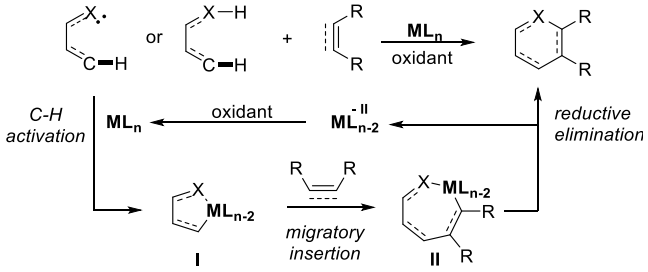
Indeed, one of the more common mechanistic scenarios in this type of annulations consists of an initial formation of heterometallacyclic intermediates of type **I**, followed by migratory

insertion into an unsaturated partner, and reductive elimination (Scheme 2). The catalyst (usually a Pd, Rh or Ru complex) needs to be reoxidized and reenter the catalytic cycle, which is often achieved using Cu^{+2} salts. In some cases it is even possible to use catalytic amounts of Cu^{2+}, usually under an oxygen atmosphere. In most of the cases, these annulations require the presence of a heteroatom in the substrate that not only enhances the reactivity but also allows controlling the regioselectivity by driving the metal complex to the reacting C-H site. The heteroatom can become part of the final ring.



Scheme 2. Standard mechanistic scheme for a metal-catalyzed cycloaddition involving a formal C-H activation and cleavage.

While many metal catalyzed annulations involving the activation of C-H bonds can be accommodated in the above mechanistic scheme, there are also related reactions in which the heteroatom of the directing group (X, usually N or O) will not be part of the final cycle. Furthermore, cycloadditions involving the activation of C-H bonds in substrates that do not have a coordinative directing group have been also described.

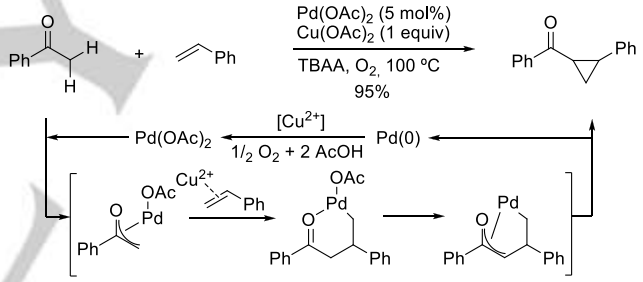
In this review we aim to showcase the state of the art in this emerging field of metal-catalyzed annulations. We have opted by a mechanistic systematization rather than by a descriptive focus, as well as a by a classification according to the number of atoms involved in the annulation. Therefore we use the notation first described by Huisgen, with parentheses, and with numbers referring to the atoms involved in the forming ring.[4b] We have not intended to be comprehensive, and therefore not all the articles in the field could be included and cited. Most of the schemes in the review have been organized to describe the main reaction conditions (top), key elements of the mechanistic proposals (middle) and some examples of the type of products that can be obtained (bottom).

2. Annulations involving an initial C-H activation followed by migratory insertion and reductive elimination

We include in this category reactions in which the C-H cleavage leads to an organometallic complex that evolves to the product by migratory insertion of the unsaturated partner followed by reductive elimination. We discuss representative examples irrespective of whether the C-H activation requires a heteroatom-directing group, and whether this group becomes part of the final ring. As commented above, we have organized the sections according to the number of atoms that are formally involved in the annulations.

(2+1) annulations

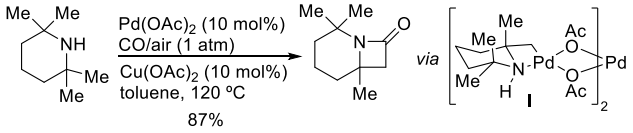
An interesting way of making cyclopropanes was described by Nacci, Monopoli and coworkers and involve a formal (2+1) annulation between aryl methylketones and styrenes.[8] The reaction, which involves the formal cleavage of two C-H bonds at the α-position of the ketone, is promoted by $Pd(OAc)_2$ and requires stoichiometric amounts of $Cu(OAc)_2$ and an oxygen atmosphere, as well as the use of molten tetrabutylammonium acetate (TBAA) as solvent. The mechanistic hypothesis considers the activation of the α-position of the acetophenone to give an oxa-π-allypalladium complex (scheme 3). Addition of styrene followed by deprotonation at the α-position yields a new oxa-π-allypalladium that undergoes a reductive elimination to give the cyclopropane product and Pd^0, which is reoxidized by O_2 with the assistance of Cu(II). Unfortunately the method does not work with other ketones or with alkenes containing aliphatic substituents, mainly because of the competitive formation of dehydrogenated products.



Scheme 3. Pd(II)-catalyzed assembly of cyclopropanes.

(3+1) annulations

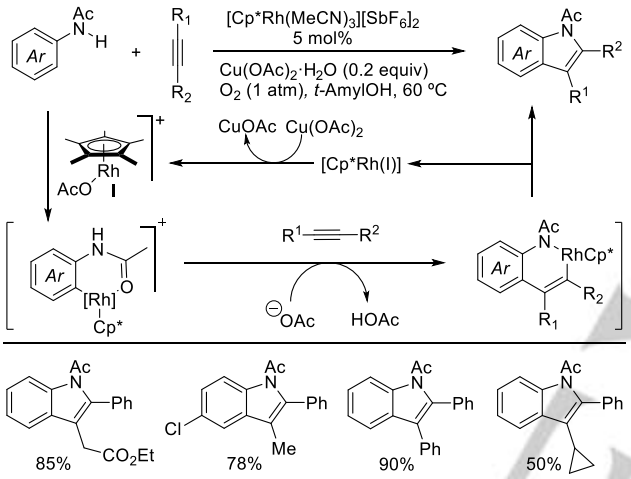
In 2014, the group of Gaunt described a palladium-catalyzed C–H carbonylation of aliphatic amines to construct β–lactames, a reaction that can be formally considered as a (3+1) annulation.[9] Key for the success of the reaction is the use of hindered amines, which avoids the formation of coordinatively saturated bis-amine palladium(II) species, and thus allows the creation of a vacant site for the C-H activation. The authors isolated the palladium dimeric complex **I**, resulting from the cleavage of the C-H bond.



Scheme 4. Pd(II)-catalyzed carbonylation of aliphatic amines.

(3+2) annulations

A remarkable example of this type of annulations is the formation of indoles by reaction between anilides and alkynes,[10] transformation pioneered by Fagnou and coworkers.[10a] The reaction, that is catalyzed by Rh(III) and requires the presence of an added oxidant, is quite general and efficient, and tolerates a wide range of substituents both in the aromatic ring and in the alkyne, albeit fails with terminal alkynes. Overall, the formal cycloaddition process, which involves the dehydrogenative cleavage of a C-H and an N-H bond, represents an atom economical and efficient way of assembling indoles from trivial, readily available precursors.



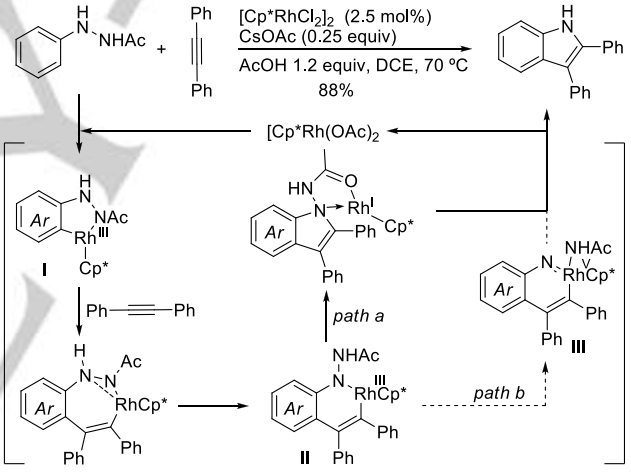
Scheme 5. Rhodium-catalyzed synthesis of indoles from anilides and alkynes.

While the initial report required the use of stoichiometric amounts of $Cu(OAc)_2$ as external oxidant and high temperatures, posterior studies led to the development of milder reaction conditions that even allow the use of oxygen as final oxidant.[10b] The reaction has been proposed to involve as initial step the coordination of the Lewis basic amide oxygen with an active form of the Rh(III) catalyst, most probably complex **I** (scheme 5). This is followed by an irreversible and rate-determining cleavage of the aromatic C-H bond in *ortho* to the amide group through a concerted metallation-deprotonation (CMD) mechanism. The resulting arylrhodium intermediate coordinates the alkyne and evolves by migratory insertion to a six-membered rhodacycle. Finally, this complex delivers the desired indole product by reductive elimination, along with [Cp*Rh(I)], that is oxidized back to the active species by copper(II) acetate.

Other authors have later developed related annulations of substrates containing 2-pyridyl, acetyl or 2-pyrimidyl directing groups instead of amides, and using not only Rh, but also Pd or Ru complexes as catalysts.[11]

Importantly, after the discovery of redox-neutral C-H functionalization processes in which an oxidizing functional group serves both as a directing group and an internal oxidant,[12] a number of groups have developed alternatives for the synthesis of indoles that avoid the requirement of external oxidants.[13] Most of them consist of using anilide derivatives like arylhydrazines, hydrazones or nitrosoanilines which incorporate an N-N bond that works as an internal oxidant.

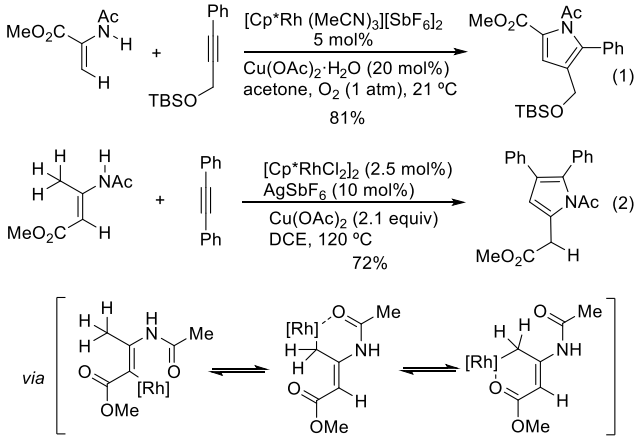
For instance, Glorius and coworkers demonstrated that 2-acetyl-1-arylhydrazines react with alkynes to give indoles when treated with catalytic amounts of $[Cp^*RhCl_2]_2$, in DCE, and in presence of AcOH and CsOAc.[14] Most probably the reaction involves the formation of $Cp^*Rh(OAc)_2$ as the active catalyst, and a reaction pathway consisting of the initial formation of a rhodacycle like **I**, followed by migratory insertion of the alkyne across the C-Rh bond (scheme 6). The resulting seven-membered rhodacycle rearranges to **II**, which can undergo a reductive elimination with concomitant cleavage the N-N bond (*path a*). The resulting indole derivative containing a N-Rh bond is protonated and thus regenerates the Rh(III) catalyst. While the authors do not discard other pathways, such as one involving the intermediacy of a cyclic Rh(V) nitrene intermediate like **III** (*path b*), recent DFT calculations support a mechanism involving a R(III)/Rh(I)/(Rh(III) cycle, at least in this type of reactions that involve a relatively weak internal oxidant (N-N bond).[15]



Scheme 6. Mechanistic proposals for the cycloaddition between *N*-acetyl-1-arylhydrazines and alkynes.

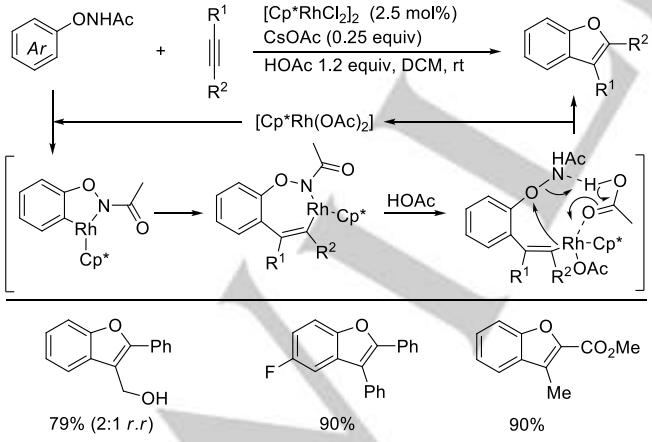
It is worth mentioning that there have been also reports on intramolecular versions of the above annulations, reactions that allow to build interesting polycyclic products from relatively simple precursors.[16]

Interestingly, the annulation can also be achieved using enamides instead of anilides, which provides a direct entry to pyrroles under mild conditions (Eq 1, scheme 7).[10b] The reaction works in fairly good yields for alpha-substituted enamides but it is low yielding when simple *N*-vinylacetamide is used. In some cases it has been even shown that it is possible to activate allylic sp^3 C-H bonds, reaction that also produces pyrrole derivatives (Eq 2, scheme 7).[17]



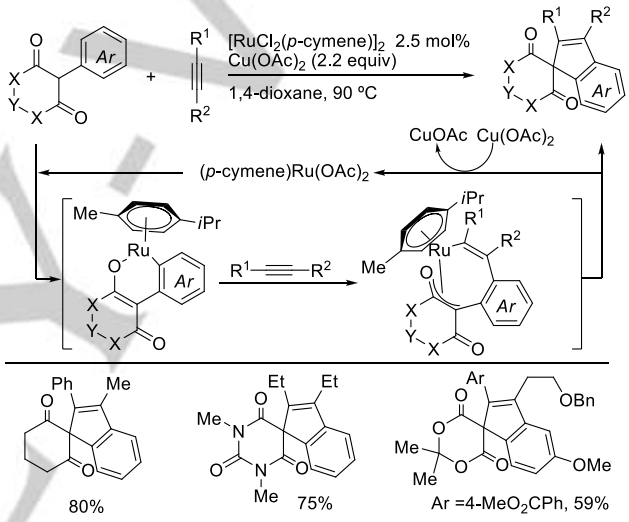
Scheme 7. Rhodium catalyzed synthesis of pyrroles from enamides and alkynes.

Using phenol instead of aniline derivatives, it is possible to make benzofuranes. Thus Liu, Lu and coworkers have shown that the treatment of N-phenoxyacetamides with alkynes under very similar conditions than those described for the synthesis of indoles, produces the expected products with good yields.[18] The mechanism most probably involves a heteroatom assisted arene rhodation by $Cp^*Rh(OAc)_2$ (generated in situ) followed by alkyne insertion to give the corresponding seven member rhodacycle (scheme 8). Protonation of the N-Rh bond gives a vinyl rhodium species that evolves to the product by an acetic acid assisted intramolecular substitution. The authors suggest that in the presence of coordinating solvents like MeOH, the seven membered rhodacycle provides acyclic enamides instead of the cycloadducts, through a mechanism invoving a reductive elimination, oxidative addition of the resulting Rh(I) into the N-O bond and protonation.



Scheme 8. Rhodium-catalyzed synthesis of benzofuranes from N-phenoxyacetamides.

While the above reactions generate heterocyclic products, it is also possible to carry out related formal [3C+2C] cycloadditions to ensemble carbocycles. For instance, the group of Lam has published several articles on the synthesis of spiroindenes from 2-aryl-1,3-carbonylic compounds and alkynes, using Ru(II) complexes as catalysts (Scheme 9), or Pd(II)-Pepsi derivatives for some substrates.[19] The mechanism proposed for the ruthenium-promoted reaction involves an initial coordination of the enolate derived from the dicarbonylic compound to the ruthenium complex followed by activation and cleavage of the *ortho* aryl C-H bond. Coordination and migratory insertion of the alkyne produces a second ruthenacycle, which although depicted as an oxa-π-allylruthenium species, could exist either in the O- or C-bound tautomeric forms. Finally, C-C reductive elimination with concomitant Cu(II) promoted oxidation of Ru(0) to Ru(II) releases the corresponding spiroindene product. The reaction can also be carried out in good yield using $[Cp^*RhCl_2]_2$ as catalyst. An asymmetric version of this reaction has also been recently reported.[19c]

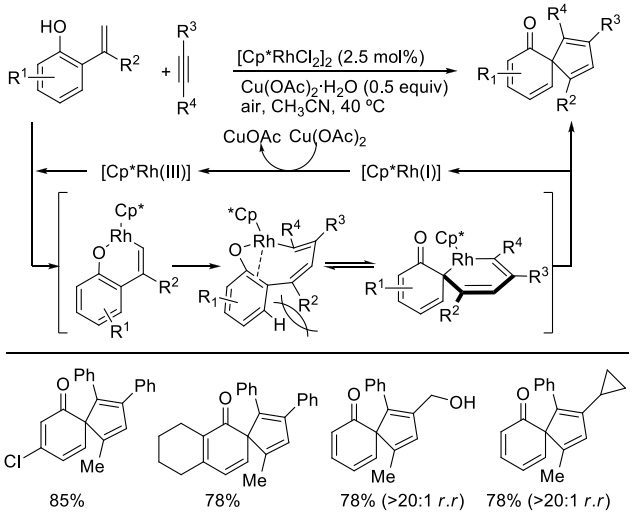


Scheme 9. Ru-promoted synthesis of spiroindenes from phenyldiones and alkynes.

Related ruthenium-catalyzed formal (3+2) annulations have been reported by Luan and coworkers using 2-phenyl naphthols or electron rich phenyl phenols as substrates.[20a,b] These authors reported a number of mechanistic experiments that suggest that the C-H cleavage step is irreversible and turnover limiting, and most probably takes place by a concerted metallation-deprotonation process. Recently, the group of You has also developed an asymmetric version of this annulation using a Rh catalyst with a chiral Cp ligand, and $(BzO)_2$ as oxidant.[20c]

Another example of a dearomatizing (3+2) cycloaddition using a Rh(III) catalyst was developed by Mascareñas and Gulías[21a] as well as by Lam,[21b] and involves the dehydrogenative annulation between 2-alkenylphenols and alkynes (scheme 9). The reaction, which requires the presence of internal substituents in the alkene, allows transforming extremely simple substrates into interesting spirocyclic products. The mechanism proposed for this transformation involves the generation of a key six-membered rhodacycle by cleavage of the terminal C-H bond of the alkene, followed by alkyne insertion. The presence of a steric clash between the alkenyl substituent and one of the C-H bonds of the aryl group in the rhodacyclooctane favours the six-

membered rhodacycle, which upon reductive elimination yields the final products.

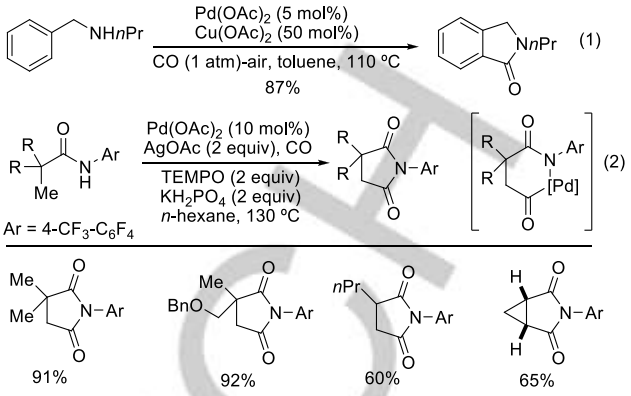


Scheme 10. Rh-catalyzed synthesis of spirocycles.

(4+1) annulations

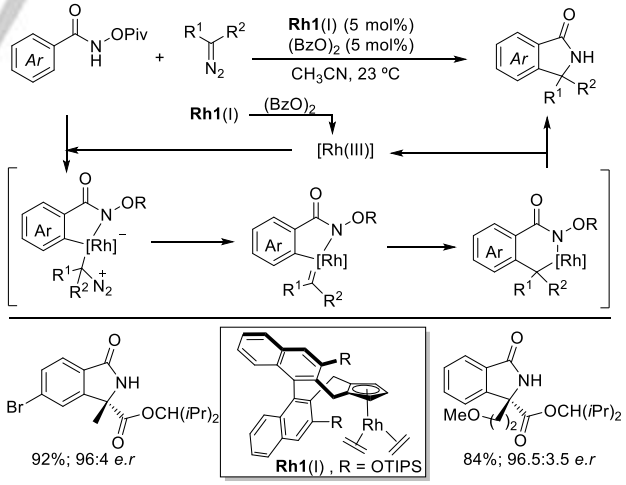
One of the earliest examples of a catalytic annulation involving a C-H activation process was reported by Orito and coworkers and consists of the Pd catalyzed reaction of *N*-monoalkylatedbenzylamines or N-phenylethylamines with carbon monoxide.[22a,b] These annulations represent a formal (4+1) cycloaddition and allow to construct a variety of interesting five membered benzolactams (Scheme 11, eq 1).

In 2010 J-Q. Yu et. al reported several interesting examples of a related annulation tactic involving the activation of sp^3 C-H bonds in alfa-substituted amides (Scheme 11, eq 2).[22c] An appropriate choice of the substituent at the nitrogen, in this case an electron poor aromatic group, is essential for the success of the reaction. The reaction even works in the presence of acidic hydrogen atoms in the carbonyl alfa position, although yields are slightly lower. The transformation is proposed to proceed through an amide-directed C(sp3)-H cleavage and insertion of CO into the resulting [Pd(II)-C(sp3)] bond, followed by Pd mediated C-N reductive elimination to give the corresponding succinimide products. TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was found to be a crucial co-oxidant for efficient reoxidation of Pd(0) to Pd(II) in the presence of CO. Zhu and Falck found that isocyanides can also be used as one carbon coupling partners.[22d]



Scheme 11. Carbonylation of sp^2 and sp^3 C-H bonds. Eq 2 also shows a palladacycle intermediate.

Another interesting example of a formal (4+1) annulation, pioneered by Rovis and coworkers, involved the Rh(III)-catalyzed annulation between O-pivaloylbenzhydroxamic acids and diazocompounds.[23a] This reaction was later developed in asymmetric fashion using chiral Cp ligands (scheme 12).[23b] The N-O bond works as an internal oxidant, as has been extensively shown in related annulations with alkynes that will be discussed later. The transformation has been proposed to involve the coordination of the diazo-bearing carbon atom to the five-membered rhodacycle formed after the C-H activation step. Upon loss of dinitrogen, these intermediates evolve to rhodium carbenoids which undergo a migratory insertion to give six membered rhodacycles, step that sets up the stereogenic center. Reductive elimination might then deliver the isoindolone products and regenerate the Rh catalyst.



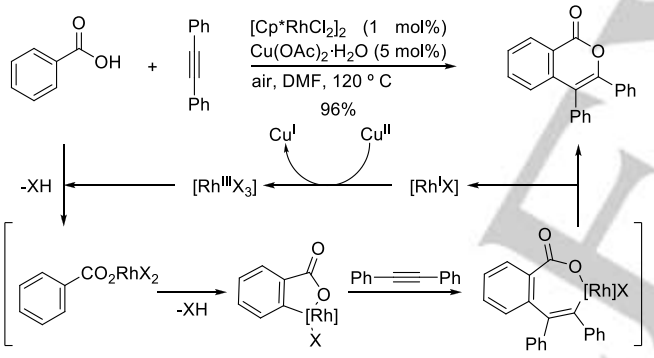
Scheme 12. Rh-catalyzed synthesis of isoindolones bearing a tetrasubstituted carbon.

Recent DFT calculations support this mechanism, but suggest that after a facile carbenoid insertion, the C-N bond is formed not by a direct reductive elimination but through a Rh(V)-

nitrenoid intermediate resulting from pivalate migration from the nitrogen to Rh, followed by reductive elimination.[23c]

(4+2) annulations

Together with five-membered rings, six-membered rings are the most abundant cyclic structures, and therefore the development of assembly methods other than classical Diels-Alder reactions is of upmost interest. A significant breakthrough in a formal (4+2) annulation involving the cleavage of a C-H bond were reported by Satoh and Miura in 2007.[24a] These authors demonstrated that heating benzoic acids with internal alkynes in presence of catalytic amounts of $[Cp^*RhCl_2]_2$ and 2 equiv of $Cu(OAc)_2 \cdot H_2O$, affords good yields of isocoumarins. It was later demonstrated that acrylic acids can undergo a similar transformation, in a reaction that involves the cleavage of a vinylic C-H bond.[24b] A plausible mechanism for these oxidative couplings is illustrated in the scheme 13. Coordination of carboxylate to a Rh(III) reagent gives a rhodium benzoate that promotes an intramolecular activation and cleavage of the ortho C-H bond. Coordination and migratory insertion of the alkyne into the resulting rhodacycle leads to a seven-membered intermediate that evolves to the product by reductive elimination. The resulting Cp*Rh(I) species is reoxidized by the Cu(II) or Ag(I) salts to regenerate the active catalytic species.

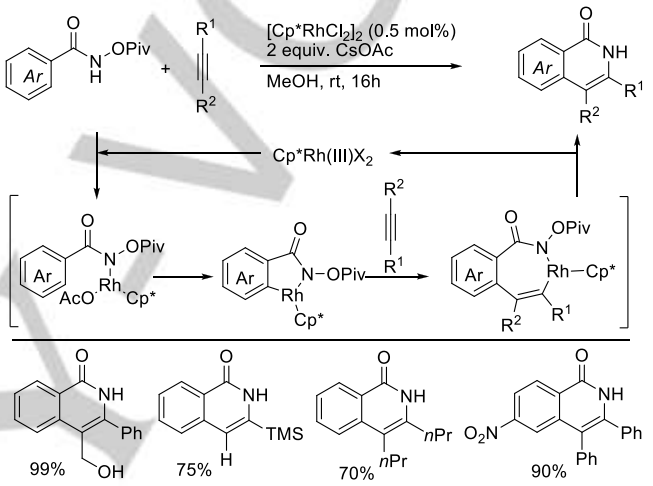


Scheme 13. Rh-catalyzed annulations between benzoic or acrylic acids with alkynes. *We keep the original nomenclature proposed by Miura, consisting of the use of X to indicate different Rh ligands*.

Recently the group of Ackermann demonstrated that the reaction can be carried out with a Ru(II) catalyst under mild conditions and using oxygen as sole oxidant.[24c]

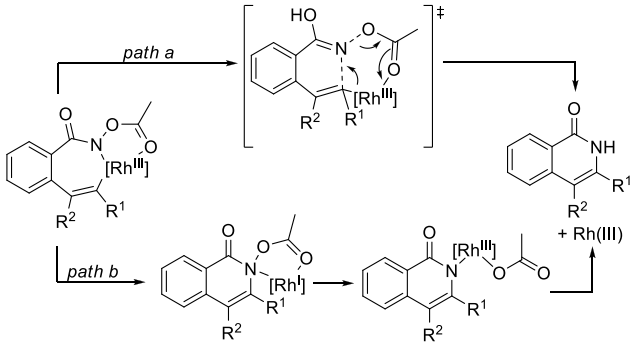
Benzamides can also undergo similar annulation reactions, as has been extensively demonstrated using rhodium,[25] or ruthenium catalysts.[26] These methods provide a step-economic and direct access to isoquinolones starting from readily available benzamides. In 2010, Guimond and Fagnou reported a redox-neutral version of these annulations that avoids the requirement of external oxidants, and is based on the use of *N*-alkoxybenzyhydroxic acid derivatives as reacting partners.[25a] The reaction is particularly effective if the internal N-O oxidant features a pivalate substituent (scheme 14). Indeed, using this type of substrates the transformation can be achieved at room temperature, and even works with terminal alkynes, which were elusive for most of other annulations which typically employ Cu(II) oxidants owing to lateral alkyne dimerizations (glaser coupling).

Mechanistic studies, including DFT calculations,[25b] suggested that the reaction involves the coordination of a rhodium (III) catalyst to the nitrogen with concomitant loss of acetic acid (Scheme 14). There is now a C-H bond cleavage that might proceed via a concerted metalation-deprotonation (CMD) mechanism, and has been proposed to be turnover determining. Coordination of the alkyne and migratory insertion onto the Rh-C bond yields a rhodacycle intermediate that rearranges to the isoquinolone product and regenerates the catalyst.



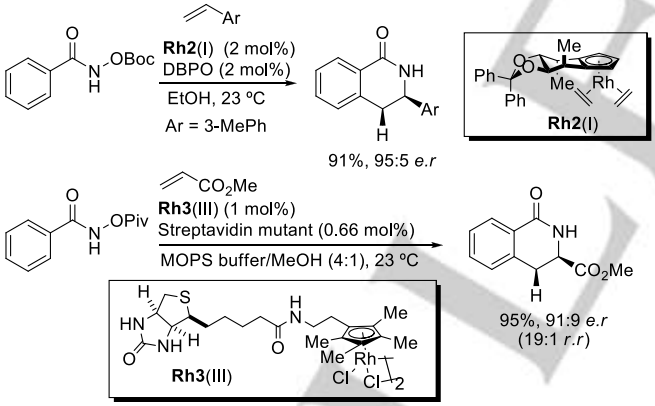
Scheme 14. Rh-catalyzed synthesis of isoquinolones from alkynes and benzhydroxamic acids.

The authors suggested two potential operative pathways for the final C-N bond-forming step (scheme 15).[25b] *Path a* consists of a concerted process where a highly organized six-membered cyclic transition state accounts for a simultaneous C-N bond formation and N-O bond cleavage. The main characteristic of such a mechanism is that the Rh(III) catalyst remains at the same oxidation state throughout the entire catalytic cycle. *Path b* is a more common reductive elimination/oxidative addition process that would occur in a stepwise fashion. The C-N bond reductive elimination would yield an intermediate that could readily undergo a N-O bond oxidative addition. Calculations carried out by the same group suggest *path b* as the more likely, however alternative pathways involving Rh(V) nitrenoid species cannot be discarded.[27]



Scheme 15. Mechanistic hypotheses for the regeneration of the Rh^{III} catalytic species.

Importantly, the use of aminoacyloxy internal oxidants allows mild reaction conditions and therefore the possibility of using alkenes as partners,[25b] something that had been elusive in other annulation reactions involving these type of C-H activation protocols owing to the competence of β-hydride elimination processes.The annulation can also be accomplished in an asymmetric manner, as recently shown by the groups of Cramer,[28] and of Rovis and Ward (Scheme 16).[29] Cramer and coworkers developed a chiral Cp ligand with C_2-symmety whereas the Rovis and Ward collaborative publication describes an elegant synthesis of a biotinylated-Cp ligand for Rh(III) that upon interacting with a biotine binding protein generates a chiral environment that is transduced in the formation of enantiomerically rich products.

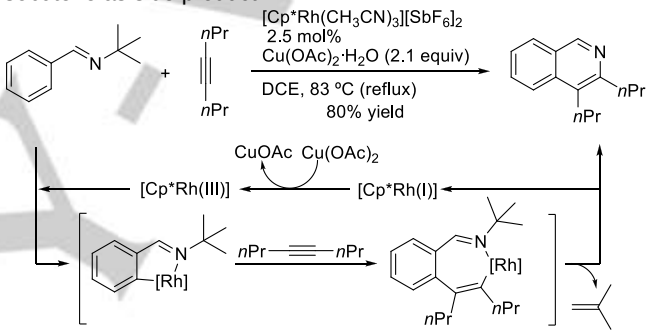


Scheme 16. Asymmetric annulation of benzamides with alkenes. DBPO: dibenzoylperoxide.

In addition to benzamides, it has been shown that other related susbtrates like acrylamides, sulfonamides, or sulfoximides, can also be engaged in mechanistically related metal-catalyzed annulations.[30] There have been also some reports on intramolecular variants, either using internal or external oxidants.[31] In 2013 Rovis and co-workers reported an interesting intramolecular version of the annulations with alkenes.[32] Ma, Zhang and coworkers have also demonstrated that it is viable to intercept seven-membered rhodacycles resulting from the reaction of specific trienes before the reductive elimination processes, which provides for extending the (4+2) process to formal (4+2+2) annulations.[33]

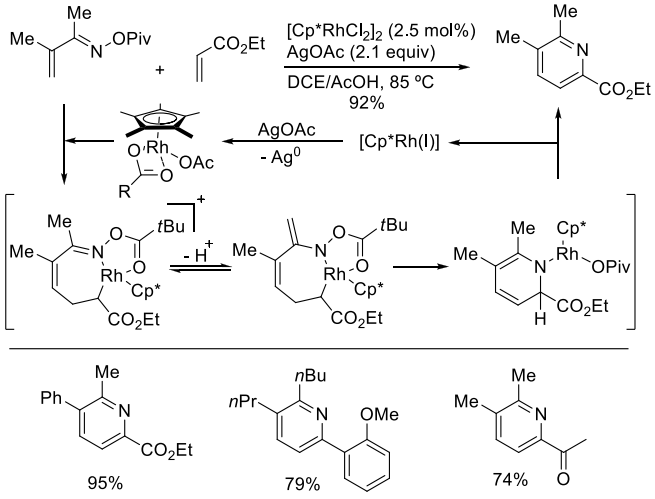
While it seems clear that all these annulations work well with Rh(III) or Ru(II) catalysts, there are also isolated examples demonstrating that Pd(II) catalysts can also promote similar annulations with alkynes, arynes or allenes.[34]

In the above reactions the initial ligand exchange between the substrate and the metal complex involves a deprotonation reaction. However, it has been shown that benzylimines, that lack an acidic hydrogen, may also engage in highly related annulations to give very interesting isoquinoline products (Scheme 17).[35] The final C-N reductive elimination of the presumably formed seven-membered rhodacyclic intermediates could take place either by protonation followed by an electrocyclization/oxidation process, or by a copper promoted oxidation to a Rh(IV) intermediate. However, Fagnou and coworkers convincingly demonstrated that most probably the C-N reductive elimination occurs directly from Rh(III), generating isobutene as side product. [35]



Scheme 17. Rh-catalyzed synthesis of isoquinolines from *tert*-butyl imines.

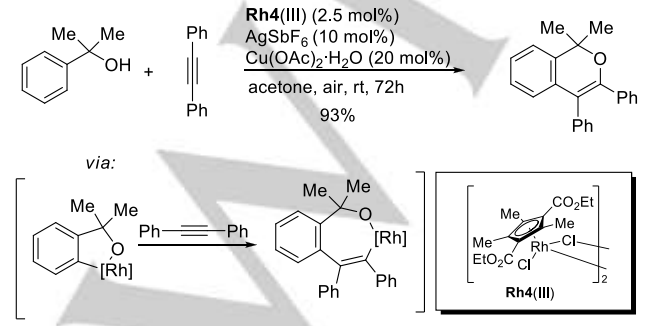
Other authors have developed different variants, including the use of benzylimine or alkenylimine derivatives, and either external or internal oxidants, the later consisting of built-in N-O or N-N bonds.[36] In this context, an interesting development consisted of the assembly of substituted pyridines from O-pivaloyl oximes and activated alkenes like acrylates, developed by Rovis and coworkers.[37a] The reaction is carried out at 85º C using a slight excess of the alkene, in the presence of $[Cp^*RhCl_2]_2$ and AgOAc (Scheme 18). While it could be expected that the seven-membered ring rhodacycle generated after the C-H activation/migratory insertion steps would evolve by β-hydride elimination to give azatriene intermediates, the authors carried out several interesting mechanistic experiments which demonstrated a different operative pathway. Most probably, the β-hydride elimination is prevented because of Rh-chelation by the carboxyl group of the pivalate substituent which generates a coordinative saturation (scheme 18). Thus the rhodacycle evolves by C-N bond formation and N−O bond cleavage, followed by tautomerization and final β-hydride elimination to furnish the pyridine product and a Rh(I) complex that is oxidized by Ag(I) to Rh(III).



Scheme 18. Rh-catalyzed synthesis of pyridines from pivaloyl oximes and alkenes.

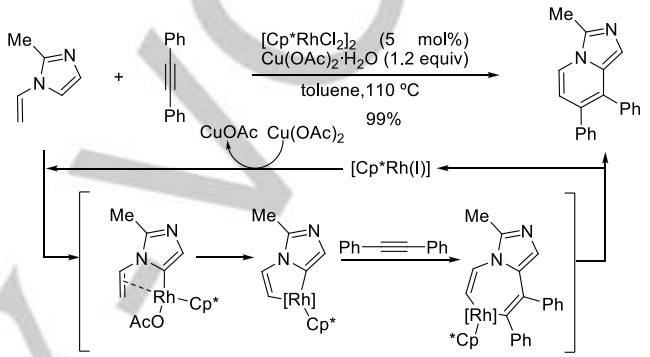
The reaction is also viable with non-activated alkenes; however, it provides mixtures of regioisomeric products. This limitation was smartly approached by the same authors by using acrylic acids as cycloaddition partners, because the carboxylic acid can be removed by decarboxylation and thus serves as a traceless activating group. The reaction affords 5-substituted pyridines with very high levels of regioselectivity.[37b] Recently, Glorius and coworkers reported related annulations using dienes as unsaturated partners, reaction that takes place with very good regioselectivity and allows to expand the type of products that can be obtained.[37c] It is also worth to mention an interesting recent example of a related dehydrogenative annulation using N-unsubstituted benzamidines and alkynes catalyzed by manganese,[38] suggesting that first row transition metals might have potential for future developments in this area.

Another formal (4+2) cycloaddtion reported by Miura and Satoh consists of the oxidative annulation of tertiary benzylic or allylic alcohols with internal alkynes. The transformation provides isochromenes, requires the use of tertiary alcohols to avoid competitive oxidations, and can be achieved using rhodium or ruthenium catalysts, albeit at high temperatures.[39a] Based on this work, the group of Tanaka demonstrated that by using electron deficient cyclopentandiendyl ligands for rhodium it is possible to perform the reaction at milder temperatures (Scheme 19).[39b]



Scheme 19. (4+2) Annulation leading to isochromenes.

All the above reactions rely on the use of a heteroatom directing group to assist the initial C-H activation step. Although less abundant, there are also related formal cycloaddition reactions in which the initial C-H activation and cleavage step doesn't require the presence of a chelating heteroatom. This type of non-directed C-H activations can also be attained using Rh catalysts, such as has been demonstrated for example by Dong and Cheng in the annulation of 2-substituted N-vinyl- or arylimidazoles with alkynes catalyzed by Rh(III) (Scheme 20).[40] Phenylheteroarenes such arylazoles, *N*-phenyl benzimidazoles, *N*-phenylindoles, phenylthiophenes or N-heterocyclic carbenes can be also engaged in similar tranformations.[41]

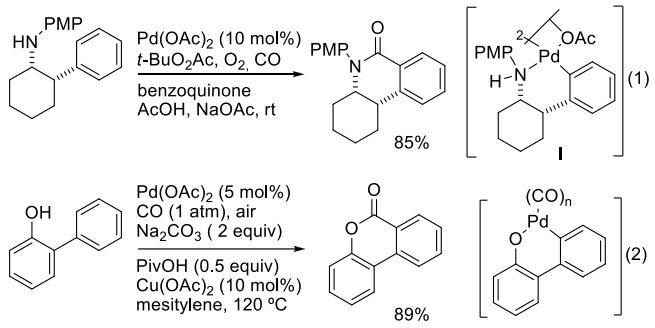


Scheme 20. Double C-H activation of 2-substituted N-vinyl- or arylimidazoles without assistance of an heteroatom-directing group.

(5+1) annulation

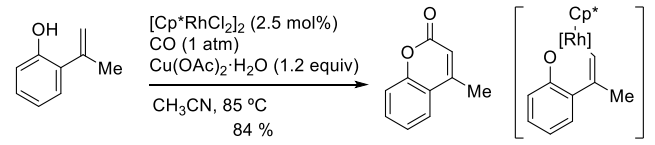
The assembly of six-membered rings by formal (5+1) cycloadditions has also been accomplished. Therefore, Gaunt and coworkers have reported a practical synthesis of six-membered lactams by means of a Pd(II)-catalyzed coupling between *β* -arylethylamines and carbon monoxide, at room temperature (Scheme 21, eq 1).[42a] Mechanistic studies demonstrated that the initial C-H activation leads to a dimeric palladium species like **I**, that could even be isolated.

The group of Shi reported a related carbonylation of 2-arylphenols that has been proposed to involve an electrophilic cyclopalladation on the non-phenolic ring.[42b] Kinetic studies suggested that the C-H activation involves a SeAr mechanism rather than a concerted metalation-deprotonation (CMD). The C-H cleavage generates a Pd-carbonyl intermediate that evolves by migratory insertion of the coordinated CO, followed by reductive elimination (scheme 21, eq 2). The resulting Pd(0) species is reoxidized to Pd (II) by $Cu(OAc)_2$ in presence of O_2. A similar carbonylation process promoted by ruthenium catalysts has been described by Inamoto, Kondo and coworkers.[42c]



Scheme 21. Carbonylation of secondary amines and 2-arylphenols. PMP: *para*-methoxyphenyl.

Related carbonylations that provide highly valuable coumarines can also be accomplished through a Rh-catalyzed reaction between *ortho*-hydroxystyrenes and carbon monoxide (scheme 22).[43a] More recently this transformation was carried out using a Co(III) catalyst.[43b]



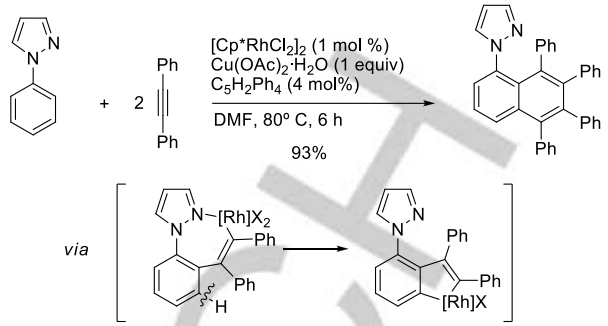
Scheme 22. Rhodium-catalyzed synthesis of coumarins.

(2+2+2) annulations

Multicomponent cycloadditions are highly interesting synthetic transformations because they allow for a rapid increase in complexity, and hence for shortening synthetic pathways. Owing to the yet scarce development of metal-promoted cycloadditions involving the activation and cleavage of C-H bonds, it is not surprising that the number of reports on multicomponent versions is still low, and essentially limited to formal (2+2+2) annulations.

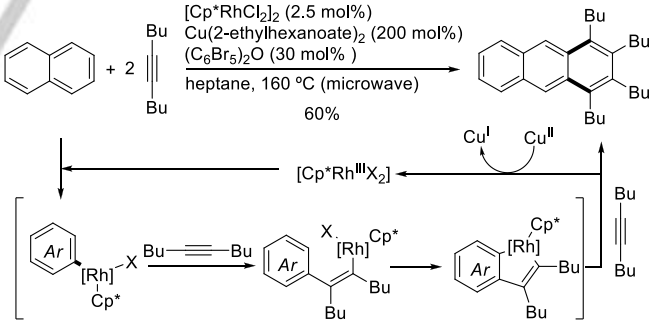
A pioneering example of this type of annulations was reported by Miura and Satoh in 2008.[44] They demonstrated that phenylazoles can react with two equivalent of alkynes to give naphthalene derivatives when treated under standard oxidative Rh(III) catalytic conditions (Scheme 23).

Mechanistic studies by the same group suggest that the reaction proceeds by initial coordination of the N-2 atom of the pyrazole group to Rh(III) followed by a standard regioselective C-H activation to give a rhodacyclic adduct. Alkyne insertion into the C-Rh bond gives a seven membered ring rhodacycle that is involved in a second C-H activation in *ortho* to the alkenyl group to give a cyclorhodapentene. Alkyne insertion and reductive elimination yields the product and Rh(I). This type of carbocyclic annulations has also been achieved with other related substrates having different heteroatom directing groups, including anilides, benzamides or phenols.[41a,45]



Scheme 23. (2+2+2) annulation of phenylazoles and alkynes catalyzed by Rh(III).

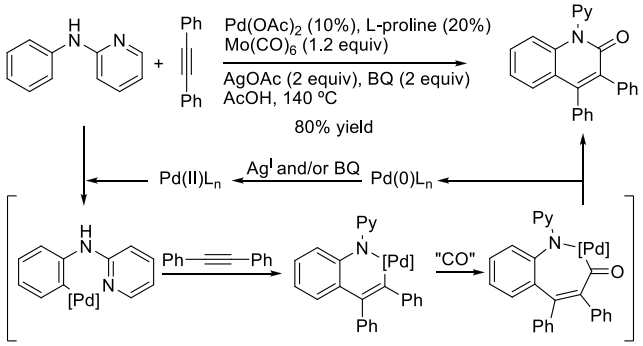
Formal (2+2+2) annulations have also been described for substrates that do not bear coordinating heteroatoms. For instance, Cramer has recently described a Rh(III)-catalyzed annulation between unbiased arenes and internal alkynes.[46] The reaction works better using copper(II) 2-ethylhexanoate and decabromodiphenyl ether as oxidants. The high solubility of copper(II) 2-ethylhexanoate in apolar solvents makes it largely superior to $Cu(OAc)_2$, while the role of aryl bromide was not clear. The reaction was suggested to involve an initial non-chelating assisted metalation of the arene, that most probably is the turnover-limiting step. Migratory insertion of the alkyne produces an alkenyl rhodium that triggers an intramolecular C-H activation to produce five membered rhodacycles (scheme 24). Incorporation of the second alkyne followed by reductive elimination expels the polyaromatic product, while reoxidation by Cu(II) regenerates the [Cp*Rh(III)] catalyst. The method is suited for the synthesis of large aromatic substrates that are of interest in material science, albeit is limited to the use of symmetrical alkynes to avoid the formation of complex mixtures.



Scheme 24. Non-assisted formal (2+2+2) cycloadditon.

(3+2+1) annulations

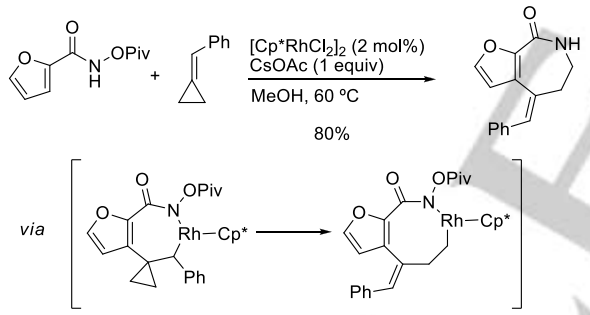
An alternative way of assembling six-membered rings consists of the carbonylative annulations of aniline derivatives and alkynes, in a formal (3+2+1) process.[47] Indeed, Wu et al demonstrated that it is possible to make quinolones by means of a Pd(II)-catalyzed reaction of 2-N-phenylpyridin-2-amines with alkynes in presence of $Mo(CO_6)$ as source of carbon monoxide. The carbon monoxide insertion prior the reductive elimination could take place either in the C-Pd or N-Pd bond.



Scheme 25. Annulation of aniline derivatives, alkynes and "CO" catalyzed by palladium. BQ: benzoquinone.

(4+3) annulations

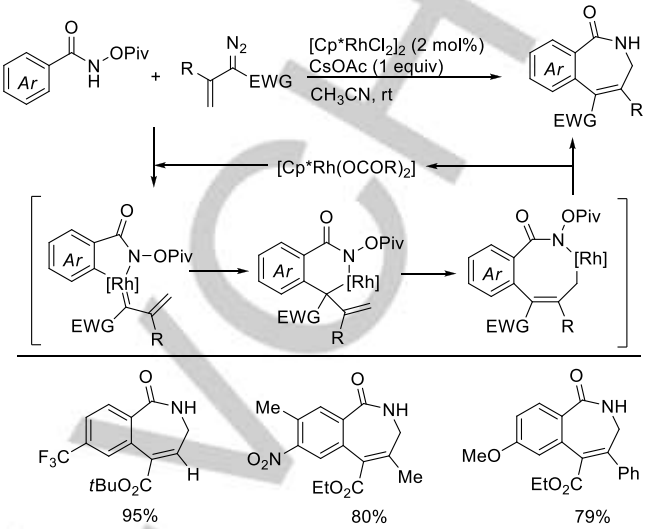
Alkylidenecyclopropanes (ACPs) and methylenecyclopropanes (MCPs), owing to their intrinsic strain, have been extensively used either as two or three carbon components in many metal-catalyzed cycloadditions.[48] They have also been investigated as partners in cycloadditions involving C-H activations of benzamides.[49a] Curiously, while most benzamides react with MCPs to form isoquinoline products, with the alkylidenecyclopropane behaving as a reactive alkene, furan-carboxiamides react with benzylidencyclopropane to give furan-fused azepinones (Scheme 26).



Scheme 26. Rh-catalyzed annulation of furan carboxiamides and ACPs.

The reaction most probably involves a standard amide-assisted C-H activation followed by migratory insertion into the alkene to give the expected seven-membered ring rhodacycle. The presence of the furan ring seems to facilitate a cyclopropylcarbinyl-butenyl rearrangement over the alternative reductive elimination, to generate an eight-member ring metallacyclic intermediate. The final C–N bond formation step yields the cycloheptanic products along with the N–O bond cleavage.[49b]

As already commented, diazo compounds can be used as 1C components in several Rh(III)-catalzyed annulations. In consonance with well-known precedents on other metal-catalyzed cycloadditions, the presence of a conjugated double bond in the diazo derivative can trigger its reactivity as a three-carbon cycloaddition partner.[50] Therefore, pivaloylbenzamides react with electron deficient alkenyldiazo derivatives under standard oxidative rhodium catalysis to give relevant azepinone products (Scheme 27).[51]



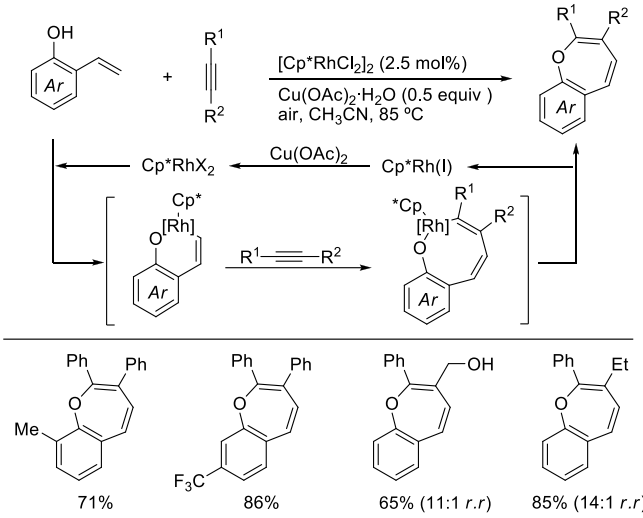
Scheme 27. Rhodium-catalyzed annulation of benzamides and vinyldiazoacetates.

Most probably the reaction involves the generation of rhodium carbene five membered metallacycles that undergo a migratory insertion to give π-allyl rhodium six-membered ring intermediates that expand to eight-membered rhodacycles. Calculations suggest that reductive elimination from this Rh(III) species is rather difficult, and it might involve a Rh(V)-nitrenoid intermediate generated by pivalate migration from the N to Rh (Scheme 27).[23c]

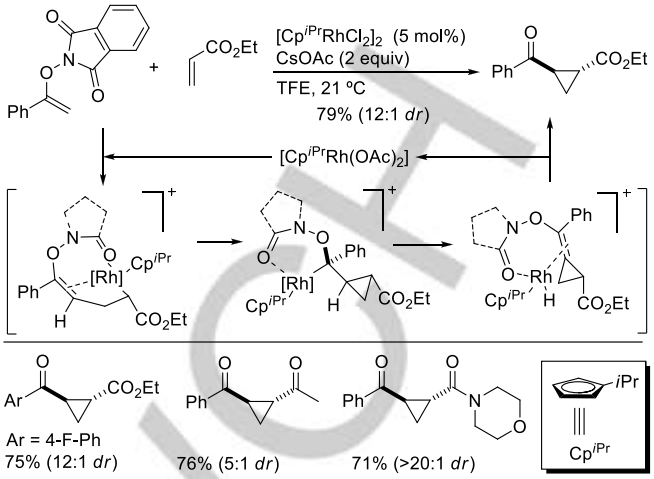
(5+2) annulations

Formal metal-catalyzed (5+2) cycloadditions involving vinylcyclopropanes are among the more remarkable metal-catalyzed transformations discovered in the nineteens.[52] However, similar annulations triggered by an initial C-H activation have not been described, except for a recent heteroannulation between hydroxystyrenes and alkynes.[43a] These reactions, promoted under standard rhodium-catalyzed oxidative conditions, produce highly attractive benzooxepines in an atom economical manner (Scheme 28).

It was proposed that the reactions involve the formation of a six-membered rhodacycle intermediate which evolves to the final observed product by standard alkyne migratory insertion and reductive elimination. Remarkably, while at a first view the generation of the key six-membered rhodacycle could be considered to occur by a CMD type of mechanism after coordination of the Cp*Rh complex to the hydroxyl group of the phenol, experimental data suggested an alternative non-concerted route involving n intramolecular attack of the conjugated alkene to the electrophilic rhodium species followed by a base-assisted deprotonation.



Scheme 28. Oxepines from *o*-vinylphenols and alkynes.



Scheme 29. Rh(III)-catalyzed synthesis of cyclopropanes.

3. Annulations in which the ring closure occurs through a migratory insertion process

While most annulation processes that involve at an early stage the cleavage of a γ-C-H bond present mechanisms in which the last step consist of a formal reductive elimination of the metal, there have been reports on cycloadditions that produce the final ring through a migratory insertion step.

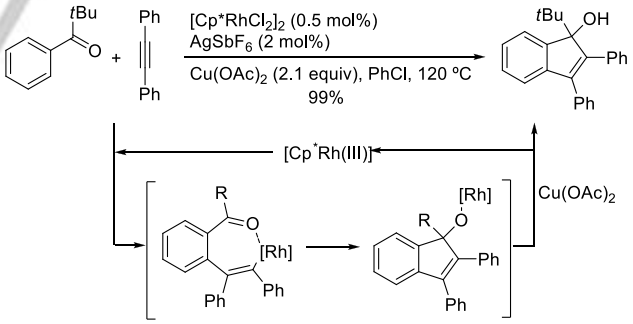
(2+1) annulations

The group of Rovis has recently demonstrated that N-enoxyphtamilides react with electron deficient alkenes in the presence of a Rh(III) complex to give cyclopropane products (Scheme 29).[53] The authors found that the reaction is more efficient when carried out with a rhodium catalyst containing an isopropylcyclopentandienyl ligand instead of the more standard 1,2,3,4,5-pentamethylcyclopentadiene (Cp*).

The reaction was proposed to start by an irreversible amide-directed C-H activation at the β-position of the double bond of the N-enoxyphtamilide. Then a migratory insertion of the external alkene gives a σ-alkylrhodium(III) complex that undergoes a 3-*exo*-trig intramolecular carborhodation to form a cyclopropyl derivative. β-Hydride elimination generates the enolate form of a cyclopropane that evolves to the product by collapse to a Rh(I) complex, followed by oxidative addition to the N−O bond and a protonation/tautomerization process (Scheme 29). However, alternative mechanisms cannot be discarded.

(3+2) annulations

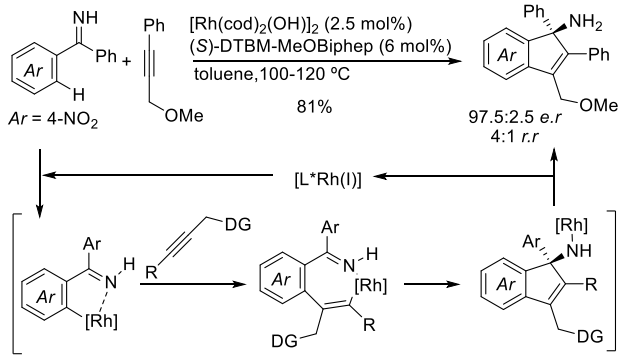
In 2011, Glorius and Cheng independently reported a formal (3+2) oxidative annulation between alkynes and aryllketone derivatives to give indenol and fulvene products (Scheme 30).[54] The transformation is proposed to involve an initial carbonyl-assisted C-H activation and cleavage, followed by alkyne insertion and subsequent intramolecular migratory insertion of the carbonyl into the C-Rh bond. The exact role of the cooper salt is not totally clear, but is essential for the success of the reaction. It may either facilitate the release of the Rh catalyst in a transmetalation step, avoid the rhodium reduction and/or provide acetate ligands.



Scheme 30. (3+2) Annulation of aromatic ketones and alkynes catalyzed by Rh(III).

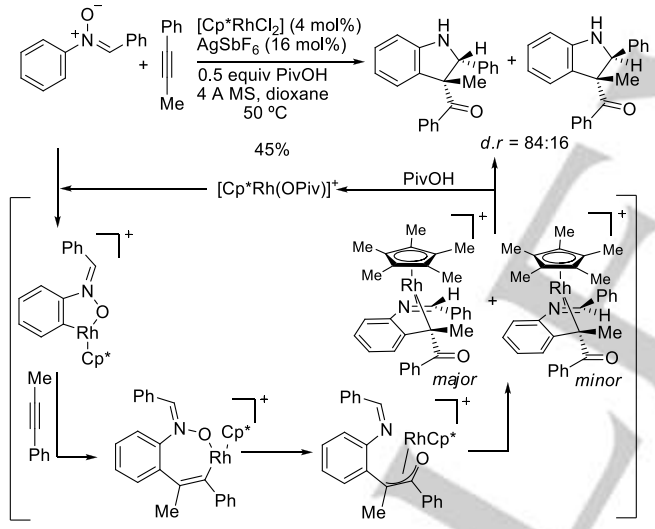
Imines can also participate in these type of formal cycloadditons. In 2010 Cramer reported the rhodium(I)-catalyzed C-H functionalization of unsubstituted ketimines with terminal allenes.[55a] Later, the same group reported asymmetric versions with alkynes[55b] and also with allenes[55c] using atropoisomeric MeOBiphep ligands (Scheme 31). In the case of the reaction with alkynes, it was proposed that it is initiated by oxidative addition of Rh(I) to the C-H bond followed by removal of the

hydrogen by reductive elimination. Migratory insertion leads to a vinylrhodium species which add in an enantioselective manner across the ketimine. When non symmetrical alkynes are used, the presence of a coordinating functional group leads preferentially to insertion at the carbon atom proximal to the directing group.



Scheme 31. Asymmetric (3+2) annulation of ketimines and alkynes.

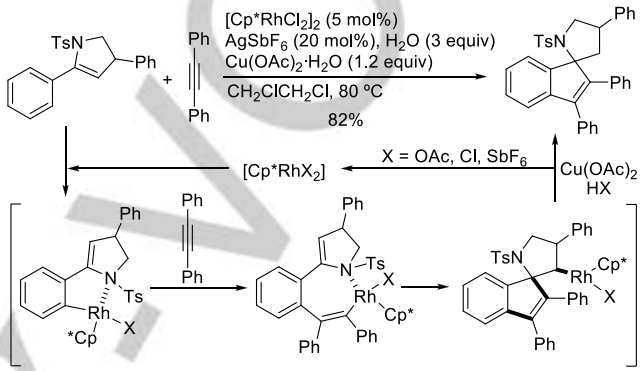
An interesting formal (3+2) annulation to give indolines was developed by Chang and coworkers, and involves the use of arylnitrones and alkynes as reaction partners (Scheme 32).[56]



Scheme 32. Rh-catalyzed synthesis of indolines from arylnitrones.

The transformation has been proposed to involve the formation of a five-membered rhodacycle from the nitrone, followed by alkyne insertion across the Rh-C bond to form the corresponding enlarged metallacycle (although insertion into the Rh-O cannot be completely ruled out). The subsequent O-atom transfer might take place via two possible pathways: a) cleavage of the N-O bond to form a Rh(V) oxo species that undergoes reductive elimination (Scheme 32), or b) reductive elimination to form a benzoxazine and Rh(I) and concomitant oxidation of Rh(I) to Rh(III) via N-O cleavage. Rearrangement of the resulting rhodium enolate and addition to the imine leads to the final product, with steric factors being the main determinants for the observed diastereomeric ratios.

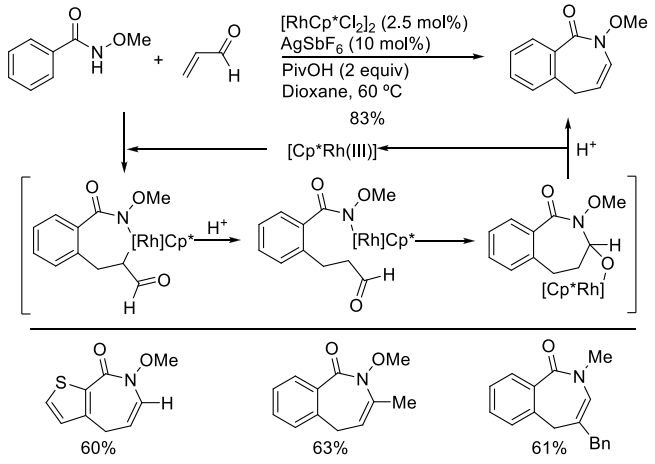
A related annulation in which the ring closing involves the addition to an alkene instead of to a carbonyl or an imine, was described by Xia, Li and coworkers, and consists of a rhodium(III)-catalyzed reaction between 5-aryl-2,3-dihydro-1H-pyrroles and internal alkynes.[57] The reaction builds interesting spirocyclic products and is proposed to involve the cleavage of an aryl C(sp^2)-H bond, migratory insertion of the alkyne, addition to the alkene and protonolysis.



Scheme 33. Formation of spirocycles in a formal (3+2) cycloaddition reaction.

(4+3) annulations

Glorius and coworkers have reported an interesting method for the synthesis of azepinones from benzamides and α,β-unsaturated aldehydes or ketones that can be formally considered as a (4+3) cycloaddition (Scheme 34).[58] The transformation involves as ring closure step a migratory insertion of the carbonyl into a N-Rh bond. Key for the observed outcome is the use of PivOH in the reaction medium. After a standard C-H activation and migratory insertion, the resulting seven-membered rhodacycle prefers to undergo a protonation by PivOH. Addition of the N-Rh bond across the carbonyl group and protonolysis gives the seven-membered ring hemiaminal which dehydrates to the final enamide.



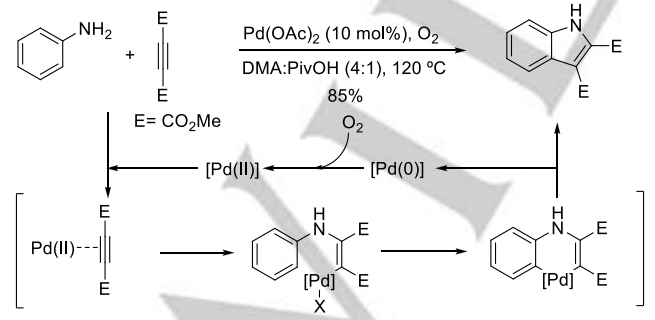
Scheme 34. Azepinone synthesis from benzamides and α,β-unsaturated ketones or aldehydes.

4. Annulations involving a migratory insertion step before the C-H activation

(3+2) annulations

In many of the cases discussed above the reactions start by a heteroatom assisted C-H activation to generate a relatively comfortable five-membered metallacycle. Substrates like anilines or phenols lack geometrically positioned heteroatom for such directed metallations, however it has been shown that they can also participate in annulations with unsaturated partners.

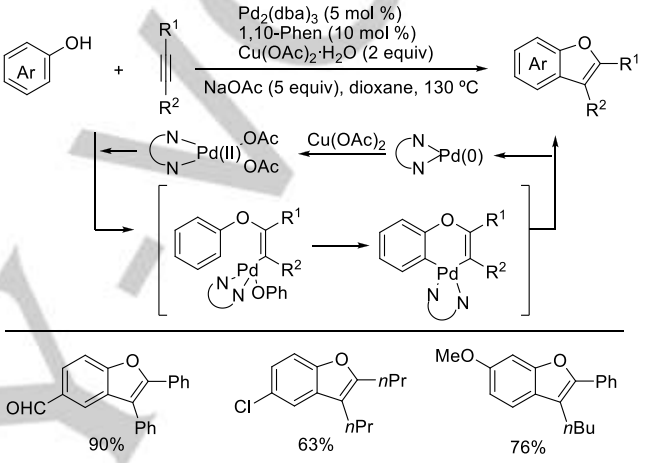
Therefore, Jiao and co-workers demonstrated that simple primary and secondary anilines react with electron deficient alkynes under palladium catalysis using oxygen as the sole oxidant.[59] The reaction does involve a formal C-H activation, but it was suggested to take place in the alkenylpalladium intermediate formed after addition of the amine to the alkyne. The C-H cleavage step has been proposed to involve an electrophilic aromatic palladation (Scheme 35).



Scheme 35. Pd(II)-catalyzed synthesis of indoles from simple anilines.

The same chemistry can be used with phenols instead of anilines. Therefore, Sahoo described in 2013 the synthesis of substituted benzofuranes from phenols and alkynes using palladium catalysis in combination with a diamine ligand.[60] The annulation tolerates a broad range of substituents both in the phenol and the alkyne, and asymmetric aryl-alkyl alkynes produce benzofurans in a regioselective manner (Scheme 36).

Although the precise reaction mechanism is still not defined, the authors proposed that it starts by coordination of the bidentate ligand to the Pd, followed by a Cu assisted oxidation to generate a Pd(II) active species. Coordination of the alkyne to the Pd(II) diamine complex is followed by phenoxypalladation. Base-assisted intramolecular *ortho* C-H insertion by the Pd catalyst and reductive elimination delivers the benzofuran and regenerates the Pd(0) species for the next cycle. However, authors do not discard other alternatives, including the *ortho*palladation of phenol by the electrophilic Pd(II) complex.

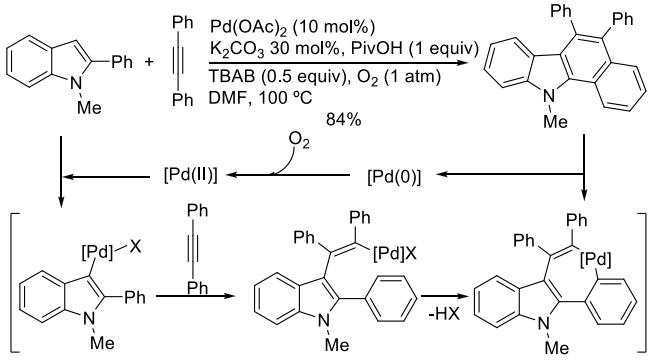


Scheme 36. Synthesis of benzofurans from phenols

Interestingly the synthesis of benzofuranes from phenols and alkynes via C-H activation was also reported using a copper complex as catalyst. This reaction is proposed to involve a reversible electrophilic carbocupration of phenol followed by alkyne insertion into the C-Cu bond. The product is then formed either via reductive elimination or through single electron transfer (SET) processes.[61]

(4+2) annulations

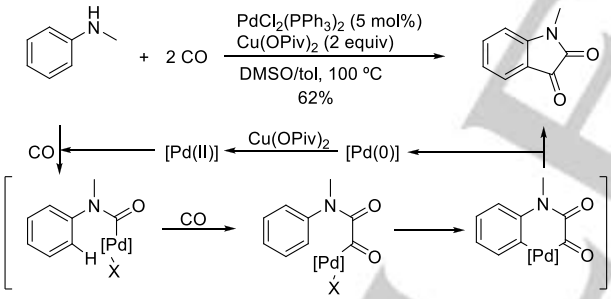
In 2009, the group of Jiao reported the synthesis of carbazole skeletons by a formal Pd-promoted (4+2) annulation between 2- or 3-arylindoles (as well as 2- and 3-arylbenzofurans) and internal alkynes (Scheme 37).[62] The process involves the cleavage of two C-H bonds and lead to carbocyclic adducts. It has been proposed that the reaction proceeds through an initial electrophilic aromatic palladation followed by migratory insertion of the alkyne to give an alkenyl palladium(II) intermediate. The final ring closure involves an acid-promoted electrophilic aromatic palladation followed by proton abstraction to afford a seven-membered palladacycle, which undergoes a reductive elimination to yield the product and a Pd(0) complex.



Scheme 37. Pd-catalyzed annulation between phenylindoles and alkynes. *TBAB* :Tetrabutylammonium bromide

(3+1+1) annulations

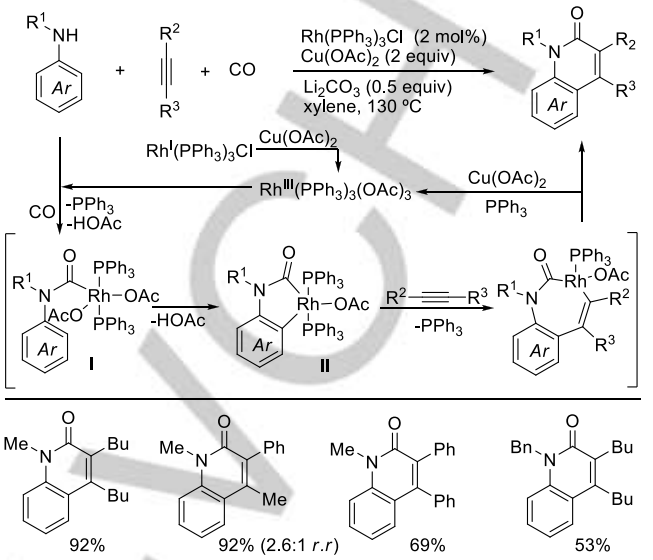
In 2015 the group of Lei reported a palladium-catalyzed double carbonylation of anilides to form isatins (Scheme 38).[63] The reaction proceeds under atmospheric pressure of CO and has been proposed to involve an N-H activation by the palladium complex, followed by coordination and insertion of CO. The resulting carbamoyl intermediate undergoes another CO insertion which is followed by a C-H activation to give a palladacycle intermediate. Reductive elimination renders the final product and Pd(0) which is reoxidized by Cu(II). Interestingly, isatins can be used as substrates in a Pd-catalyzed (3+2+2) annulation with alkynes to produce benzoazepines.[64]



Scheme 38. Isatines from anilines and carbon monoxide under palladium catalysis.

(3+2+1) annulations

Jiao and coworkers reported in 2015 a Rh-catalyzed annulation of simple anilines with CO and alkynes through N-H and C-H bond activation for the direct synthesis of quinolin-2(1*H*)-ones.[65] The reaction works for simple anilines and has a broad scope. The mechanism is proposed to start with the formation of Rh(III) complex from Rh(I) by oxidation with $Cu(OAc)_2$. Then insertion of CO after ligand exchange forms an intermediate which undergoes a concerted metalation-deprotonation (CMD) process to give rhodacycle **II** (Scheme 39). Subsequent ligand exchange with alkyne and migratory insertion generates a seven-membered Rh(III) complex. Finally, reductive elimination delivers the product while the Rh(I) species is reoxidized to Rh(III) in the presence of $Cu(OAc)_2$.



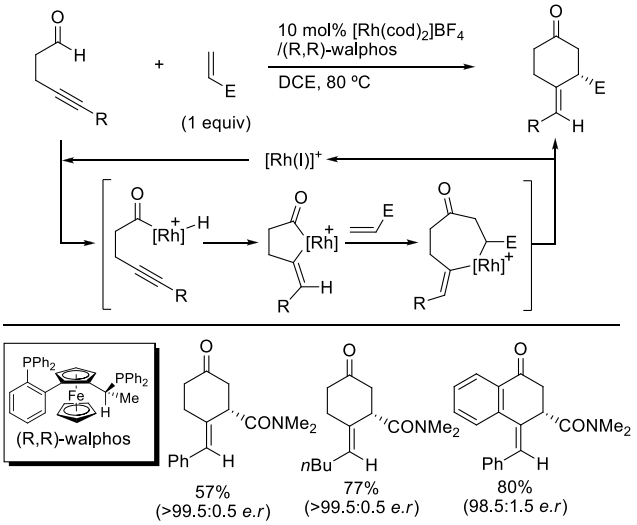
Scheme 39. (3+2+1) annulation between anilines, alkynes and carbon monoxide.

5. Annulations involving metallacycles generated by hydrometallation processes

(4+2) annulations

Although yet scarcely explored, an interesting way of generating metallacycles consists of the use of intramolecular migratory insertions of metal hydrides into unsaturated moieties. Subsequent insertion of an unsaturated partner allows for a formal cycloaddition process.

Therefore, based on initial work by Fu et al,[66a] Tanaka developed a rhodium-catalyzed regio- and enantioselective intermolecular (4+2) carbocyclization of 4-alkynals with *N*,*N*-dialkylacrylamides (Scheme 40).[66b] This method serves as an attractive new route to optically active cyclohexanones, as 4-alkynals are readily available from terminal alkynes. It is proposed that the reaction starts with oxidative insertion of the rhodium catalyst into the aldehyde C-H bond to afford a rhodium acyl hydride. A *cis* addition of the rhodium hydride species to the metal-bound alkyne provides of a five-membered acyl rhodium cyclic intermediate. At this point the complexation of the alkene is followed by insertion to form seven-member metallacycles which after reductive elimination furnish the cyclohexanone products and regenerates the Rh catalyst. Alternatively, migratory insertion of the alkene into the rhodium acyl intermediate prior to hydrometallation of the alkyne can also be operative.

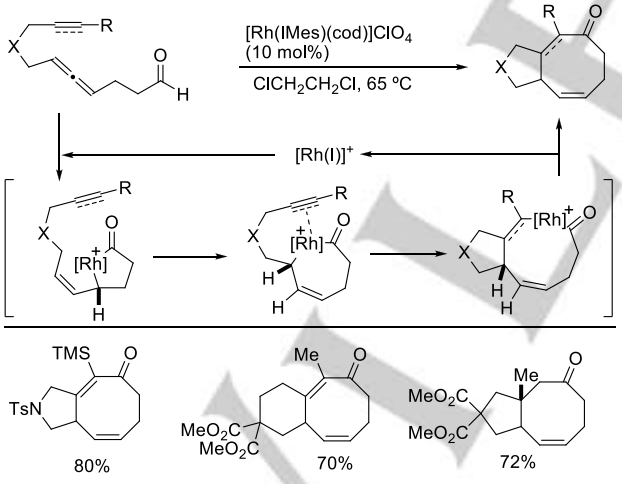


Scheme 40. Asymmetric annulation between alkynals and alkenes catalyzed by Rh(I).

It has been later demonstrated that the reaction is also possible with other partners in addition to alkynes and alkenes, such as isocyanates, carbonylic compounds, carbodiimides.[67]

(6+2) annulations

An interesting intramolecular tandem process that can be classified as a (6 + 2) cycloaddition, consists of the Rh-promoted intramolecular annulation of allenynals like those shown in the scheme 41, which produce fused bicyclic ketone derivatives in good to high yields.[68a]



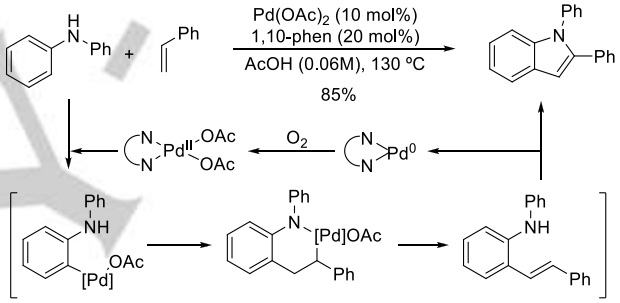
Scheme 41. Formal (6+2) annulation leading to cyclooctanones.

A possible reaction mechanism involves the formation of a five membered oxo-rhodacycle which might isomerize to a seven member oxo-rhodacycle via π–allylrhodium intermediate. Alkyne insertion and reductive elimination closes the catalytic cycle. The authors also reported an intermolecular version of this reaction using terminal alkynes.[68b]

6. Annulations involving tandem addition-cyclization processes

While many of the annulations that involve a C-H activation/cleavage step can be classified according to the previous mechanistic schemes, there are other formal annulations that are not truly organometallic formal cycloadditions as they involve the formation of acyclic organic intermediates that evolve to the product through a cyclization reaction.

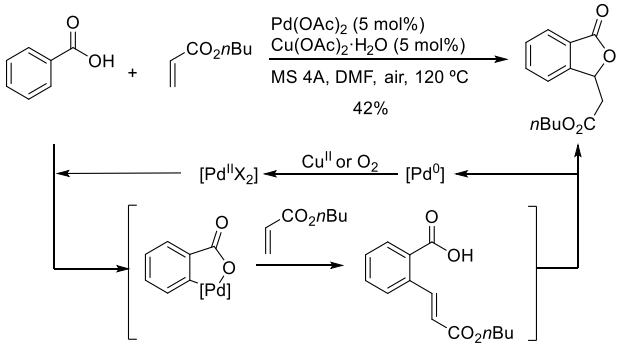
Maiti et. al reported the synthesis of indole products by reaction of secondary anilines and simple alkenes like styrene under palladium catalysis.[69] The authors suggested that the reaction starts by an orthopalladation followed by olefin coordination and migratory insertion. β-Hydride elimination produces an alfa-alkenylenamine that evolves to the product by means of a Pd-promoted cyclization, although other mechanisms cannot be rule out. Similar reactivity was found using simple phenols as starting materials.[70]



Scheme 42. Pd(II)-catalyzed synthesis of indoles from simple anilines.

A related annulation from dialkylanilines involving an initial alkenylation followed by insertion of CO has been recently described by Lei and coworkers.[71]

Another example of these formal annulations that involves a coupling reaction followed by cyclization has be reported by Miura, and consists of the formal (4+1) annulation between 2-benzoic acids and alkenes (Scheme 43).[72]

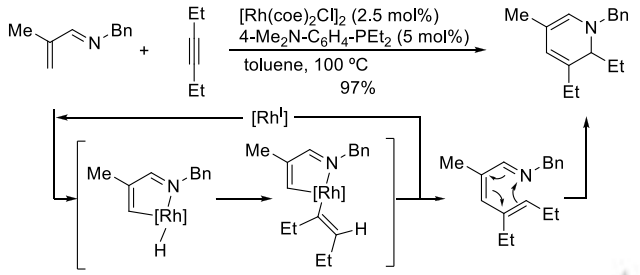


Scheme 43. Formal annulation between benzoic acids and activated alkenes.

The reaction is promoted by a Pd complex and might involve the formation of a five-membered palladacycle, alkene insertion

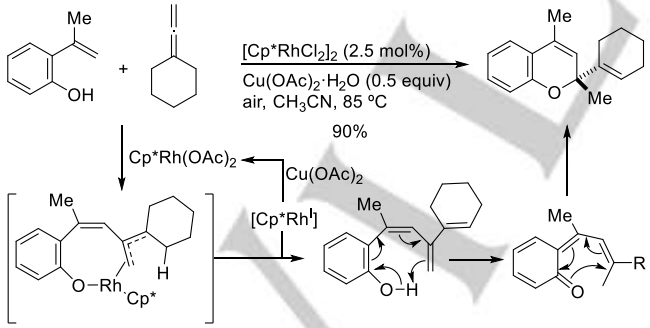
and β-hydride elimination to generate an alkenyl derivative and Rh(I) which is subsequently reoxidized by Cu(II) or oxygen. If the alkene contains an electron withdrawing group, then nucleophilic cyclization leads to the final product.

Since this report, many other examples of this type of transformation has been developed.[5] Ellman and Bergman's groups developed an interesting cascade transformation that enables the one-pot preparation of highly substituted piperidine derivatives from imines and alkynes in good overall yields and with excellent diastereoselectivities (Scheme 44).[73] The author found that the reaction benefits from the use of an electron-donor phosphine ligand. The mechanism starts with a Rh-catalyzed β-C−H bond activation of α,β-unsaturated imines followed by addition across alkynes to give azatriene intermediates which undergo an in situ electrocyclization to 1,2-dihydropyridines.



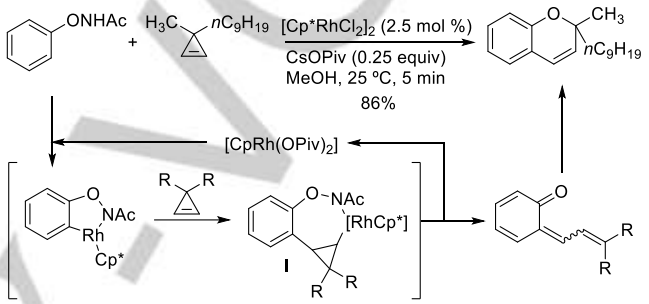
Scheme 44. Synthesis of dihydropyridines from imines and alkynes.

Another example which involves an electrocyclic process was described by Mascareñas and Gulías and consists of a formal (5+1) annulation of 2-alkenylphenols and allenes that gives highly valuable chromene skeletons (scheme 45).[74] The mechanism is proposed to involve π-allylic rhodacycle intermediates, which instead of undergoing a reductive elimination evolve by β-hydride elimination to a triene intermediate which rapidly undergo a [1,7]-*H* sigmatropic shift. The resulting dearomatized tetraenone evolves by means of a 6 π-electrocyclic reaction to the observed chromene.



Scheme 45. Synthesis of chromenes from 2-alkenylphenols and allenes.

Finally, there have been some reports demonstrating the viability of using annulation precursors that contribute with three atoms to the final cycle. For instance, Wang et al have reported a Rh(III)-catalyzed synthesis of *2H*-chromenes from N-phenoxyacetamides and cyclopropenes.[75a] The reaction takes place under mild conditions in only five minutes and, owing to the presence of the aminooxy group, does not need external oxidants. Mechanistically, the transformation was proposed to start by ligand exchange of the Rh catalyst with the nitrogen atom followed by a typical C-H activation/cleavage step and migratory insertion of the cyclopropene to give rhodacycle **I** (Scheme 46).[75a] The initial proposal by Wang considered that this intermediate might evolve by β-carbon elimination followed by reductive elimination with concomitant cleavage of the O-N bond. However, recent computational DFT studies suggest that this seven-membered rhodacycle might evolve by an alternative pathway involving the formations alkenylcyclohexa-2,4-dienone intermediates which reorganize to the observed chromene products through an electrocyclic cyclization.[75b,c]



Scheme 46. Isochromenes through formal (3+3) annulations.

7. Summary and Outlook

The enormous constructive potential of annulation reactions calls for a continuous innovation in cycloaddition tactics and methodologies. While metal catalyzed formal cycloadditions of unsaturated partners have demonstrated an enormous potential to make cyclic systems from otherwise unreactive acyclic precursors, recent years have witnesses an exponential progress in the development of catalytic annulations involving the formal activation and cleavage of "inert" C-H bonds. The field can yet be considered in its infancy and therefore many more transformations that allow atom economical transformations of readily available precursors remain to be discovered. In addition to further studies that can shed further light into the mechanisms of these transformations, next years will also witness the development of asymmetric versions that could allow the assembly of valuable carbo- and heterocyclic products in an optically active form. The use of other, more abundant metals than Rh, Ru or Pd as catalysts for this type of reactions is also being increasingly explored.

Acknowledgements

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Keywords: C-H activation • cycloaddition • transition metals • heterocycles • homogeneous catalysis

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Recent years there have witnessed a boost on C-H activation-based annulations that can be formally considered as cycloaddition processes. These transformations are particularly appealing from a synthetic perspective because they allow the conversion of readily available substrates into highly valuable cyclic products in a rapid and sustainable manner.

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Metal-catalyzed annulations involving the activation and cleavage of C-H bonds

Layout 2:

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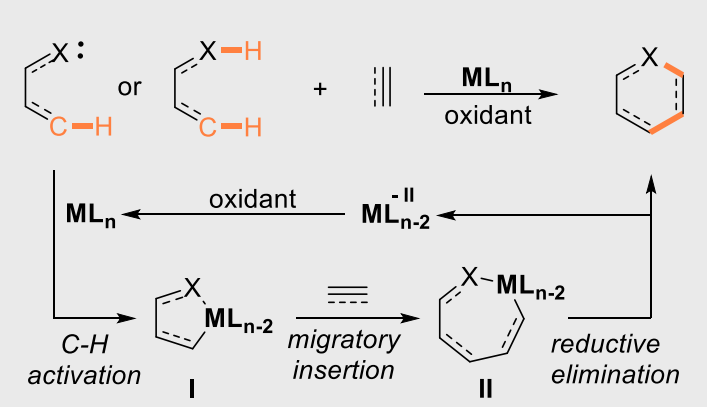

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