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Metal-Catalyzed Annulations through Activation and Cleavage of C−H Bonds

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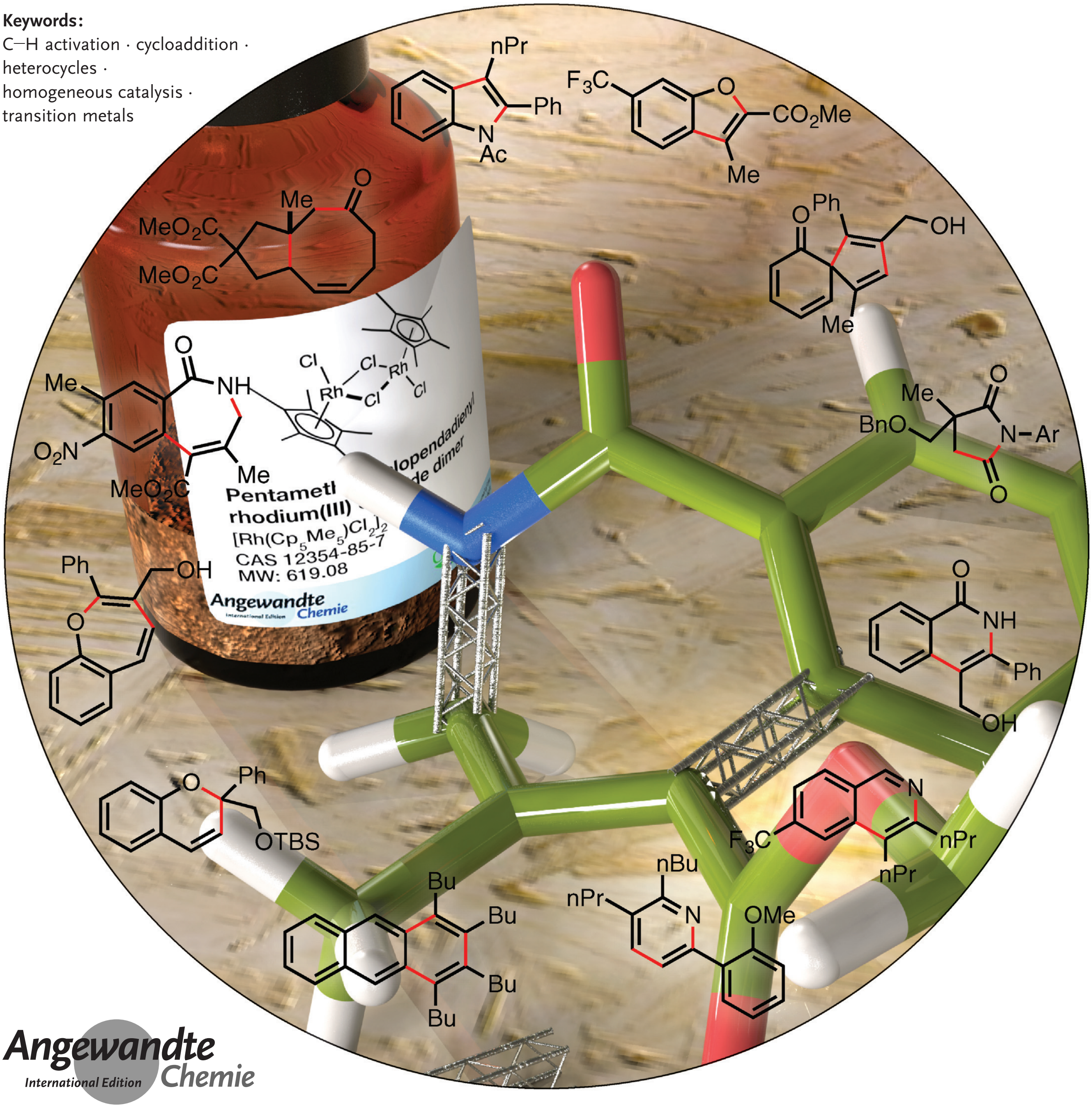

The exponential increase in the number of catalytic transformations that involve a metal-promoted activation of hitherto considered inert C–H bonds is promoting a fundamental change in the field of synthetic chemistry. Although most reactions involving C–H activations consist of simple functionalizations or additions, recent years have witnessed an upsurge in 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.

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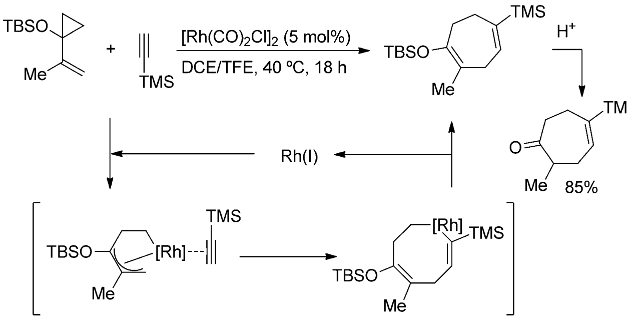
1. Introduction

A major goal in synthetic chemistry is the development of methods that allow readily available precursors to be transformed into desired products in an atom- and step-economical manner.[1] Especially challenging is the construction of products with relatively complex cyclic scaffolds from simpler, acyclic starting materials. In this context, cycloaddition reactions are extremely appealing as they allow the formation of two bonds and one ring in a single step.[2] While classical cycloadditions, such as Diels—Alder reactions, are restricted to substrates that are appropriately matched from an electronic point of view, it has been widely shown that it is possible to induce the annulation of substrates that are otherwise unreactive by using metal catalysts.[3] These metal-catalyzed reactions can be formally viewed as cycloaddition processes, although from consideration of the IUPAC Gold Book 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 such as alkylidenecyclopropanes or -cyclobutenes—and usually require late-transition-metal reagents in a low oxidation state.[3] In general, these cycloadditions take place through a mechanism based on an initial oxidative cyclometalation, in which the valence of the metal is increased, followed by migratory insertion of a second partner and a final reductive elimination. This mechanistic path is exemplified in Scheme 1 for a formal (5+2) cycloaddition developed by Wender and co-workers.[5]



Scheme 1. Rh-catalyzed formal (5+2) cycloaddition discovered by Wender and co-workers. DCE = 1,2-dichloroethane, TMS = trimethylsilyl.

Recent years have witnessed an upsurge in 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, and addition reactions, but more recently there has been an increasing number of reports dealing with formal catalytic cycloaddition processes.[7] Although 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 cyclometalations.

Indeed, one of the more common mechanistic scenarios in this type of annulation consists of an initial formation of heterometallacyclic intermediates of type **I**, followed by migratory insertion of an unsaturated partner, and reductive elimination (Scheme 2). The catalyst (usually a Pd, Rh, or Ru

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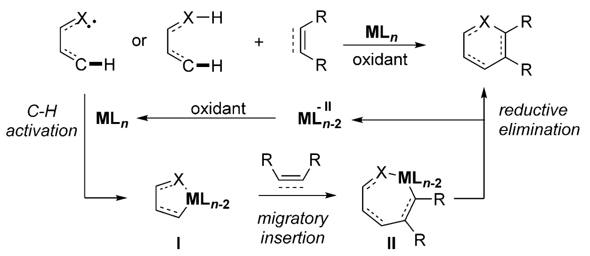


Scheme 2. General mechanism for a metal-catalyzed cycloaddition involving a formal C–H activation and cleavage.

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 cases, these annulations require the presence of a heteroatom in the substrate that not only enhances the reactivity but also allows the regioselectivity to be controlled by driving the metal complex to the reacting C–H site. The heteroatom can become part of the final ring.

While many metal-catalyzed annulations involving the activation of C–H bonds can be accommodated in the above mechanism, 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 coordinating directing group have also been described.

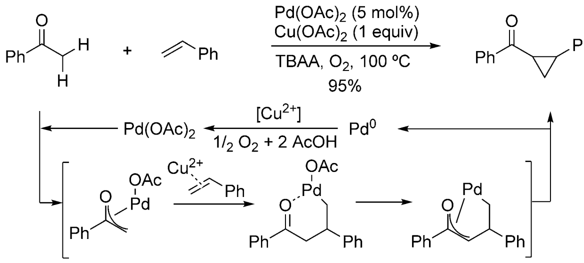
In this Review we aim to showcase the state of the art in this emerging field of metal-catalyzed annulations. We have opted for systematization based on mechanistic aspects rather than a descriptive focus, as well as a classification according to the number of atoms involved in the annulation. Thus, we use the notation first described by Huisgen, with parentheses, and with numbers referring to the atoms involved in the forming ring.[4b] This Review is not intended to be comprehensive, and thus not all the articles in the field are included and cited. Most of the schemes 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 C–H Activation, Migratory Insertion, and Reductive Elimination

This category includes reactions in which the C–H cleavage leads to an organometallic complex that evolves into the product by migratory insertion of the unsaturated partner followed by reductive elimination. Representative examples are discussed, 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. (2+1) Annulations

An interesting method of making cyclopropanes was described by Cotugno et al. and involves a formal (2+1) annulation between aryl methyl ketones 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 hypothesized mechanism considers activation of the α-position of the acetophenone to give an oxa-π-allylpalladium complex (Scheme 3). Addition of styrene followed by deprotonation at the α-position yields a new oxa-π-allylpalladium that undergoes a reductive elimination to give the cyclopropane product and Pd^0, which is reoxidized by O_2 with the



Scheme 3. Pd^{II}-catalyzed assembly of a cyclopropane.

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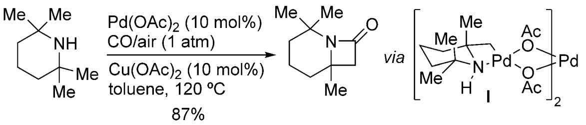
assistance of Cu^{II}. Unfortunately the method does not work with other ketones or with alkenes containing aliphatic substituents, mainly because of the competitive formation of dehydrogenated products.

2.2. (3+1) Annulations

In 2014, the Gaunt research group 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 bisamine-palladium(II) species, and thus allows the creation of a vacant site for the C–H activation. The authors isolated the dimeric palladium complex **I** resulting from cleavage of the C–H bond (Scheme 4).

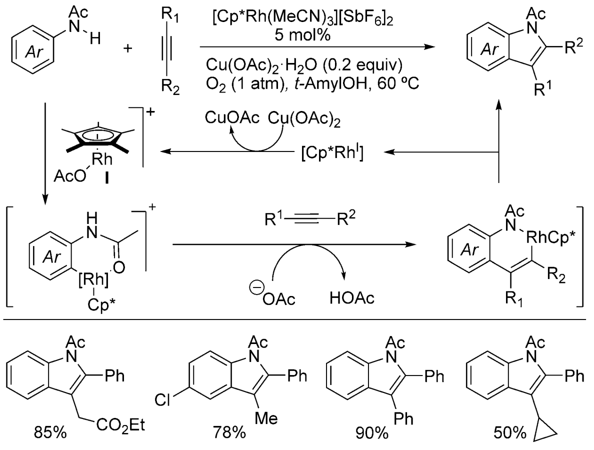


Scheme 4. Pd^{II}-catalyzed carbonylation of an aliphatic amine.

2.3. (3+2) Annulations

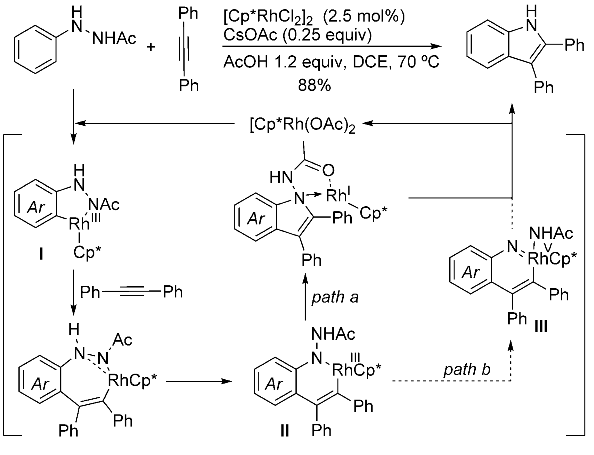
A remarkable example of this type of annulation is the formation of indoles by the reaction of anilides with alkynes,[10] a transformation pioneered by Fagnou and coworkers.[10a] The reaction, which is catalyzed by Rh^{III} and requires the presence of an added oxidant, is quite general and efficient, and tolerates a wide range of substituents, both in the aromatic ring and in the alkyne, although it 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.

Initially, stoichiometric amounts of $Cu(OAc)_2$ as the external oxidant and high temperatures were needed; however, subsequent studies led to the development of milder reaction conditions that even allow the use of oxygen as the final oxidant.[10b] The initial step of the reaction has been proposed to involve the coordination of the Lewis-basic amide oxygen atom with an active form of the Rh^{III} catalyst (most probably complex **I** in Scheme 5). This is followed by an irreversible and rate-determining cleavage of the aromatic C–H bond *ortho* to the amide group through a concerted metalation/deprotonation (CMD) mechanism. The resulting arylrhodium intermediate coordinates the alkyne and evolves by migratory insertion into a six-membered rhodacycle. Finally, this complex delivers the desired indole product by reductive elimination, along with $[Cp^{*}Rh^{I}]$, which is oxidized back to the active species by copper(II) acetate. Other authors later developed related annulations of substrates containing 2-pyridyl or 2-pyrimidyl directing groups instead of amides, and using not only Rh, but also Pd or Ru complexes as catalysts.[11]



Scheme 5. Rhodium-catalyzed synthesis of indoles from anilides and alkynes. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

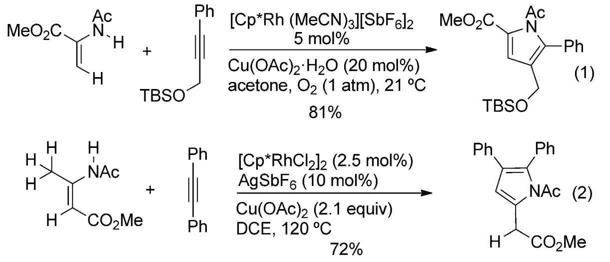
Importantly, after the discovery of redox-neutral C–H functionalization processes in which an oxidizing functional group serves both as a directing group and an internal oxidant,[12] a number of research groups developed alternatives for the synthesis of indoles that avoid the requirement of external oxidants.[13] Most of them consist of using anilide derivatives such as arylhydrazines, hydrazones, or nitrosoanilines, the N–N bond of which functions as an internal oxidant. For example, Glorius and co-workers demonstrated that 2-acetyl-1-arylhydrazines react with alkynes to give indoles when treated with catalytic amounts of $[Cp^{*}RhCl_2]_2$ in DCE in the 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 (such as **I** in Scheme 6), followed by migratory insertion of the alkyne across the C–Rh bond. The resulting seven-membered rhodacycle rearranges to **II**, which can undergo a reductive elimination with concomitant cleavage of the N–N bond (path a). The resulting indole



Scheme 6. Proposed mechanism for the cycloaddition between an *N*-acetyl-1-arylhydrazine and an alkyne.

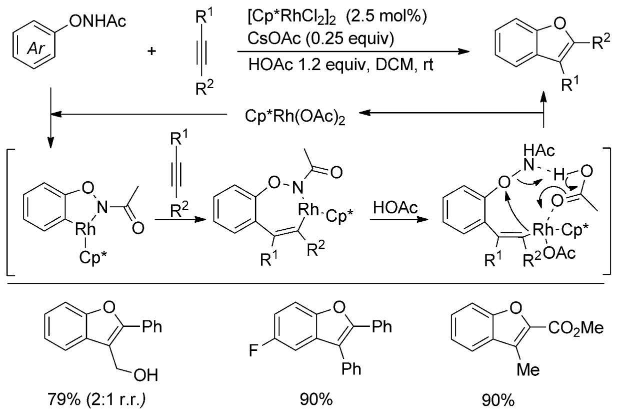
derivative containing a N−Rh bond is protonated and, thus, regenerates the Rh^{III} catalyst. Although the authors do not discount other pathways, such as one involving the intermediacy of a cyclic Rh^{V} nitrene intermediate such as **III** (path b), recent DFT calculations support a mechanism involving a $Rh^{III}/Rh^{I}/Rh^{III}$ cycle, at least in this type of reaction, which involves a relatively weak internal oxidant (N−N bond).[15] There have also been reports on intramolecular versions of the above annulations, reactions that allow interesting polycyclic products to be built from relatively simple precursors.[16]

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

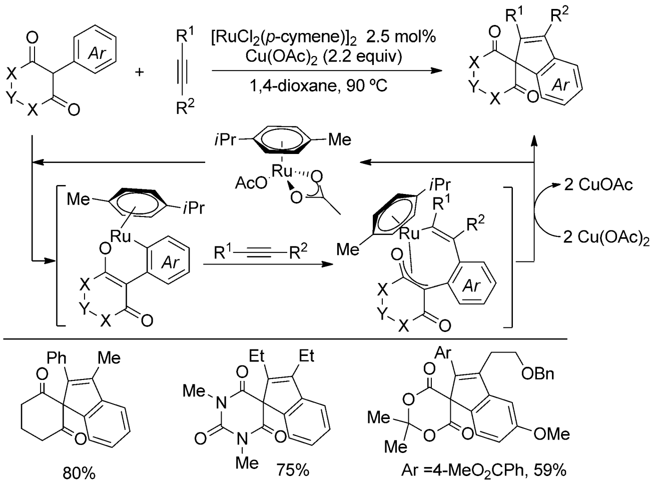


Scheme 7. Rh-catalyzed synthesis of pyrroles from enamides and alkynes. TBS = *tert*-butyldimethylsilyl.

The use of phenol instead of aniline derivatives allows the generation of benzofurans. Thus, Liu, Lu et al. have shown that treating N-phenoxyacetamides with alkynes under conditions very similar to those described for the synthesis of indoles gives the expected products in 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-membered rhodacycle (Scheme 8). The authors suggest that protonation of the N−Rh bond gives a vinylrhodium species that evolves into the product through an acetic acid assisted intramolecular substitution. Curiously, in the presence of coordinating solvents such as MeOH, the seven-membered rhodacycle provides acyclic enamides instead of the cycloadducts. The proposed mechanism invoves a reductive elimination, oxidative addition of the resulting Rh^{I} to the N−O bond, and protonation.



Scheme 8. Rh-catalyzed synthesis of benzofurans from N-phenoxyacetamides. r.r. = regioisomeric ratio.



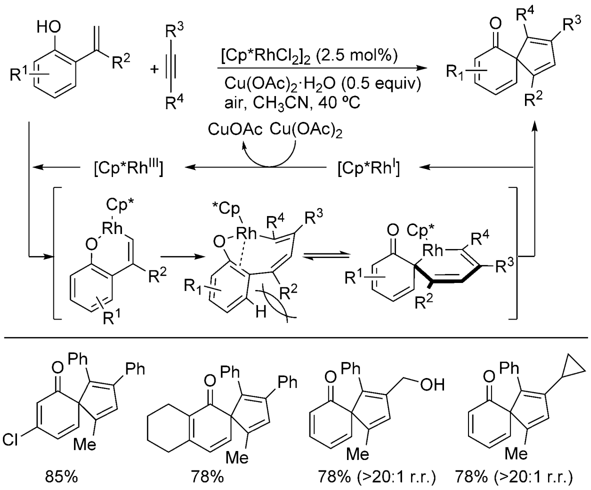
Scheme 9. Ru-promoted synthesis of spiroindenes from phenyldiones and alkynes.

The above reactions generate heterocyclic products, but it is also possible to carry out related formal [3C+2C] cycloadditions to generate carbocycles. For example, the Lam research group has published several articles on the synthesis of spiroindenes from 2-aryl-1,3-carbonylic compounds and alkynes by using Ru^{II} complexes as the catalysts (Scheme 9) or Pd^{II} 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*-C(aryl)−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, reductive C−C 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 the catalyst. An asymmetric version of this reaction has recently been reported.[19c]

Related ruthenium-catalyzed formal (3+2) annulations have been reported by Luan and co-workers, who used 2-phenylnaphthols or electron-rich phenylphenols 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 metalation/deprotonation process.

Recently, the You research group also developed an asymmetric version of this annulation by using a Rh catalyst with a chiral cyclopentadienyl (Cp) ligand and dibenzoyl peroxide ($(BzO)_2$) as oxidant.[20c]

Another example of a dearomatizing (3+2) cycloaddition using a Rh^{III} catalyst was developed by Mascareñas, Gulías, and co-workers[21a] as well as by Lam and co-workers,[21b] and involves the dehydrogenative annulation between 2-alkenylphenols and alkynes (Scheme 10). The reaction, which requires the presence of internal substituents on the alkene, allows extremely simple substrates to be transformed into interesting spirocyclic products. The proposed mechanism 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. A steric clash between the alkenyl substituent and one of the C–H bonds of the aryl group in the rhodacyclooctane might favor the six-membered rhodacycles, which upon reductive elimination yield the final products.

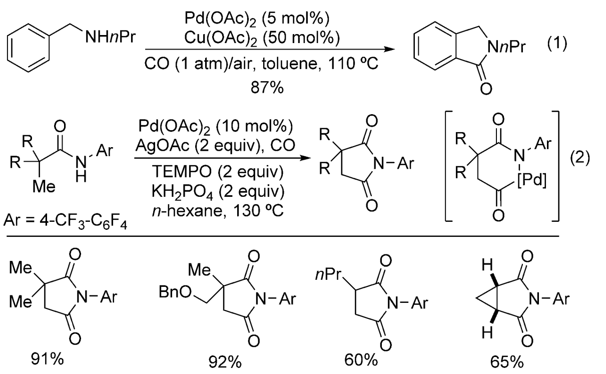


Scheme 10. Rh-catalyzed synthesis of spirocycles.

2.4. (4+1) Annulations

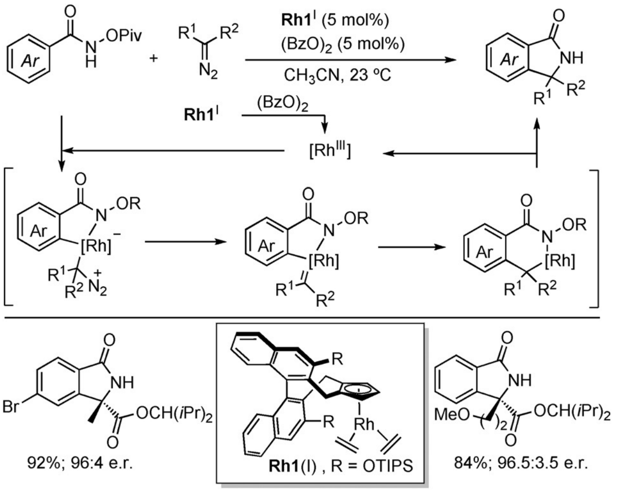
One of the earliest examples of a catalytic annulation involving a C–H activation process was reported by Orito et al., and consists of the Pd-catalyzed reaction of N-monoalkylated benzylamines or *N*-phenylethylamines with carbon monoxide.[22a,b] These annulations represent a formal (4+1) cycloaddition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

In 2010 Yu and co-workers reported several interesting examples of a related annulation tactic involving the activation of $C(sp^3)$–H bonds in α-substituted amides [Eq. (2) in Scheme 11].[22c] An appropriate choice of the substituent at the nitrogen atom, 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 α-position to the carbonyl group, although the yields are slightly lower. The transformation is proposed to proceed through an amide-directed cleavage of a $C(sp^3)$–H bond and insertion of CO into the resulting $[Pd^{II}–C(sp^3)]$ bond, followed by Pd-mediated C–N reductive elimination to give the corresponding succinimide products. TEMPO was found to be a crucial co-oxidant for the efficient reoxidation of Pd^0 to Pd^{II} in the presence of CO. Zhu et al. found that isocyanides can also be used as 1C coupling partners.[22d]



Scheme 11. Carbonylation of $C(sp^2)$–H and $C(sp^3)$–H bonds. Equation (2) also shows a palladacycle intermediate. TEMPO = 2,2,6,6-tetramethyl-1-piperidinoxyl.

Another interesting example of a formal (4+1) annulation, pioneered by Rovis and co-workers, involved the Rh^{III}-catalyzed annulation between *O*-pivaloylbenzhydroxamic acids and diazo compounds.[23a] An asymmetric version of this reaction was later developed using chiral Cp ligands (Scheme 12).[23b] The N–O bond works as an internal oxidant, as has been shown extensively in related annulations with alkynes (see Scheme 14). 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 into rhodium carbenoids, which undergo a migratory insertion to give six-membered rhodacycles,



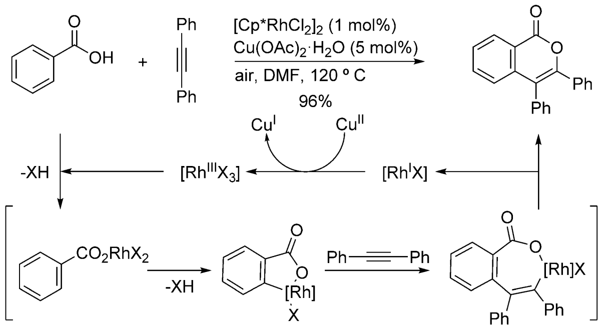
Scheme 12. Rh-catalyzed synthesis of isoindolones with a tetrasubstituted carbon atom. Piv = pivaloyl, TIPS = triisopropylsilyl.

a step that sets up the stereogenic center. Reductive elimination might then deliver the isoindolone products and regenerate the Rh catalyst.

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 atom to the Rh center, followed by reductive elimination.[23c]

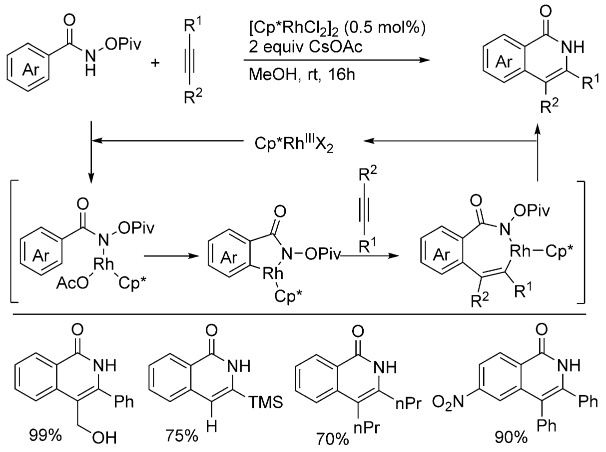
2.5. [4+2] Annulations

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 was reported by Ueura et al. in 2007.[24a] The authors demonstrated that heating benzoic acids with internal alkynes in the presence of catalytic amounts of $[Cp^{*}RhCl_2]_2$ and 2 equivalents 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 coupling reactions is illustrated in Scheme 13. Coordination of the carboxylate group 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 into the product through reductive elimination. The resulting $Cp^{*}Rh^{I}$ species is reoxidized by the Cu^{II} or Ag^{I} salts to regenerate the active catalytic species. Recently, the Ackermann research group demonstrated that the reaction can be carried out with a Ru^{II} catalyst under mild conditions with oxygen as the sole oxidant.[24c]



Scheme 13. Rh-catalyzed annulations between benzoic acids and alkynes. We keep the original nomenclature proposed by Miura and co-workers, where X indicates different Rh ligands.

Benzamides can also undergo similar annulation reactions, as has been demonstrated extensively 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 et al. reported a redox-neutral version of these annulations that avoids the requirement of external oxidants, and is based on the use of benzhydroxamic acid derivatives as reaction partners.[25a] The reaction is particularly effective if the internal oxidizing N–O group features a pivalate substituent (Scheme 14).[25b] Indeed, the transformation of this type of substrates can be achieved at room temperature, and even works with terminal alkynes, which are elusive for most other annulations, which typically employ Cu^{II} oxidants.

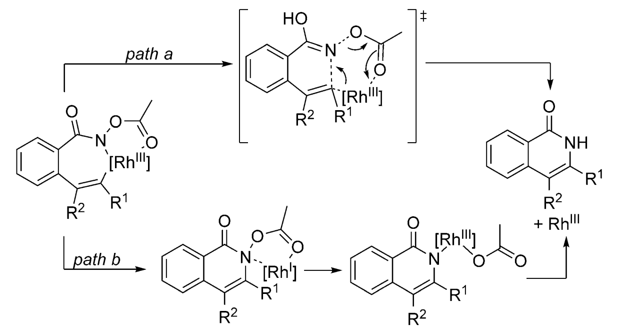


Scheme 14. Rh-catalyzed synthesis of isoquinolones from an alkyne and a benzhydroxamic acid.

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

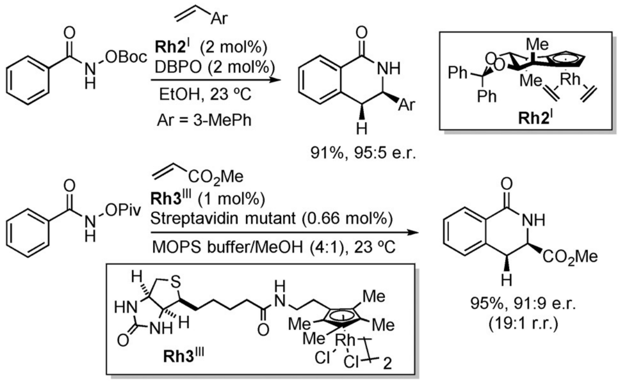
The authors suggested two potential operative pathways for the final C–N bond-forming step (Scheme 15).[25b] Path a consists of a concerted process where a highly organized six-membered cyclic transition state accounts for a simultaneous C–N bond formation and N–O bond cleavage. The main characteristic 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 reductive elimination of a C–N bond would yield an intermediate that could readily undergo oxidative addition of an N–O bond. Calculations carried out by the same research group suggest path b to be the more likely; however, alternative pathways involving Rh^{V} nitrenoid species cannot be discarded.[27]

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



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

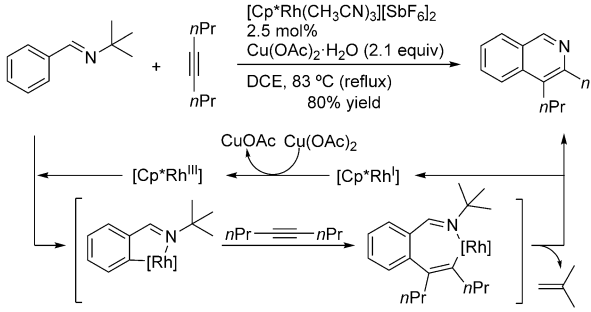
other annulation reactions involving these types of C–H activation processes because of competing β-hydride eliminations. The annulation can also be accomplished in an asymmetric manner, as recently shown by Ye and Cramer[28] as well as by Hyster et al. (Scheme 16).[29] Ye and Cramer developed a chiral Cp ligand with C_2 symmetry. Hyster et al. reported an elegant synthesis of a biotinylated Cp ligand for Rh^{III} that, upon interacting with a biotin binding protein, generates a chiral environment that is transduced to the formation of enantiomerically rich products.



Scheme 16. Asymmetric annulation of benzamides with alkenes. DBPO = dibenzoylperoxide, MOPS = 3-(*N*-morpholino)propanesulfonic acid.

In addition to benzamides, it has been shown that other related substrates, such as acrylamides, sulfonamides, and sulfoximides, can also undergo mechanistically related metal-catalyzed annulations.[30] There have also been 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] Wu et al. 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 allows the (4+2) process to be extended formal (4+2+2) annulations.[33] Although it seems clear that all these annulations work well with Rh^{III} or Ru^{II} catalysts, there are also isolated examples that demonstrate that Pd^{II} complexes can also promote similar annulations with alkynes, arynes, or allenes.[34]

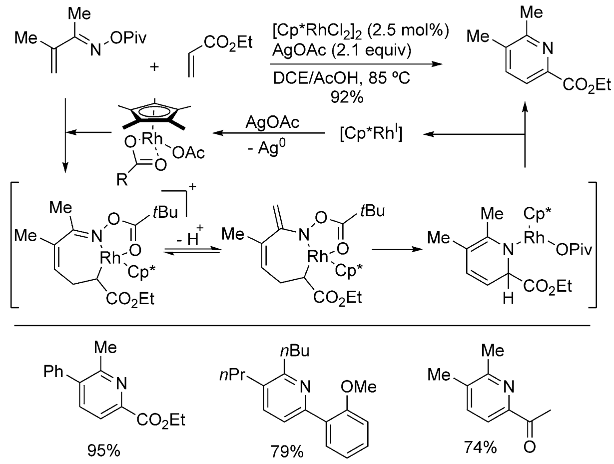
In the above reactions, the initial ligand exchange between the substrate and the metal complex involves a deprotonation reaction. However, it has been shown that benzylimines, which lack an acidic hydrogen atom, may also engage in highly related annulations to give very interesting isoquinoline products (Scheme 17).[35] The final reductive C–N 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, Guimond and Fagnou convincingly demonstrated that the C–N reductive elimination most probably occurs directly from the Rh^{III} complex, with isobutene generated as the side product.[35]



Scheme 17. Rh-catalyzed synthesis of an isoquinoline from a *tert*-butylimine.

Other authors have developed different variants, including the use of benzylimine or alkenylimine derivatives, and either external or internal oxidants, with the latter version consisting of built-in N–O or N–N bonds.[36] In this context, an interesting development described by Neely and Rovis consisted of the assembly of substituted pyridines from *O*-pivaloyloximes and activated alkenes such as acrylates.[37a] The reaction is carried out at 85 °C with a slight excess of the alkene in the presence of $[Cp^*RhCl_2]_2$ and AgOAc (Scheme 18). Although it could be expected that the seven-membered 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 chelation of the Rh center by the carboxy group of the pivalate substituent which generates coordinative saturation (Scheme 18). Thus, the rhodacycle evolves by C–N bond formation and N–O bond cleavage, followed by tautomerization and a final β-hydride elimination to furnish the pyridine product and a Rh^{I} complex that is oxidized by Ag^{I} to Rh^{III}.

The reaction is also viable with non-activated alkenes, but provides mixtures of regioisomeric products. This limitation was circumvented by the same authors by using acrylic acids as cycloaddition partners, because the carboxylic acid can be

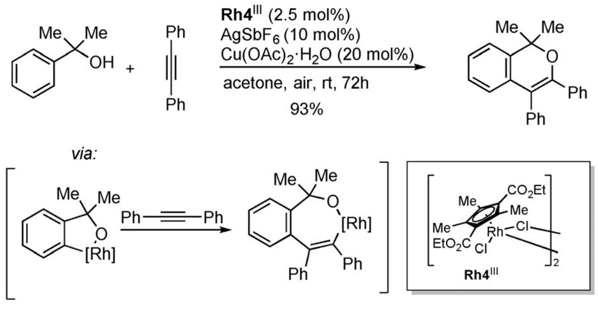


Scheme 18. Rh-catalyzed synthesis of pyridine derivatives from a pivaloyloxime and an alkene.

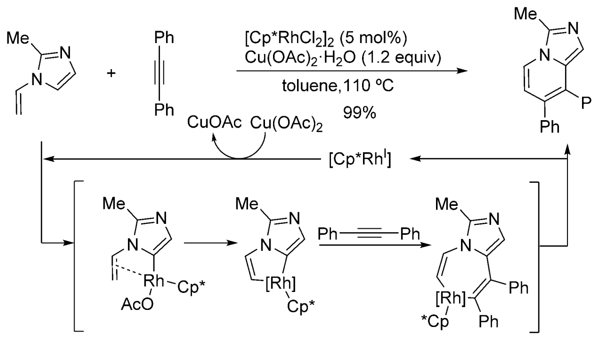
removed by decarboxylation and thus serves as a traceless activating group. The reaction affords 5-substituted pyridines with very high levels of regioselectivity.[37b] Recently, the Glorius research group reported related annulations by using dienes as unsaturated partners. These reactions take place with very good regioselectivity and allows the range of products that can be obtained to be expanded.[37c] It is also worth mentioning an interesting recent example of a related dehydrogenative annulation using N-unsubstituted benzamidines and alkynes catalyzed by manganese.[38] This study suggests that first row transition metals might have potential for future developments in this area.

Another formal (4+2) cycloaddition reported by Satoh, Miura, and co-workers 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, although at high temperatures.[39a] Based on this study, the Tanaka research group demonstrated that it is possible to perform the reaction at milder temperatures by using electron-deficient cyclopentadiendyl ligands for the rhodium center (Scheme 19).[39b]

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 does not require the presence of a chelating heteroatom. This type of nondirected C−H activation can also be attained using Rh catalysts, such as that demonstrated, for example, by Huang et al. in the annulation of 2-substituted *N*-vinyl- or *N*-arylimidazoles with alkynes in the presence of a Rh^{III} catalyst (Scheme 20).[40] Phenylheteroarenes such arylazoles, *N*-phenylbenzimidazoles, *N*-phenylindoles, phenylthiophenes, and N-heterocyclic carbenes can also be engaged in similar transformations.[41]



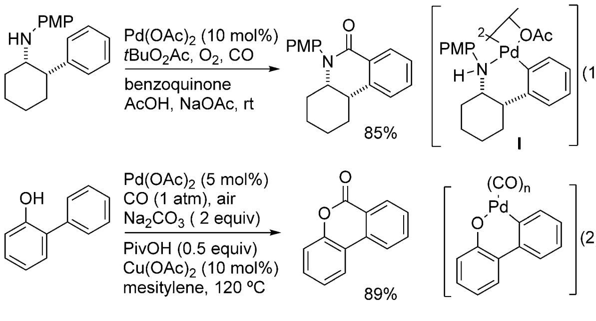
Scheme 19. [4+2] Annulation leading to an isochromene.



Scheme 20. Double C−H activation of a 2-substituted *N*-vinylimidazole without assistance of a heteroatom directing group.

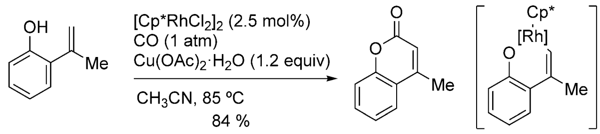
2.6. (5+1) Annulation

The assembly of six-membered rings by formal (5+1) cycloadditions has also been accomplished. Gaunt and co-workers 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 [Eq. (1) in Scheme 21].[42a] Mechanistic studies demonstrated that the initial C−H activation leads to the dimeric palladium species **I**, which could even be isolated.



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

The Shi research group reported a related carbonylation of 2-arylphenols, which has been proposed to involve an electrophilic cyclopalladation of the non-phenolic ring.[42b] Kinetic studies suggested that the C−H activation involves a S_EAr mechanism rather than a concerted CMD. The C−H bond cleavage generates a Pd-carbonyl intermediate, which evolves by migratory insertion of the coordinated CO followed by reductive elimination [Eq. (2) in Scheme 21]. The resulting Pd^0 species is reoxidized to Pd^{II} by $Cu(OAc)_2$ in the presence of O_2. A similar carbonylation process promoted by ruthenium catalysts has been described by Inamoto et al.[42c]

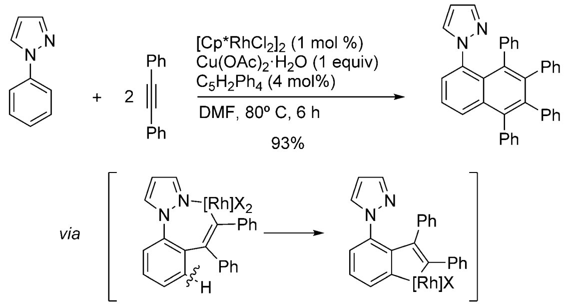


Scheme 22. Rh-catalyzed synthesis of a coumarin.

Related carbonylations that provide highly valuable coumarins 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]

2.7. (2+2+2) Annulations

Multicomponent cycloadditions are highly interesting synthetic transformations because they allow for a rapid increase in complexity, and hence for shortened synthetic pathways. Owing to the limited 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.

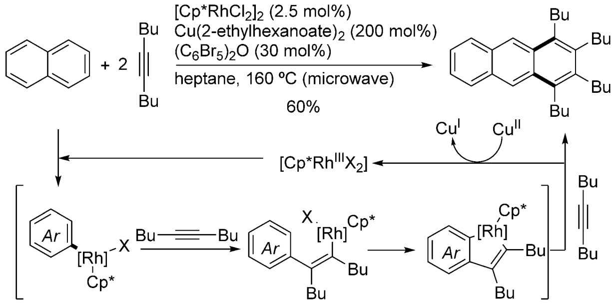


Scheme 23. (2+2+2]) Annulation of 1-phenylpyrazole and an alkyne catalyzed by a Rh^{III} species.

A pioneering example of this type of annulation was reported by Umeda et al. in 2008.[44] They demonstrated that 1-phenylpyrazoles can react with two equivalents 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 the Rh^{III} center, followed by a standard regioselective C−H activation to give a rhodacyclic adduct. Alkyne insertion into the C−Rh bond gives a seven-membered rhodacycle that is involved in a second C−H activation in the position *ortho* to the alkenyl group to give a cyclorhodapentene. Alkyne insertion and reductive elimination yields the product and Rh^I. This type of carbocyclic annulation has also been achieved with other related substrates having different heteroatom directing groups, including anilides, benzamides, and phenols.[41a,44,45]

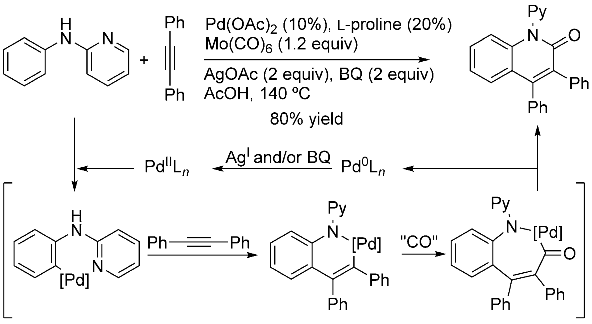
Formal (2+2+2) annulations have also been described for substrates that do not contain coordinating heteroatoms. For example, Pham and Cramer recently described a Rh^{III}-catalyzed annulation between neutral arenes and internal alkynes.[46] The reaction is more efficient when a combination of copper(II) 2-ethylhexanoate and decabromodiphenyl ether are used as oxidants. The high solubility of copper(II) 2-ethylhexanoate in apolar solvents makes it superior to $Cu(OAc)_2$, while the role of aryl bromide was not clear. The reaction was suggested to involve an initial metalation of the arene that is not assisted by chelation, which is most probably the turnover-limiting step. Migratory insertion of the alkyne produces an alkenyl rhodium species 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 to the synthesis of large aromatic substrates that are of interest in material science, but is limited to the use of symmetrical alkynes to avoid the formation of complex mixtures.



Scheme 24. Non-assisted formal [2+2+2] cycloaddition.

2.8. (3+2+1) Annulations

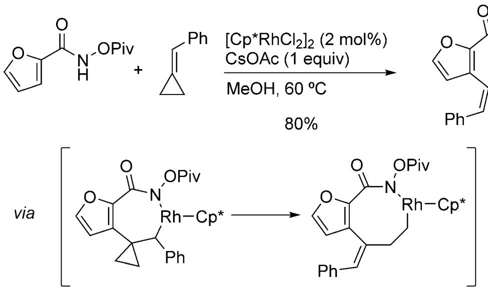
An alternative way of assembling six-membered rings consists of the carbonylative annulation of aniline derivatives and alkynes in a formal [3+2+1] process.[47] Indeed, Wu and co-workers demonstrated that it is possible to synthesize quinolones by means of a Pd^{II}-catalyzed reaction of 2-*N*-phenylpyridin-2-amines with alkynes in the presence of $Mo(CO_6)$ as the source of carbon monoxide. The insertion of carbon monoxide prior to the reductive elimination could occur in either the C−Pd or N−Pd bond (Scheme 25).



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

2.9. (4+3) Annulations

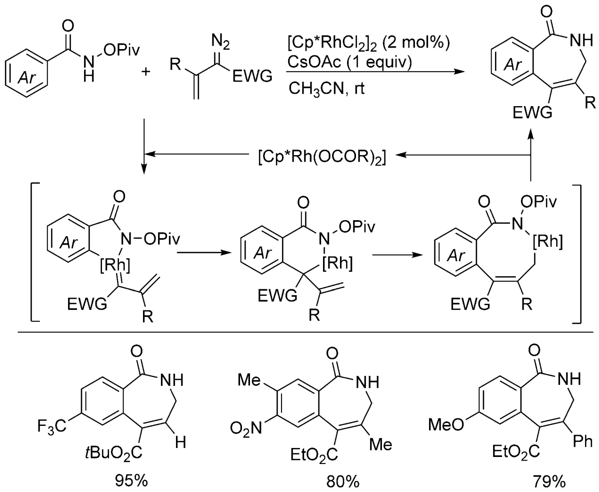
Alkylidenecyclopropanes (ACPs) and methylenecyclopropanes (MCPs), as a result of their intrinsic strain, have been used extensively as either two or three carbon components in many metal-catalyzed cycloadditions.[48] They have also been investigated as partners in cycloadditions involving the C–H activation of benzamides.[49a] Curiously, whereas most benzamides react with ACPs to form isoquinoline products, furancarboxyamides react with benzylidenecyclopropanes to give furan-fused azepinones (Scheme 26).



Scheme 26. Rh-catalyzed annulation of a furancarboxyamide and an ACP.

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 rhodacycle. The presence of the furan ring seems to facilitate a cyclopropylcarbinyl-butenyl rearrangement over the alternative reductive elimination, to generate an eight-membered metallacyclic intermediate. The final C–N bond-formation step together with N–O bond cleavage yields the cycloheptanic products.[49b]

As already commented, diazo compounds can be used as 1C components in several Rh^{III}-catalzyed annulations. In accord with well-known precedents of 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] Thus, pivaloylbenzamides react with electron-deficient alkenyldiazo derivatives under standard oxidative rhodium catalysis to give relevant azepinone products (Scheme 27).[51]



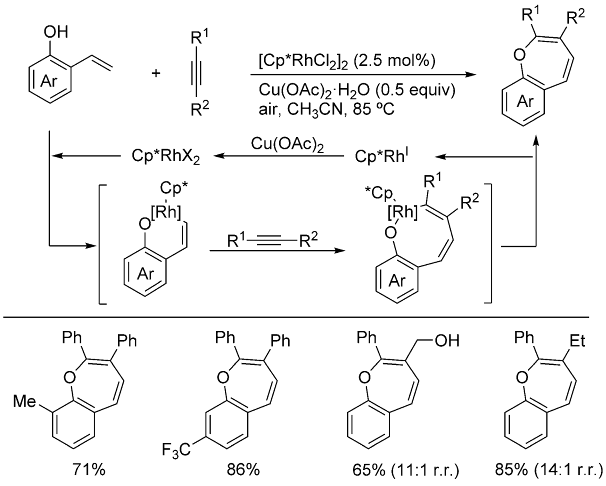
Scheme 27. Rh-catalyzed annulation of benzamides and vinyldiazoacetates. EWG = electron-withdrawing group.

Most probably the reaction involves the generation of five-membered rhodium carbene metallacycles that undergo a migratory insertion to give six-membered π-allylrhodium 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 the Rh atom (Scheme 27).[23c]

2.10. (5+2) Annulations

Formal metal-catalyzed (5+2) cycloadditions involving vinylcyclopropanes are among the more remarkable metal-catalyzed transformations discovered in the last decades.[5] However, similar annulations triggered by an initial C–H activation have not been described until recently.

In 2014, Mascareñas, Gulías, and co-workers reported a (5+2) heteroannulation between hydroxystyrenes and



Scheme 28. Synthesis of oxepines from *o*-vinylphenols and alkynes.

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 an intermediate six-membered rhodacycle, which evolves into the final observed product by standard migratory alkyne insertion and reductive elimination. Remarkably, while at first sight 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 hydroxy group of the phenol, experimental data point to an alternative nonconcerted route involving an intramolecular attack of the conjugated alkene to the electrophilic rhodium species followed by a base-assisted deprotonation. Recently a (5+2) annulation of 2-alkenylphenols with allenes using Pd^{II} as catalyst has been described.[52]

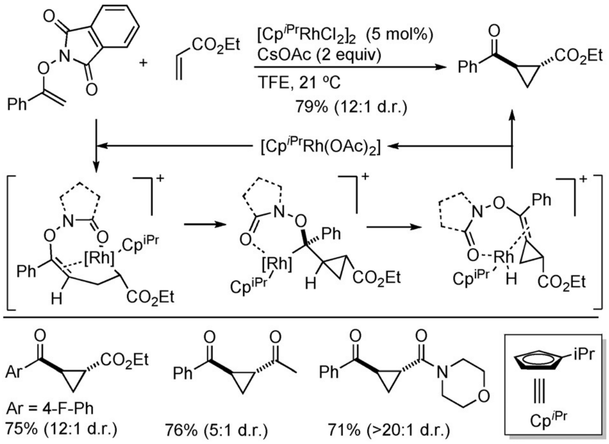
3. Annulations with Ring Closure Occurring through a Migratory Insertion Process

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

3.1. (2+1) Annulations

Piou and Rovis recently demonstrated that *N*-enoxyphthalimides 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 isopropylcyclopentadienyl ligand instead of the more standard Cp*.

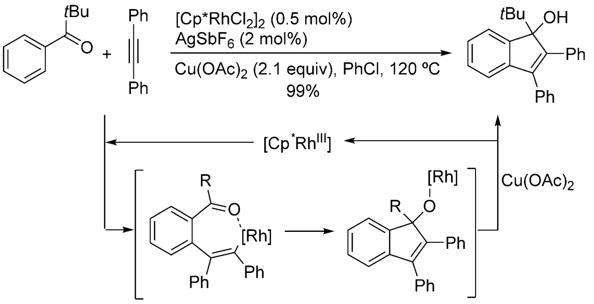
The reaction was proposed to start by an irreversible amide-directed C–H activation at the β-position of the double bond of the *N*-enoxyphthalimide. A migratory insertion of the external alkene then gives a σ-alkylrhodium(III) complex that undergoes a 3-*exo*-trig intramolecular carborhodation to form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



Scheme 29. Rh^{III}-catalyzed synthesis of cyclopropanes. TFE = 2,2,2-trifluoroethanol.

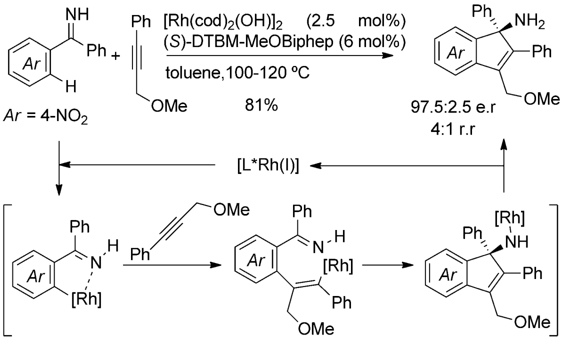
3.2. (3+2) Annulations

In 2011, the groups of Glorius and Cheng independently reported a formal [3C+2C] oxidative annulation between alkynes and arylketone derivatives to give indenol (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 group into the C–Rh bond. The exact role of the copper salt is not totally clear, but is essential for the success of the reaction. It may facilitate the release of the Rh catalyst in a transmetalation step and thus prevent the rhodium reduction, and/or provide acetate ligands.



Scheme 30. [3C+2C] Annulation of an aromatic ketone and an alkyne catalyzed by a Rh^{III} species.

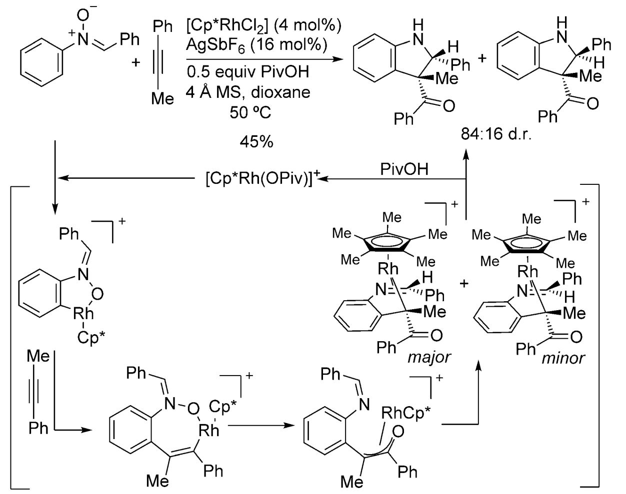
Imines can also participate in these types of formal cycloadditions. In 2010 Tran and Cramer reported the rhodium(I)-catalyzed C–H functionalization of unsubstituted



Scheme 31. Asymmetric (3+2) annulation of ketimines and alkynes. (*S*)-DTBM-MeOBiphep = (*S*)-(6,6′-dimethoxybiphenyl-2,2′-diyl)bis-[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine].

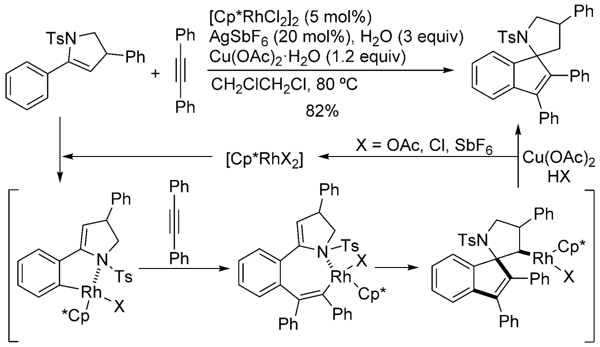
ketimines with terminal allenes.[55a] Later, the same group reported asymmetric versions with alkynes[55b] and also with allenes[55c] by using atropoisomeric MeOBiphep ligands (Scheme 31). It was proposed that the reaction with alkynes is initiated by oxidative addition of Rh^{I} to the C–H bond followed by removal of the hydrogen atom. Migratory insertion of the alkyne leads to a vinylrhodium species which adds intramolecularly across the ketimine in an enantioselective manner. When unsymmetrical alkynes are used, the presence of a coordinating functional group leads preferentially to insertion at the carbon atom proximal to the directing group.

An interesting formal (3+2) annulation involving the use of arylnitrones and alkynes as reaction partners to give indolines was developed by Dateer and Chang (Scheme 32).[56] 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 bond cannot be completely ruled out). The subsequent transfer of an O atom might take place either by cleavage of the N–O bond to form a Rh^{V}-oxo species that undergoes reductive elimination (Scheme 32), or by reductive elimination to form a benzoxazine and Rh^{I} with concomitant oxidation of Rh^{I} to Rh^{III} and 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.



Scheme 32. Rh-catalyzed synthesis of an indoline from an arylnitrone.

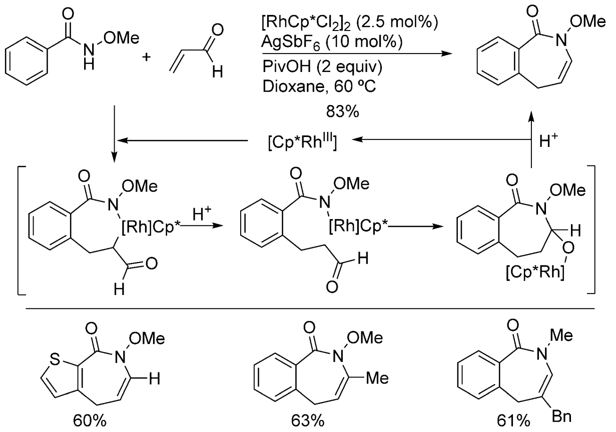
A related annulation in which the ring closure involves the addition to an alkene, instead of to a carbonyl group or an imine, was described by Zhou et al., and consists of a rhodium(III)-catalyzed reaction between 5-aryl-2,3-dihydro-1*H*-pyrroles and internal alkynes.[57] The reaction builds interesting 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).



Scheme 33. Formation of a spirocycle in a formal (3+2) cycloaddition reaction. Ts = tosyl.

3.3. (4+3) Annulations

Glorius and co-workers 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 a migratory insertion of the carbonyl group into a N–Rh bond as the ring-closing step. 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 hemiaminal, which dehydrates to the final enamide.

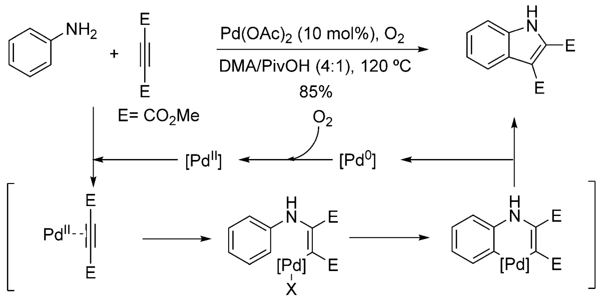


Scheme 34. Synthesis of an azepinone from a benzamide and an α,β-unsaturated ketone or aldehyde. Bn = benzyl.

4. Annulations with Migratory Insertion before the C–H Activation

4.1. (3+2) Annulations

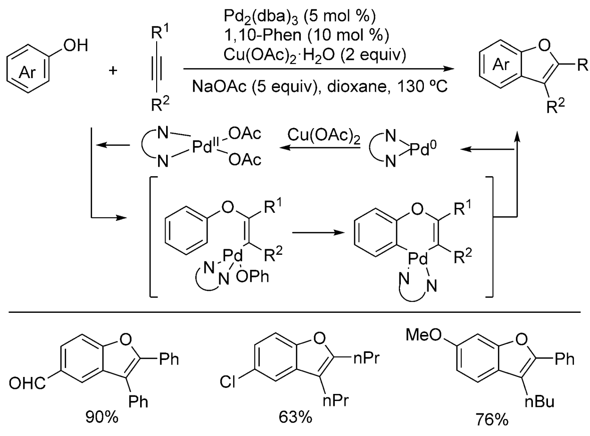
In many of the cases discussed above, the reactions start by a heteroatom-assisted C–H activation to generate a relatively strain-free five-membered metallacycle. Substrates such as anilines and phenols lack geometrically positioned heteroatoms for such directed metalations; however, it has been shown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



Scheme 35. $\mathrm{Pd^{II}}$-catalyzed synthesis of an indole from simple anilines. DMA = *N*,*N*-dimethylacetamide.

Jiao and co-workers demonstrated that simple primary and secondary anilines react with electron-deficient alkynes under palladium catalysis by using oxygen as the sole oxidant.[59] The reaction involves 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).

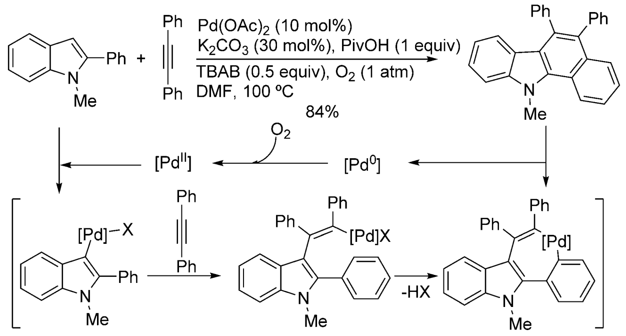
The same approach can be used with phenols instead of anilines. For example, Sahoo and co-workers described in 2013 the synthesis of substituted benzofurans from phenols and alkynes by using palladium catalysts in combination with a diamine ligand.[60] The annulation tolerates a broad range of substituents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



Scheme 36. Synthesis of benzofurans from phenols. dba = dibenzylideneacetone, 1,10-Phen = 1,10-phenanthroline.

Although the precise reaction mechanism is still not known, the authors proposed that it starts by coordination of the bidentate ligand to the Pd atom, followed by a Cu-assisted oxidation to generate an active $\mathrm{Pd^{II}}$ species. Coordination of the alkyne to the $\mathrm{Pd^{II}}$-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 $\mathrm{Pd^{0}}$ species for the next cycle. However, the authors do not discount other alternatives, including *ortho*-palladation of the phenol by the electrophilic $\mathrm{Pd^{II}}$ complex.

Interestingly, the synthesis of benzofurans from phenols and alkynes by C–H activation through the use of a copper complex as catalyst was also reported. 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 through reductive elimination or through single-electron-transfer (SET) processes.[61]



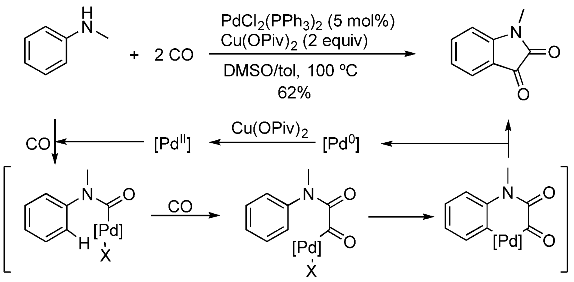
Scheme 37. Pd-catalyzed annulation between a phenylindole and an alkyne. TBAB = tetrabutylammonium bromide

4.2. (4+2) Annulations

In 2009, the Jiao research group reported the synthesis of carbazole skeletons by a formal Pd-promoted [4C+2C] 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 leads 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 $\mathrm{Pd^{0}}$ complex.

4.3. (3+1+1) Annulations

In 2015 the Lei research group reported a palladium-catalyzed double carbonylation of anilides to form isatins (Scheme 38).[63] The reaction proceeds under an atmospheric

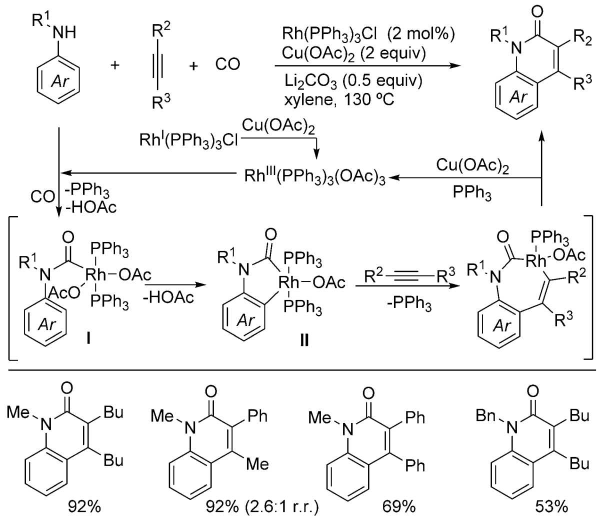


Scheme 38. Synthesis of an isatin from an aniline and carbon monoxide under palladium catalysis. tol = toluene.

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, followed by a C–H activation to give a palladacycle intermediate. Reductive elimination generates 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]

4.4. (3+2+1) Annulations

Jiao and co-workers reported in 2015 a Rh-catalyzed annulation of simple anilines with CO and alkynes for the direct synthesis of quinolin-2(1*H*)-ones through N–H and C–H bond activation.[65] The reaction works for simple anilines and has a broad scope. The mechanism is proposed to start with the formation of a 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 CMD process to give rhodacycle **II** (Scheme 39). Subsequent ligand exchange with the 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} by Cu(OAc)$_2$.



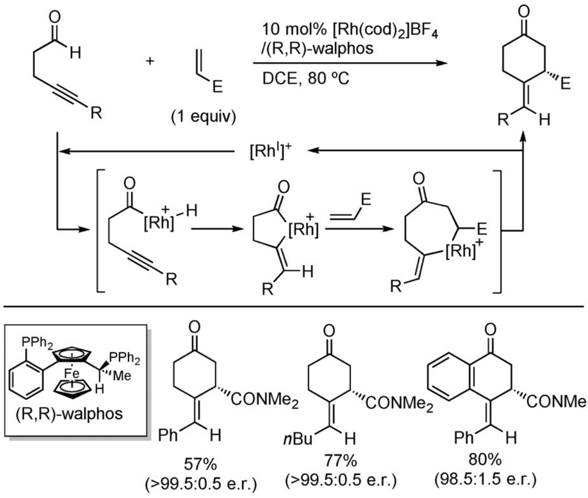
Scheme 39. (3+2+1) Annulation between anilines, alkynes, and carbon monoxide.

5. Annulations Involving Metallacycles Generated by Hydrometalation Processes

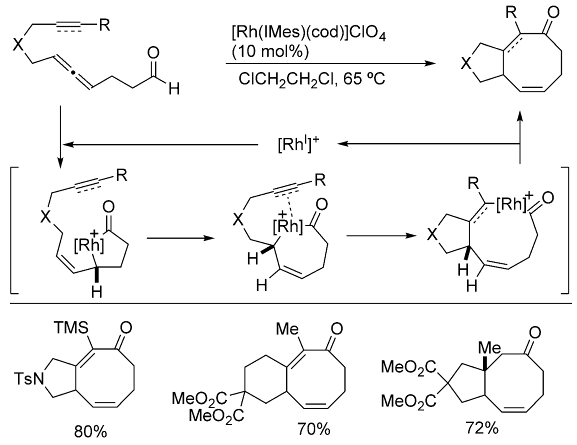
5.1. (4+2) Annulations

Although so far rarely explored, an interesting way of generating metallacycles is through the intramolecular migratory insertions of metal hydrides into unsaturated moieties. Subsequent insertion of an unsaturated partner allows for a formal cycloaddition process.

Tanaka et al. developed a rhodium-catalyzed regio- and enantioselective intermolecular [4C+2C] carbocyclization of 4-alkynals with *N*,*N*-dialkylacrylamides (Scheme 40).[66a] 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 a five-membered rhodium-acyl cyclic intermediate. After complexation of the alkene and insertion to form seven-membered metallacycles, reductive elimination furnishes the cyclohexanone products and regenerates the Rh catalyst. Alternatively, migratory insertion of the alkene into the rhodium-acyl intermediate prior to hydrometalation of the alkyne may also be operative. It was later demonstrated that the reaction is also possible with partners other than alkynes and alkenes, such as isocyanates, carbonylic compounds, and carbodiimides.[67]



Scheme 40. Asymmetric annulation between alkynals and alkenes (E = *N*,*N*-dialkylamides) catalyzed by Rh^I species. cod = 1,5-cyclooctadiene.



Scheme 41. Formal (6+2) annulation leading to cyclooctanones. IMes = 1,3-dimesitylimidazol-2-ylidene.

5.2. (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 (Scheme 41), which produces fused bicyclic ketone derivatives in good to high yields.[68a]

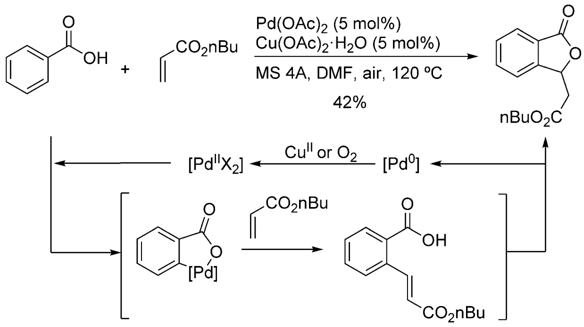
A possible reaction mechanism involves the formation of a five-membered oxo-rhodacycle which might isomerize to a seven-membered oxo-rhodacycle via a π-allylrhodium intermediate. Alkyne insertion and reductive elimination closes the catalytic cycle. The authors also reported an intermolecular version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

6. Annulations Involving Tandem Addition-Cyclization Processes

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

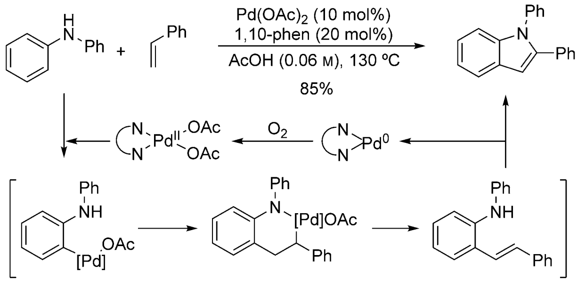
Maiti and co-workers reported the synthesis of indole products by the reaction of secondary anilines and simple alkenes such as styrene under palladium catalysis.[69] The authors suggested that the reaction starts by an orthopalladation followed by olefin coordination and migratory insertion. β-Hydride elimination produces an α-alkenylenamine, which evolves into the product by means of a Pd-promoted cyclization, although other mechanisms cannot be ruled out (Scheme 42). Similar reactivity was found using simple phenols as starting materials.[70] A related annulation from dialkylanilines involving an initial alkenylation followed by insertion of CO has recently been described by Lei and co-workers.[71]

Another example of these formal annulations that involves a coupling reaction followed by cyclization has been reported by Miura et al. The reaction consists of the formal (4+1) annulation between 2-benzoic acids and alkenes (Scheme 43).[72] 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, nucleophilic cyclization leads to the final product. Many other examples of this type of transformation have since been developed.[6]

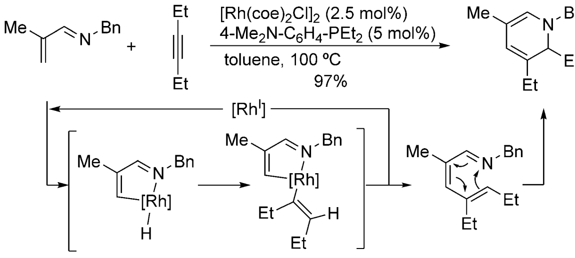


Scheme 43. Formal annulation between benzoic acid and an activated alkene.

The Ellman and Bergman research 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 authors found that the reaction benefits from the use of an electron-donating phosphine ligand. The proposed mechanism starts with a Rh-



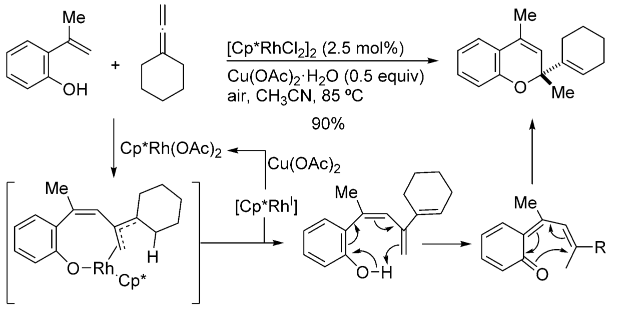
Scheme 42. Pd^{II}-catalyzed synthesis of an indole from a simple aniline.



Scheme 44. Synthesis of a dihydropyridine from an imine and an alkyne. coe = cyclooctene.

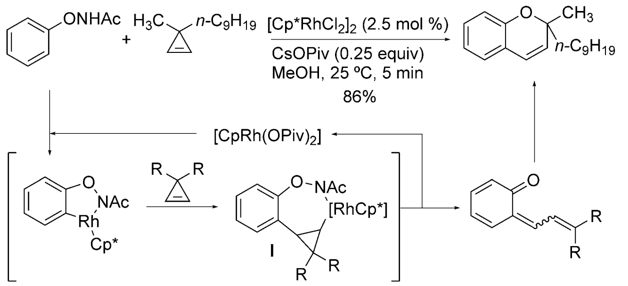
catalyzed β-C−H bond activation of α,β-unsaturated imines followed by addition across the alkyne to give azatriene intermediates, which undergo an in situ electrocyclization to afford 1,2-dihydropyridines.

Another example which involves an electrocyclic process was described by Mascareñas, Gulías, and co-workers, and consists of a formal (5+1) annulation of 2-alkenylphenols and allenes to give 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 into a triene intermediate, which rapidly undergoes a [1,7]-H sigmatropic shift. The resulting dearomatized tetraenone evolves by means of a 6π-electrocyclic reaction into the observed chromene.



Scheme 45. Synthesis of a chromene from a 2-alkenylphenol and an allene.

There have been some reports demonstrating the viability of using annulation precursors that contribute three atoms to the final cycle. For example, Wang and co-workers reported a Rh^{III}-catalyzed synthesis of 2*H*-chromenes from *N*-phenoxyacetamides and cyclopropenes.[75a] The reaction takes place under mild conditions in only five minutes and, because of the presence of the aminooxy group, does not need external oxidants (Scheme 46).[75a] Recent computational DFT studies on the mechanism of this reaction suggest that after a typical C−H activation/cleavage step and migratory insertion of the cyclopropene to give rhodacycle **I,** this seven-membered rhodacycle might evolve by an alternative pathway involving the formation of alkenylcyclohexa-2,4-dienone intermediates, which reorganize to the observed chromene products through an electrocyclic cyclization (Scheme 46).[75b,c]



Scheme 46. Synthesis of an isochromene through a formal (3+3) annulation.

7. Summary and Outlook

The enormous constructive potential of annulation reactions calls for a continuous innovation in cycloaddition tactics and methods. Whereas metal-catalyzed formal cycloadditions of unsaturated partners have demonstrated enormous potential to make cyclic systems from otherwise unreactive acyclic precursors, recent years have witnessed exponential progress in the development of catalytic annulations involving the formal activation and cleavage of “inert” C−H bonds. The field can still be considered to be in its infancy and, therefore, many more transformations that allow atom-economical transformations of readily available precursors remain to be discovered. In addition to new studies that can shed further light on the mechanisms of these transformations, the coming years will also witness the development of asymmetric versions, which 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 reaction is also being increasingly explored.

Acknowledgements

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