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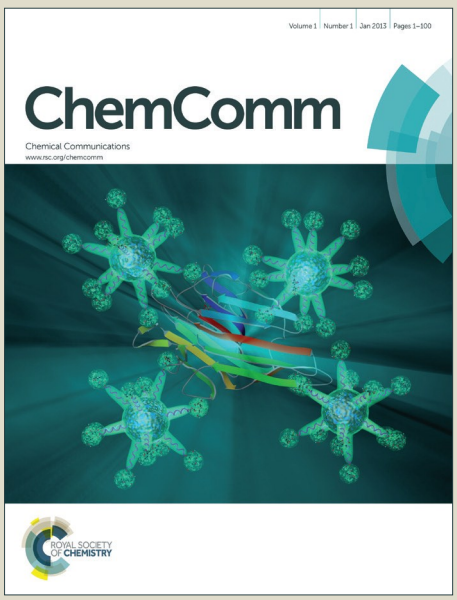

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FEATURE ARTICLE

Rhodium-Catalyzed Annulation of Arenes with Alkynes through Weakly Chelation-Assisted C–H Activation

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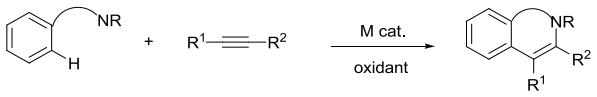
The purpose of this article is to give a brief review of weak chelation-assistance as a powerful means in the rhodium-catalyzed annulation of arenes with alkynes. The use of commonly occurring functional groups (e.g., ketones, aldehydes, carboxylic aicds and alcohols) as the directing groups enriches the versatility of auxiliary ligands and extends the scope of products. This short article offers an overview on emerging procedures, highlights their advantages and limitations, and covers the latest progress in the rapid synthesis of organic functional materials and natural products.

1. Introduction

The development of new strategies and synthetic methods for the construction of complex molecules from simple precursors with high efficiency is an important goal in modern organic chemistry. From the viewpoint of sustainable chemistry and economy, the newly exploited transformations should be lowly toxic, environmentally friendly, atom- and step-economic. Catalytic annulation of aromatic compounds with alkynes is able to fulfill these requirements and referred as one of the most powerful tools to afford diverse carbocycles and heterocycles. A continuous interest has been attracted in this field due to the significant importance of these compounds in pharmaceuticals, agrochemicals and materials. Significantly, recent progresses in transition metal-catalyzed direct C–H functionalizations further improve the efficiency and expediency of this tactics, in which C–H bond instead of C–X bond is used as the valid functional groups to obviate the preparation of preactivated substrates and eliminate the generation of stoichiometric amounts of salt wastes.[1] However, two common barriers are required to be circumvented in this elegant strategy, including disassociation of unactivated C–H bond and securement of high site-selectivity. For the former, a transition-metal complex is often introduced to facilitate the cleavage of C–H bond via either an electrophilic aromatic C–H metalation or concerted metalation-deprotonation (CMD) process. For the latter, a directing group (DG), which could bring the metal center in close proximity to a single C–H bond and enhance the effective concentration of catalyst, is generally installed on the given substrate to assist the selective functionalization of C–H bond. Notably, the DGs in catalytic annulation of arenes with alkynes enable themselves to participate in subsequent organometallic transformations as a nucleophile or electrophile and remain as an intrinsic part of the desired cyclic products, thus avoiding the extra steps for removal of an external directing group. Thus far, a number of DGs have been devised to ensure the site-selectivity and diverse product structures. In particular, nitrogen-based functional groups, such as 2-pyridinyl, 2-oxazolinyl, 1-pyrazolyl, and azo group, easily form well-defined stoichiometric cyclometalated complexes and deliver azacyclic products (Scheme 1).[2]



Scheme 1 Oxidative annulation of aromatic substrates with alkynes via nitrogen-based functional groups.

Aromatic compounds with oxygen-containing functional groups, including ketones, aldehydes, carboxylic acids and alcohols, are widespread and easily-available. Catalytic annulation directed by these synthetically useful functional groups would be an ideal approach to extend product scope and streamline accesses to a variety of appealing polycyclic compounds. Following metal-mediated C–H cleavage and alkyne insertion, these DGs next participate in the transformations as a nucleophile or electrophile to afford structurally diverse cyclic compounds. However, these oxygen-based DGs are typically weakly coordinating to transition metals and the resulting metallacycles are less thermodynamically stable, thus raising the handicap in C–H metalation process.[3]

In recent years, rhodium catalysis has been demonstrated as an efficient means for the catalytic annulation of aromatic C–H bonds with unsaturated substrates due to its high reactivity, wide substrate scope, mild conditions and good functional group tolerance.[1a,b] In particular, Cp*Rh(III) complex is

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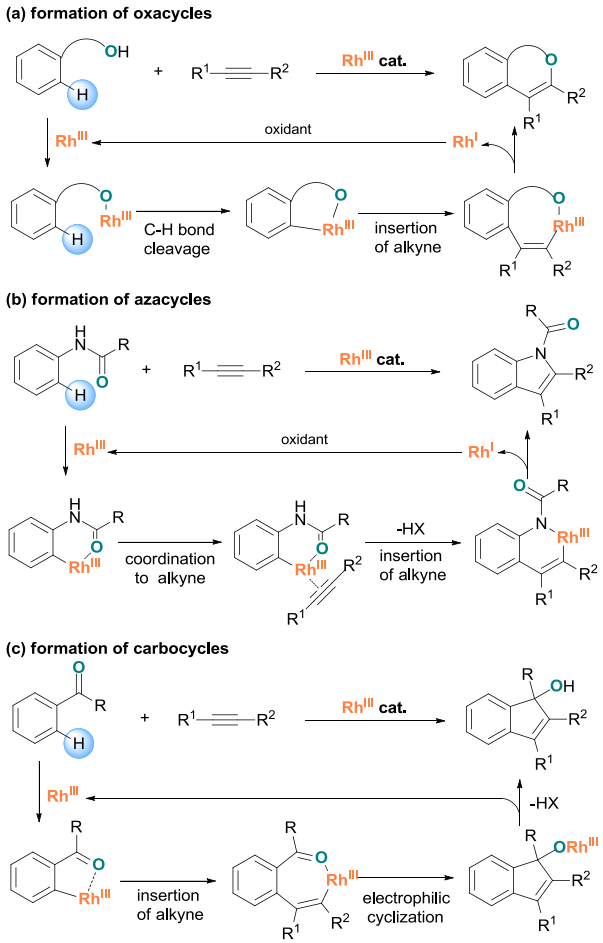
regarded as a preferential catalyst for this type of transformations, presumably because of the following reasons: (a) Rh(III) species serves as a π-acceptor to coordinate to unsaturated substrates, such as alkynes and alkenes, leading to the activation of carbon-carbon multiple bond; (b) As an electron-rich moiety, Cp* stabilizes the organorhodium intermediates by coordination to Rh center; (c) The large bulk of Cp* facilitates the reductive elimination of organorhodium(III) complex; and (d) The solely left coordination site in Cp*Rh(III)Ar complex is reserved for the coupling partner, and no additional ligand is thus required.[4] Although the choice of the Rh(III) catalyst varies from case to case, a neutral $[Cp^*RhCl_2]_2$ is typically used in transformations involved a CMD mechanism, whereas a cationic rhodium catalyst represented by $[Cp^*Rh(MeCN)_3][SbF_6]_2$ and $[Cp^*RhCl_2]_2/AgSbF_6$ is often employed for electrophilic C–H activation reactions.

Pioneered by Miura and Satoh,[5] many endeavours have been devoted to the rhodium-catalyzed C–H activation/annulation of aromatic compounds with alkynes.[6] In this process, diverse carbocycles and heterocycles are achieved with the assistance of a weakly coordinating directing group. Currently, the existing rhodium-catalyzed weakly chelation-assisted C–H activation/annulations involve three general patterns as follows: (a) Hydroxy oxygen-directed metalation forms a metallacycle, which then undergoes alkyne insertion and subsequent reductive elimination to afford an oxacycle product (Scheme 2a); (b) Anilide oxygen-directed C–H metalation, subsequent azacyclorhodation, and reductive elimination yield an azacycle (often indole derivatives) (Scheme 2b); and (c) Carbonyl oxygen-assisted metalation process gives an organometallic intermediate, which undergoes sequential alkyne insertion and electrophilic cyclization to yield a carbocycle (Scheme 2c). For the former two types of reactions, oxidants such as $Cu(OAc)_2$ and AgOAc are generally required for the reoxidation of the Rh(I) to Rh(III). Furthermore, the anions such as OAc^- associated with these oxidants enable to affect the C–H cleavage process as well. Diverse solvents, including DMF, *o*-xylene, *t*-BuOH, *t*-AmOH, 1,2-DCE and acetone, have been successfully used in these transformations. For the third type of reactions, although a formal oxidant is not required, a metal salt additive is still often added as either a Lewis acid to increase the electrophilicity of carbonyl moieties or a reagent facilitating the release of Rh center via transmetalation. Nonpolar and low-polar solvents are typically used in these reactions.

Although several reviews on the Rh(III)-catalyzed C–H functionalization have been published,[1a,b,4] the rapid expansion of this field still attracts us to update this fascinating chemistry. In this feature article, we would like to focus on the recent achievements of rhodium-catalyzed annulation of aromatic compounds with alkynes through weakly chelation-assisted C–H activation, which have not been solely discussed before. Applications of these methodologies in the synthesis of natural products and exploitation of novel fluorescent materials will also be involved. The versatility and limitations of these reactions will be categorized by the DGs. In general, the works cited in this article cover the period from 2012 until the end of April 2015 and literature introduced previously will only be provided as background information if necessary. It should be noted that some of these transformations have been achieved through the catalysis of ruthenium as well and the regioselectivities were even further improved with these methods.[3b,7,8]

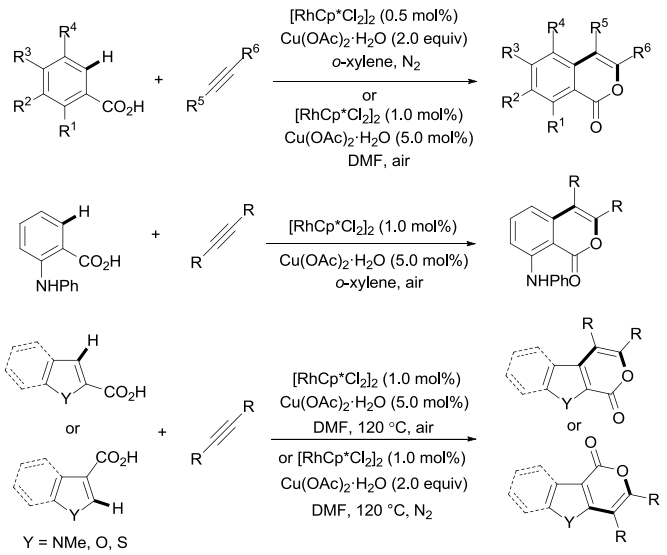


Scheme 2 Rhodium-catalyzed annulation of aromatic substrates with alkynes through weak chelation-assistance.

2. Rhodium-catalyzed annulation of arenes with alkynes through weak chelation-assistance

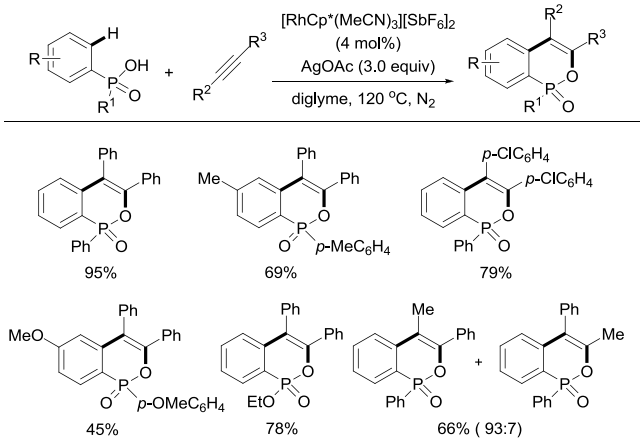
2.1 Carboxylic, phosphonic, phosphinic and sulfonic acids

Carboxylate oxygen can coordinate to the Rh(III) species and form a rhodacycle intermediate, which undergoes alkyne insertion and subsequent reductive elimination to give a lactone product. Based on this proposed mechanism, a broad scope of isocoumarins and their analogues have been constructed by rhodium-catalyzed oxidative annulation of aromatic carboxylic acids with alkynes (Scheme 3).[5,9] Recently, the substrates for this reaction are further extended to aromatic phosphonic, phosphinic and sulfonic acids, which deliver the corresponding phosphorous and sulphurous analogues, respectively.[10]



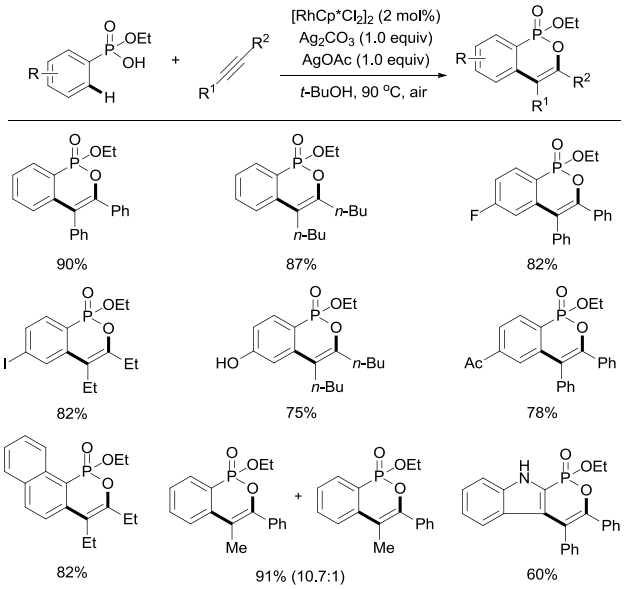
Scheme 3 Oxidative annulation of aromatic carboxylic acids with internal alkynes.

In the presence of $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (4 mol%) and AgOAc (3.0 equiv), diarylphosphinic acids and phenylphosphonic acid monoethyl ester cyclized with aromatic internal alkynes to afford phosphaisocoumarins in 45-95% yields (Scheme 4).[10a] Unsymmetrical 1-phenyl-1-propyne could also work under the standard conditions to provide the isomer with the phenyl substituent proximal to oxygen as the major product.

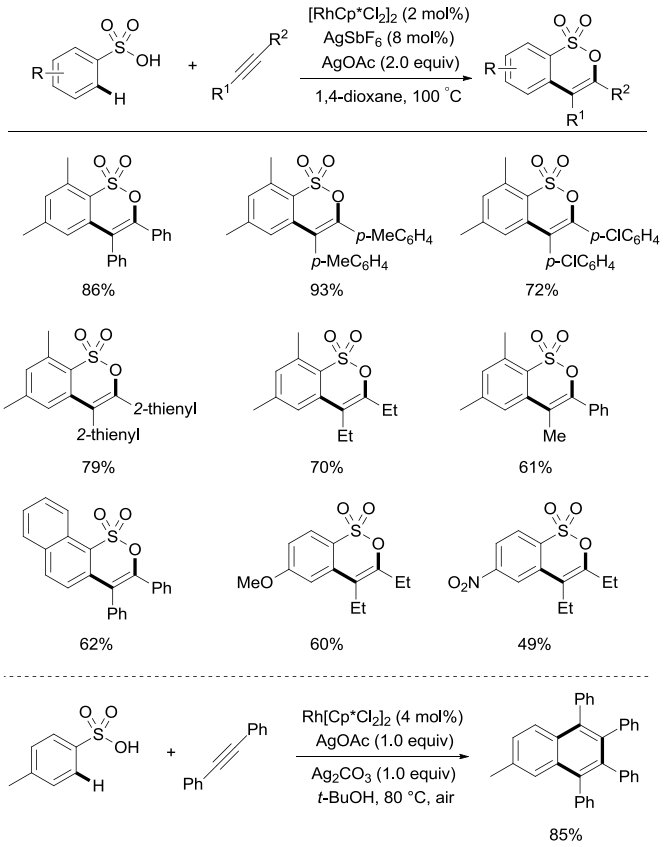


Scheme 4 Oxidative annulation of phenylphosphinic acids and phenylphosphonic acid monoethyl ester with alkynes.

Almost at the same time, the Lee group reported the synthesis of phosphaisocoumarins through rhodium-catalyzed cyclization of arylphosphonic acid monoesters with internal alkynes (Scheme 5).[10b] The reaction was found to be sensitive to the choice of oxidants. No desired product was detected when other oxidants were used instead, such as $AgSbF_5$, AgOTf and Ag_2O. A broad scope of functional groups could be tolerated under the standard conditions, including fluoro, iodo, acetyl and hydroxyl. Both aromatic alkynes and dialkylalkynes could be effectively converted to the desired products in good yields. Similar regioselectivities were observed in the case of arylalkyl alkynes as mentioned above.[10a] Competition experiments between alkynes showed that the reaction of diphenylacetylene was faster than that of dialkylalkyne (5-decyne), and the electron-rich diarylalkyne (*p*-methoxy) was more reactive than the electron-poor analogues (*p*-bromo). It is noteworthy that $[RuCl_2(p\text{-Cymene})]_2$ and $(PCy_3)_2HRu(CO)Cl$ did not provide phosphaisocoumarin, implying the superiority of rhodium catalysis in this type of annulation.



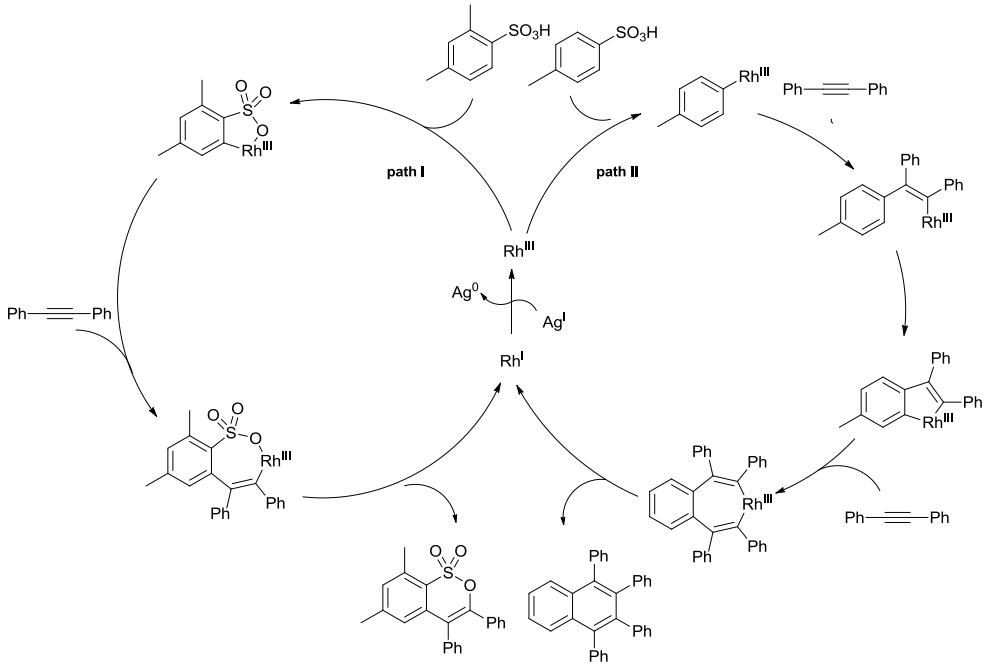
Scheme 5 Oxidative annulation of arylphosphonic acid monoesters with internal alkynes.



Scheme 6 Oxidative annulation of arylsulfonic acids with alkynes.

Sulfonic acids enable to direct the aromatic C–H activation. By employing aromatic sulfonic acids and internal alkynes as the coupling precursors, Li and co-workers successfully synthesized sultones through the catalysis of Rh(III) (Scheme 6).[10c] $AgSbF_6$ was essential in this reaction, which could sequester the chloride anion and generate a cationic rhodium species. However, an *ortho* blocking group on the *para*-substituted arylsulfonic acids was generally required to ensure high selectivity when diarylalkynes were employed. Otherwise, a 1:2 arene/alkyne adduct was generated. In contrast, no such selectivity issue occurred when dialkylalkynes coupled with various arylsulfonic acids. These results indicated that C–H activation/diarylalkyne insertion of (both) *ortho* C–H bonds was faster than the subsequent steps and C–H activation/dialkylalkyne insertion was slower than or comparable to the subsequent steps. Interestingly, a naphthalene derivative could be formed instead of a sultone under slightly modified reaction conditions, in which the sulfonic acid underwent desulfonative metalation as an aryl source.

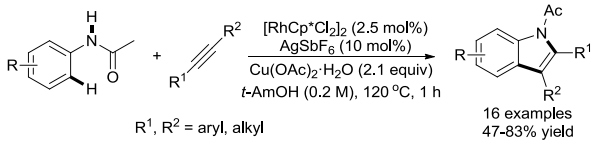
A mechanism that accounts for the different reaction pathway is proposed in Scheme 7. Coordination of the sulfonate oxygen to the rhodium species followed by C–H metalation affords a five-membered rhodacycle. Subsequent insertion of alkynes and C–O reductive elimination gives the sultone product. The released Rh(I) species is then reoxidized to Rh(III) with a silver salt to complete the catalytic cycle (Path I). Alternatively, desulfonation occurs to deliver a arylrhodium(III) species, which subsequently undergoes double alkyne insertions and reductive elimination to afford the naphthalene product (Path II).



Scheme 7 Proposed mechanism for the oxidative annulation of arylsulfonic acids with alkynes.

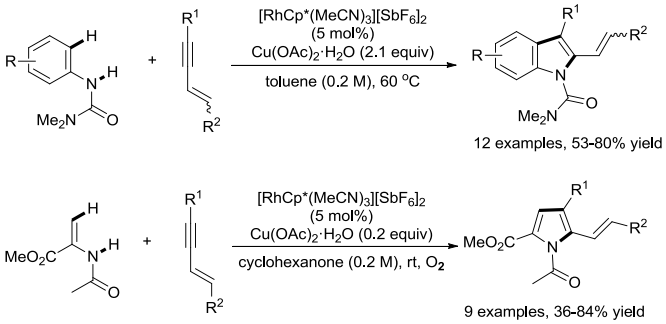
2.2 Anilides

In 2008, Fagnou reported that *N*-acetyl indoles could be synthesized by rhodium-catalyzed oxidative annulation of *N*-acetylanilines with internal alkynes, in which the acetyl oxygen directed the cyclometallation via cleavage of aromatic C–H bond (Scheme 8).[11]



Scheme 8 Oxidative annulation of of acetanilides with internal alkynes.

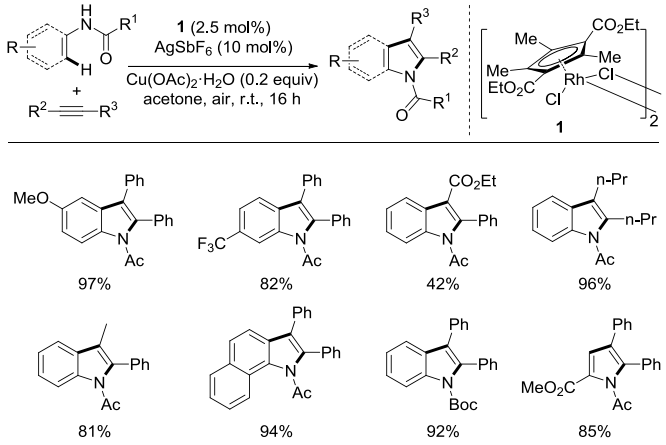
Subsequently, this chemistry is extended for the synthesis of unsymmetrical 2,3-aliphatic-substituted indoles.[12] In the presence of $[RhCp^*(MeCN)_3][SbF_6]_2$ and $Cu(OAc)_2{\cdot}H_2O$, *N*,*N*-dimethyl-*N*'-arylureas and 2-acetamidoacrylates could react with enynes to afford the corresponding 2-alkenylindoles and pyrroles with excellent regioselectivity and preserved *E*/*Z* configuration (Scheme 9). The corresponding unsymmetrical 2,3-aliphatic-substituted indoles and pyrroles could be obtained easily by further hydrogenation.



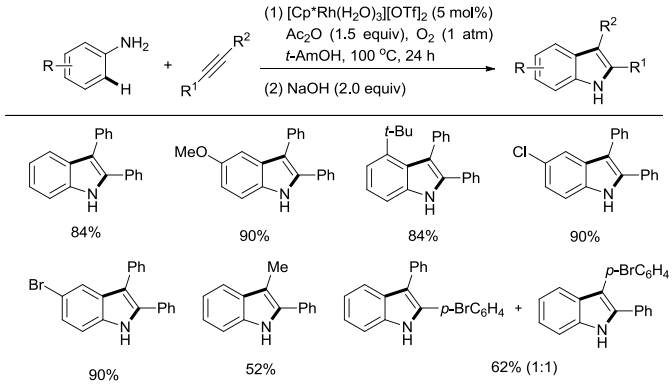
Scheme 9 Rhodium-catalyzed C–H activation/annulation of arylureas and acetamidoacrylates with internal enynes.

The steric and electronical characters of cyclopentadienyl ligands on $RhCp^*X_2$ could affect the selectivity and reactivity of

rhodium-catalyzed oxidative C–H functionalizations.[13] Tanaka and co-workers developed an electron-deficient η^5-cyclopentadienyl rhodium(III) catalyst **1** by reductive complexation of siylfulvenes with rhodium(III) chloride in ethanol and invested its reactivity in rhodium-catalyzed oxidative annulation of acetanilides and alkynes (Scheme 10).[14] This electron-deficient catalyst precursor was proved to be more active than the conventional $[RhCp^*Cl_2]_2$ for the directed C–H bond functionalization of electron-rich arenes. This new catalyst preferred the cleavage of C–H bonds in electron-rich substrates over electron-deficient substrates. For example, treatment of 4-fluoro and 4-methyl substituted *N*-acetyl anilines with diphenylacetylene in one-pot predominately afforded the product derived from electron-rich anilide. In addition, a preference for the migratory insertion across electron-rich alkyne over electron-deficient alkyne was found when complex **1** was used, whereas almost no selectivity was observed in the case of $[RhCp^*Cl_2]_2$.



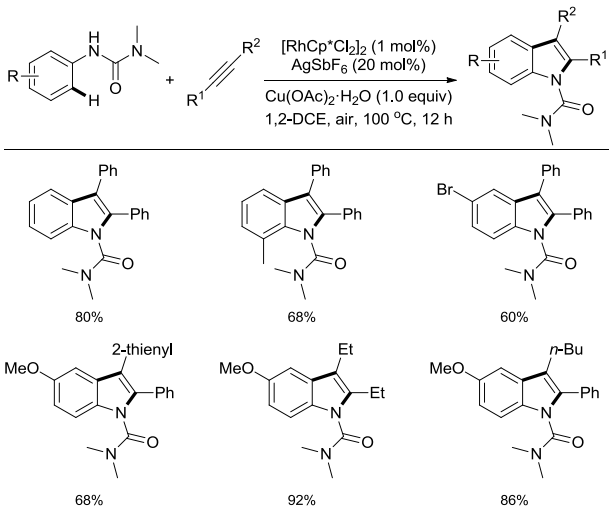
Scheme 10 Rhodium-catalyzed C–H activation/annulation of acetanilides with alkynes using dinuclear electron-deficient η^5-cyclopentadienyl rhodium(III) complex.



Scheme 11 Oxidative annulation of anilines with alkynes to synthesize indoles.

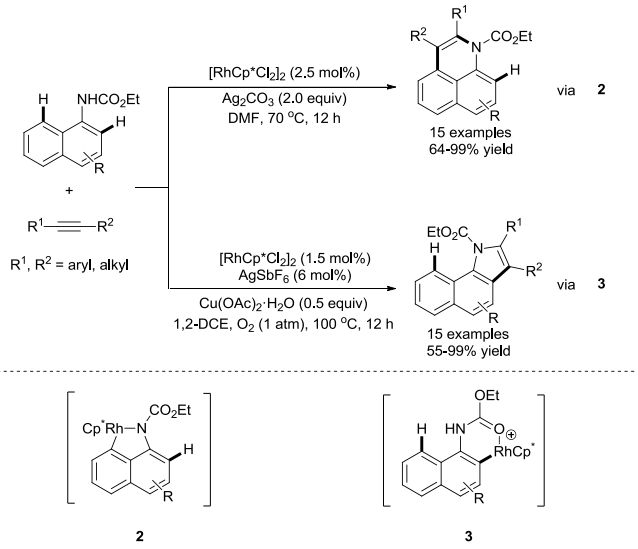
Using O_2 as the sole oxidant is very attractive in oxidative C–H functionalization because it allows the obviation of stoichiometric amounts of metal oxidants and generation of water as the only by-product. Huang and co-workers demonstrated that O_2 enabled oxidation of Rh(I) to Rh(III) species in the presence of acid.[15] In a follow-up work, the Huang group successfully developed a rhodium-catalyzed aerobic C–H activation/annulation for the synthesis of indoles from simple anilines and internal alkynes, in which O_2 was used as the sole oxidant (Scheme 11).[16] It was found that the reactivity of rhodium catalyst was highly affected by the nature of the counterion. $Cp^*Rh(H_2O)_3(OTf)_2$ was proved to be the optimal. Other rhodium species, including $Cp^*Rh(H_2O)(OAc)$, $Cp^*Rh(CH_3CN)_3(SbF_6)_2$, $[Cp^*RhCl_2]_2$, gave much lower yields.

Nicholls and co-workers illustrated urea as an efficient directing group in Rh-catalyzed aerobic synthesis of indoles through C–H activation (Scheme 12).[17] In the presence of $[RhCp^*Cl_2]_2$ (1 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1.0 equiv), indoles could be obtained in moderate to excellent yields in 1,2-dichloroethane (1,2-DCE) under air. Other solvents, such as *t*-AmOH, THF, DMF and toluene, exhibited much less efficiency in this reaction. It is noteworthy that unsymmetrical alkynes exclusively gave the indoles with alkyl group at the 3-position as subjected to the standard conditions, exhibiting an excellent regioselectivity. In addition, the *N*-carbamoyl moiety could be easily removed in the presence of a base, providing an expedient access to NH-free indole derivatives.



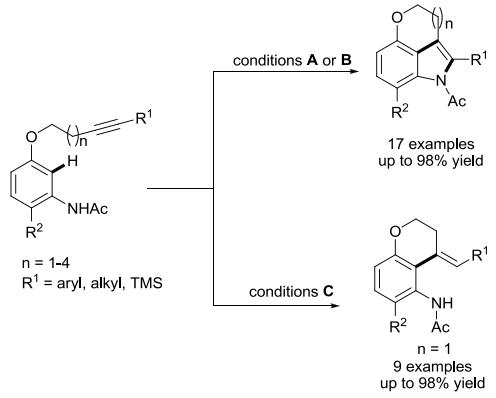
Scheme 12 Oxidative annulation of *N*-arylureas with alkynes for the synthesis of indoles.

By simply tuning the catalyst systems, Jin and co-workers realized the chemoselective construction of various fused π-conjugated polyheterocycles (Scheme 13).[18] In the case of neutral Rh(III) catalyst system, the rhodium preferentially coordinates to the nitrogen atom of carbamates, followed by cyclorhodation at the *peri* C–H bond to afford a five-membered azarhodacycle. Then this azarhodacycle sequentially undergoes migratory insertion of alkyne and reductive elimination to give the benzoquinoline product and the released Rh(I) complex is oxidized by Ag_2CO_3 to regenerate the active Rh(III) complex. In contrast, in the presence of $AgSbF_6$ and $Cu(OAc)_2$, the generated cationic Rh(III) complex coordinates to the carbamate oxygen prior to nitrogen, thus giving the benzoindole derivatives. The choice of solvent was crucial to this selective oxidative annulation. The cationic Rh(III) complex may exhibit a higher Lewis acidity in non-coordinative 1,2-dicholoroethane than DMF, thus favouring the coordination of Rh complex to the carbamate oxygen.



Scheme 13 Rhodium-catalyzed regioselective C–H activation/annulation of naphthylcarbamates with alkynes.

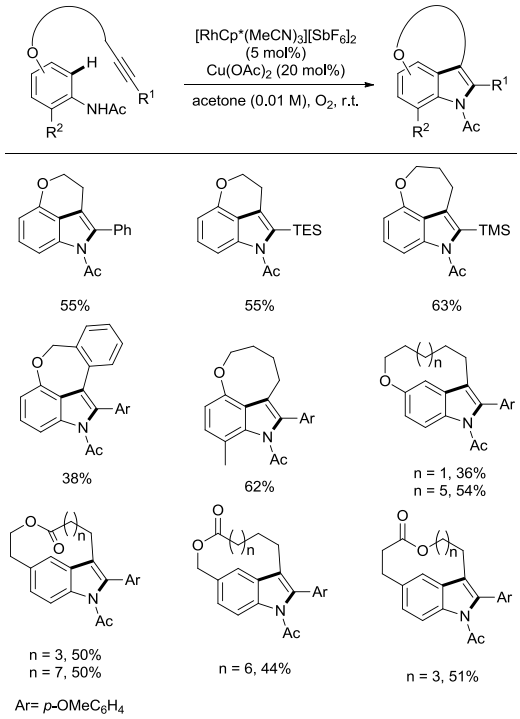
Xu and Liu described an intramolecular oxidative annulation for switchable synthesis of 3,4-fused tricyclic indoles and chromans (Scheme 14).[19] Under the conditions of $[Cp^*RhCl_2]_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), and *t*-AmOH (0.1 M) or $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), and CH_3CN (0.1 M), the intramolecular amidoarylation of alkynes generally gave tricyclic indoles as major products. On the other hand, the intramolecular hydroarylation of alkynes predominantly occurred to afford chromans in the presence of pivalic acid.



A: $[RhCp^*Cl_2]_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), *t*-AmOH, 120 °C
B: $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv), CH_3CN, 120 °C
C: $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH (1.0 equiv), *t*-AmOH , 120 °C

Scheme 14 Intramolecular C–H activation/annulation for the synthesis of 3,4-fused tricyclic indoles and chromans.

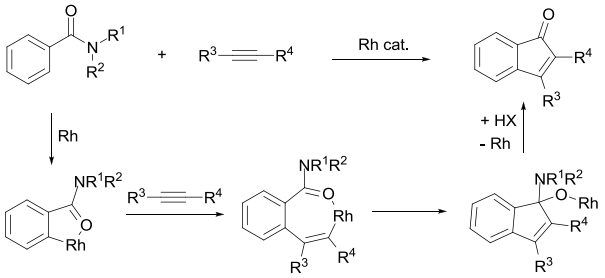
Almost at the same time, Jia reported the intramolecular synthesis of tricyclic indoles through a similar strategy (Scheme 15).[20] In the presence of $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (5 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), alkyne-tethered acetanilides could be smoothly converted to the corresponding tricyclic indoles at room temperature under an O_2 atmosphere. Both 3,4-fused indoles and 3,5-macrocycle indoles could be synthesized in moderate yields under the standard conditions. In addition, it is noteworthy that the trialkylsilyl substituted alkynes were also compatible with the conditions.



Scheme 15 Intramolecular oxidative annulation for the synthesis of fused tricyclic indoles.

2.3 Amides

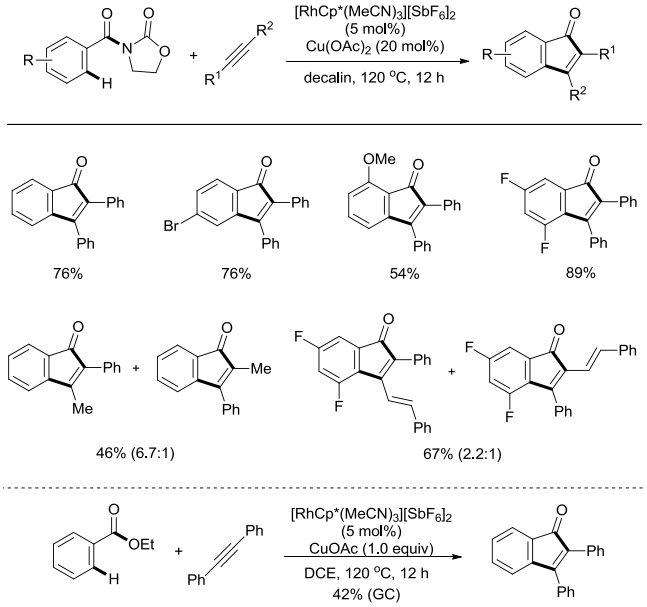
Typically, nitrogen atom of amides could coordinate to metal center to accomplish the chelation-assisted C–H activation. However, in the case of tertiary amide, oxygen of the C=O could serve as a coordinating atom instead. Furthermore, the electrophilicity of carbonyl group would allow the nucleophilic attack of a transiently formed Rh–C bond, followed by the elimination of the amino moiety to deliver a carbocycle product (often five-membered rings, Scheme 16). External oxidant is generally not requied in this kind of transofrmations. However, a Lewis acid is often added for the activation of the carbonyl moiety and/or alkynes by coodination.



Scheme 16 Rhodium-catalyzed annulation of benzamides with alkynes.

Shi and co-workers reported the rhodium/copper-catalyzed annulation of benzimides with internal alkynes to afford indenones after extensive investigation of directing groups (Scheme 17).[21] The use of oxazolidinone as a directing group

was crucial for this reaction. In the case of other amides such as NHMe, NMe_2, NMe(Ac), none or trace amount of products were obtained. Copper salt may coordinate to the imide moiety, thus increasing the electrophilicity of C=O group. And changing $Cu(OAc)_2$ to other Lewis acids, such as $Zn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_2$, was failed to promote this reaction, presumably because of OAc^- was essential for C–H cleavage. Nonpolar solvent was found to be more suitable than polar solvent for this reaction. Unfortunately, trimethylsilyl-substituted phenylacetylene did not work under the standard conditions. In addition, ethyl benzoate was also a viable candidate to give the corresponding indenones in moderate yield under a slightly modified condition.

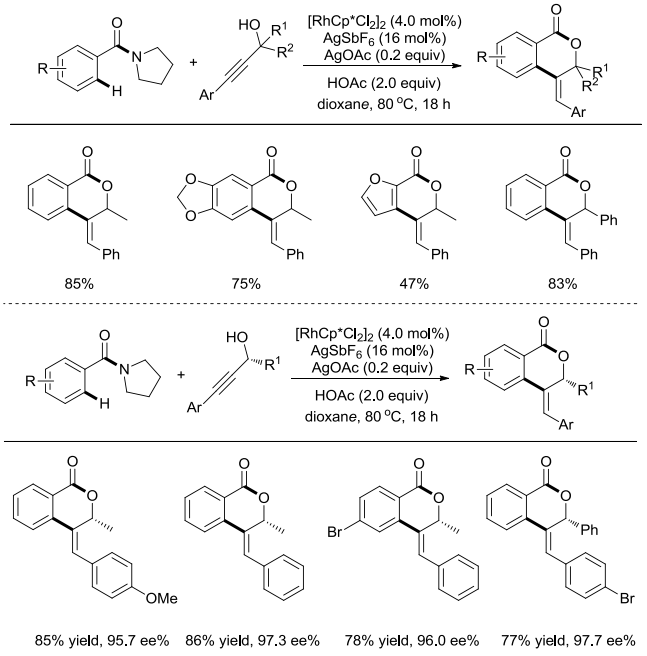


Scheme 17 Rhodium-catalyzed annulation of benzimides and benzoic ester with internal alkynes for the synthesis of indenones.

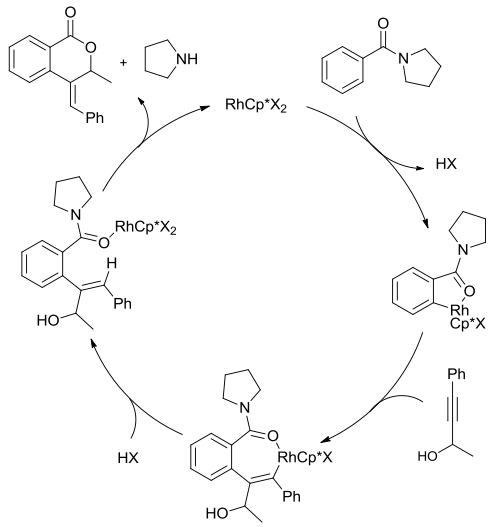
Subsequently, Li reported a Rh(III)-catalyzed coupling of benzamides with propargyl alcohols to afford (4-benzylidene)isochroman-1-one in high regioselectivity and *Z*-selectivity (Scheme 18).[22] It is noted that the synthesis of such lactones started from 2-iodobenzoic acid and allenes via Pd(0)-catalyzed C–I functionalization might lead to a mixture of *Z*/*E* isomers.[23] In addition, highly enantioenriched products were obtained when optically pure prapargyl alcohols were employed as the reaction precursors. Mechanism studies indicated that the cleavage of the aromatic C–H bond might be involved in the rate-limiting step. No desired product was obtained when a proposed ester intermediate 4-phenylbut-3-yn-2-yl benzoate was subjected to the standard conditions, thus indicating the hydroarylation should occur prior to the esterification.

A plausible mechanism for this annulation reaction is shown in Scheme 19. Initially, an amide oxygen directed C–H metalation process furnishes a five-membered cyclorhodium species. Following regioselective insertion of propargyl alcohol affords a seven-membered rhodacycle, which is subsequently converted to an alkenyl intermediate through protonolysis. Then, metal-catalyzed lactonization delivers the final product and releases a pyrrolidine simultaneously.

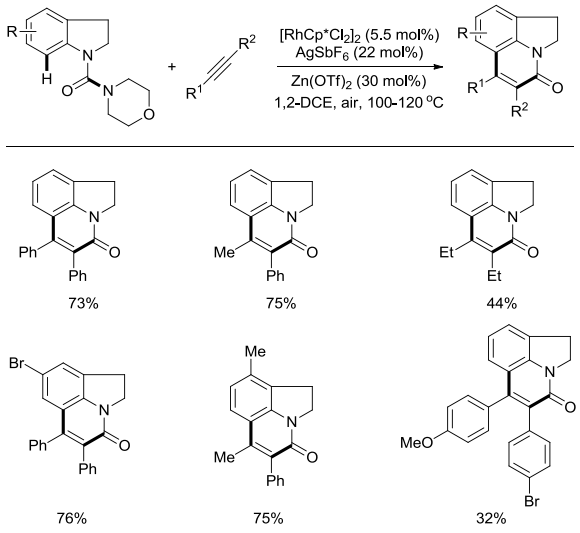
A Rh-catalyzed redox-neutral annulation of *N*-carbamoyl indolines with alkynes was reported to synthesize pyrroloquinolinones through an amide-directed C–H/C–N bond cleavage sequence by Loh and co-workers (Scheme 20).[24] Interestingly, despite only 32% yield, the reaction of electronically differentiated diaryl-substituted alkyne gave the corresponding product in a high regioselective manner. $Zn(OTf)_2$ in this reaction was deemed to activate the alkyne substrates by cooridnation as well as to increase the electrophilicity of the urea motif, which was similar to the role of copper in Shi's condition.[21] It is noted that a cationic rhodium complex $[RhCp^*(MeCN)_3](SbF_6)_2$ alone failed to catalyze this reaction.



Scheme 18 Rhodium-catalyzed annulation of benzamides with propargyl alcohols.

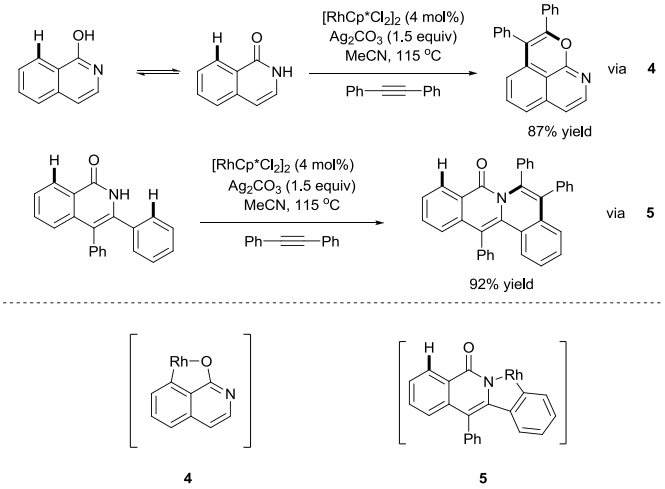


Scheme 19 Proposed mechanism for annulation of benzamides with propargyl alcohols



Scheme 20 Rhodium-catalyzed annulation of *N*−carbamoyl indolines with alkynes for the synthesis of pyrroloquinolinones.

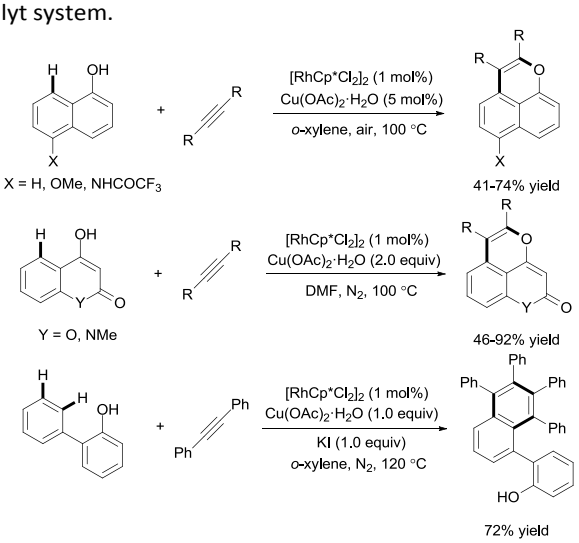
The oxidative coupling of 1-hydroxyisoquinoline with diphenyl acetylene could give a pyran derivative in 87% yield (Scheme 21).[25] In this transformation, the −OH of imidic acid, a tautomer of amide, was considered to play a key role in the formation of rhodacycle species. Interestingly, if two phenyl groups were preinstalled on the olefinic carbons, a six-membered azacyclic compound was formed instead, indicating the essential role of the phenyl moiety in the determination of the reaction pathway.



Scheme 21 Oxidative annulation of isoquinolones with alkynes.

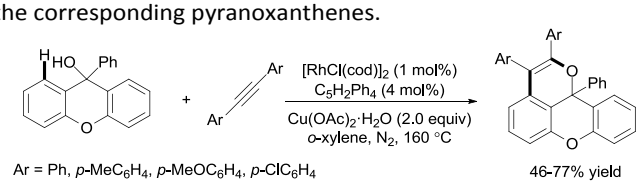
2.4 Hydroxyl

In 2010, Miura and Satoh reported the oxidative annulation of 1-naphthol with internal alkynes for the construction of naphtho[1,8-*bc*]pyran structures (Scheme 22).[26] The obtained tricyclic pyran derivatives exhibited solid-state fluorescence in a range of 410-560 nm. Especially, 2,3-diarylnaphtho[1,8-*bc*]pyran starting from 1-naphthol and 4-$MeOC_6H_4C{\equiv}CC_6H_4$-4-OMe showed a relatively stronger emission at wavelength of 484 nm than a typical emitter Coumarin 153. Furthermore, the reaction of 2-phenylphenol with diphenylacetylene gave rise to a coupled product in the ratio of 1:2 under the similar catalyt system.



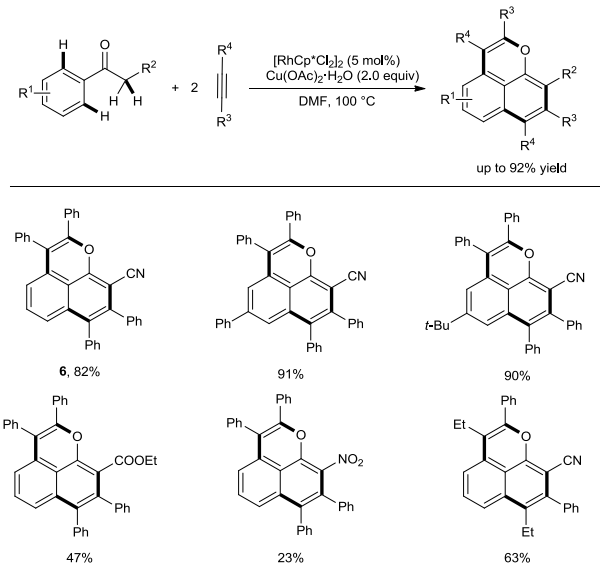
Scheme 22 Oxidaitve annulation of phenol, 1-naphthol and analogues with internal alkynes.

Tertiary alcohol could also undergo the oxidative coupling reaction with diarylacetylenes to form the corresponding annulated product (Scheme 23).[26] In the presence of $[RhCl(cod)]_2$ (1 mol%), $C_5H_2Ph_4$ (1,2,3,4-tetraphenyl-1,3-cyclopentadiene, 4 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (2 equiv), 9-phenylxanthen-9-ol could react with diarylacetylene to afford the corresponding pyranoxanthenes.



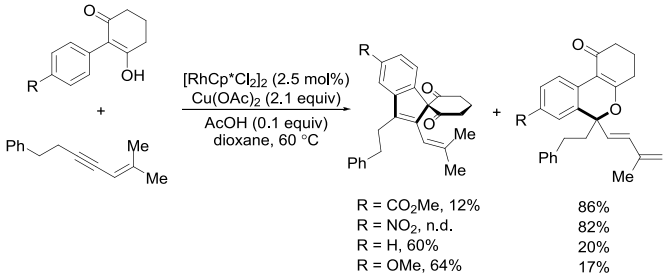
Scheme 23 Oxidaitve annulation of 9-phenylxanthen-9-ol with diarylacetylenes.

With benzoylacetonitriles and alkynes as the substrates, Wang and co-workers successfully synthesized substituted naphthol[1,8-*bc*]pyrans through a rhdoum-catalyzed cascade oxidative annulation (Scheme 24).[27] Polar aprotic solvents, such as DMF and CH_3CN, gave higher yields than other solvents in this reaction. Excellent regioselectivity was observed when arylalkyl alkynes were subjected to the standard conditions, giving single regioisomeric products in moderate to good yields. In spite of low to moderate yields, ethyl benzoylacetate and 2-nitro-1-phenylethanone could also work. The mechanism investigation revealed that 1-naphthols might be the intermediate products, which were accessed by annulation of $C(sp^2)$–H and $C(sp^3)$–H bonds with an alkyne. The subsequent reaction with another alkyne afforded the 1:2 arene/alkyne adduct by cleavage of $C(sp^2)$–H/O–H bonds. Most of these naphthol[1,8-*bc*]pyran derivatives showed solid-state fluorescence in a range of 490-580 nm. In particular, compound **6** exhibited a luminescence at λ_{em} = 535 nm of which intensity was almost four-fold stronger than that of tris(8-quinolinolato)aluminum (Alq_3).

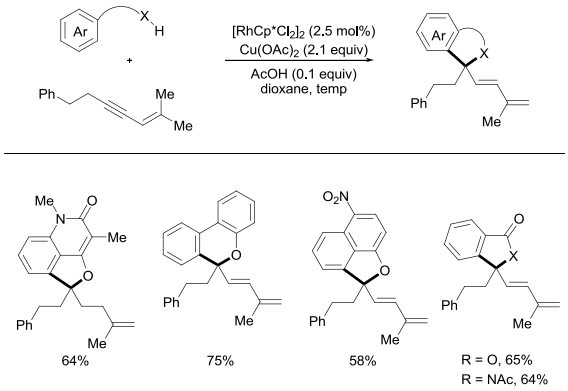


Scheme 24 Oxidative annulation of acetophenone derivatives with alkynes.

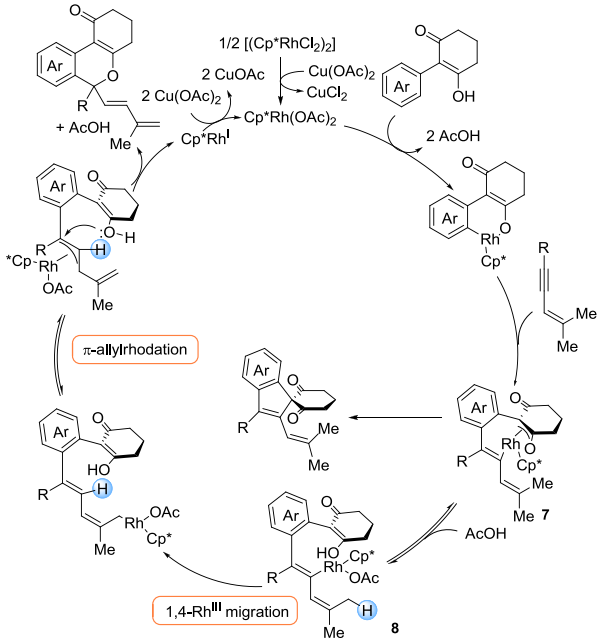
The oxidative annulation of 2-aryl cyclic 1,3-dicarbonyl compounds with 1,3-enynes was achieved by Lam (Scheme 25).[28] In the presence of $[RhCp^*Cl_2]_2$ (2.5 mol%) and $Cu(OAc)_2$ (2.1 equiv), the reaction of 2-aryl 3-hydroxy-2-cyclohexenones with 1,3-enynes gave a mixture of spiroindenes and benzopyrans in dioxane at 60 °C. This reaction was highly sensetive to the electronic nature of the aryl moiety of 1,3-dicarbonyl compounds. With the substrates containing electron-withdrawing substituent at the 4-position of the aromatic ring, the benzopyrans was the major products. In contrast, the substrates with phenyl or 4-methoxyphenyl groups would predominantly result in the spiroindenes. In addition to 2-aryl 3-hydroxy-2-cyclohexenones, other aromatic substrates containing enol, phenol, carboxylic acid or imide directing group also underwent oxidative annulation with 1,3-enyne to give oxa-and aza-heterocycles (Scheme 26).



Scheme 25 Oxidative annulation of 2-aryl cyclic 1,3-dicarbonyl compounds with 1,3-enynes.



Scheme 26 Oxidative annulation of aromatic substrates with 1,3-enynes.



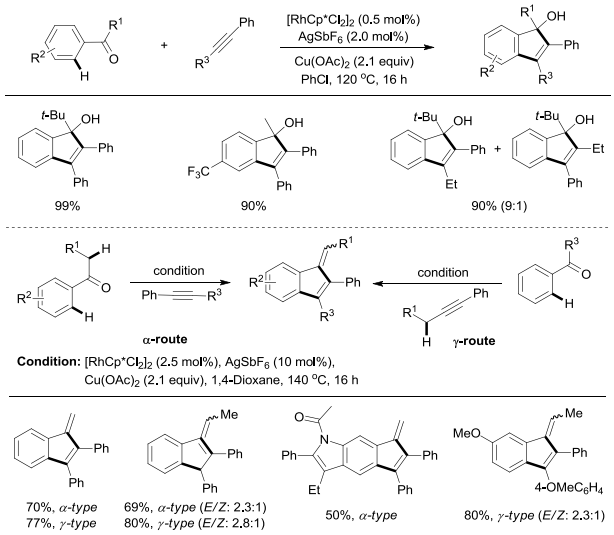
Scheme 27 Proposed catalytic cycle for the annulation of 2-aryl cyclic 1,3-dicarbonyl compounds with 1,3- enynes.

A plausible mechanism for this oxidative annulation is shown in Scheme 27. Directed by the enol oxygen, cyclorhodation and sequential insertion of 1,3-enyne result in a rhodacycle complex **7**. In the case of substrate with the electron-neutral or -rich aromatic ring, a spiroindene product is obtained. When the substrate contains the electron-poor aromatic ring, protonolysis with HOAc generates an alkenylrhodium species **8** due to the increased barrier for the following reductive elimination, thus affording benzopyrans as major product through sequential 1,4-migration of rhodium(III), π-allylrhodation and nucleophilic substitution.

2.5 Aldehydes and Ketones

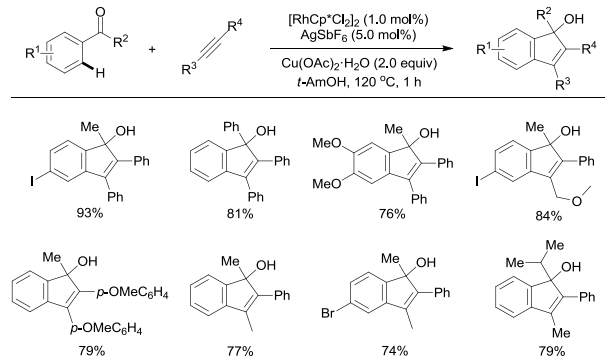
Aldehydes and ketones are rarely used as the directing groups due to their weak coordination ability. Examples of catalytic annulation of aromatic aldehydes and ketones with alkynes involving C–H activation directed by these groups are still underrepresented. In 2011, Glorious described the Rh(III)-

catalyzed coupling of aryl ketones with internal alkynes to afford indenol and fulvene derivatives.[29] In the case of ketones lacking a hydrogen atom at α-site, indenol products would be generated under the catalytic system comprising $[RhCp^*Cl_2]_2$ (0.5 mol%), $AgSbF_5$ (2 mol%) and $Cu(OAc)_2$ (2.1 equiv). Interestingly, 2-methyl-1-phenylpropan-1-one and electron-withdrawing phenones even bearing proton at potentially dehydrative position also gave the corresponding indenols rather than fulvenes. On another hand, electron-neutral and -rich phenones having α-proton and internal alkynes having γ-proton generally delivered the corresponding fulvenes in moderate to good yields. Stoichiometric amounts of $Cu(OAc)_2$ were essential for this reaction. Copper salt seemed to play a role in the release of Rh catalyst in the transmetalation process rather than as an oxidant (Scheme 28).



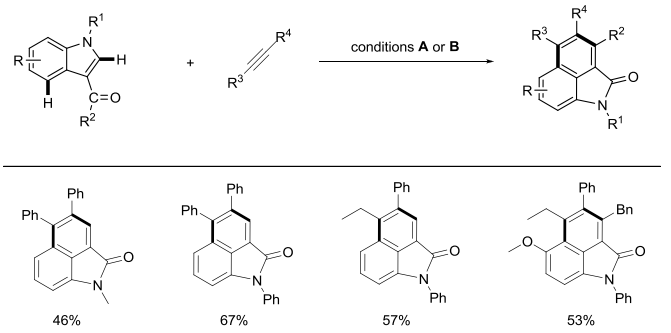
Scheme 28 Rhodium-catalyzed annulation of aryl ketones with internal alkynes for the synthesis of indenols and fulvenes.

Almost simultaneously, Cheng and co-workers independently reported the synthesis of indenols by carbocyclization of aryl ketones with alkynes.[30] Under similar conditions, aryl ketones reacted with alkynes to give indenols exclusively. However, different from Glorious's work,[29] the authors claimed that one important role of copper acetate in this reaction was used for the oxidation of Rh(I) species, which might originate from reduction of Rh(III) by solvent or substrate, to regenerate the active Rh(III) species (Scheme 29).



Scheme 29 Rhodium-catalyzed annulation of aryl ketones with internal alkynes for the synthesis of indenols.

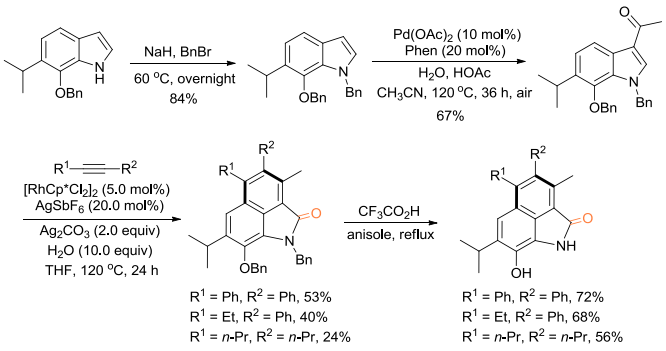
In 2014, You's group described an unexpected rhodium-catalyzed regioselective C–H bond activation/cyclization of easily available indolyl-3-aldehydes or ketones with alkynes to afford benzo-fused oxindoles (Scheme 30).[31] ^{18}O-labelling experiments demonstrated that the oxygen of carbonyl group in the product originated from the starting material and/or water. Thus, the addition of appropriate amounts of water would favor this reaction. Furthermore, starting from 7-benzyloxy-6-isopropylindole, a four-step synthesis involving this rhodium-catalyzed reaction as the key step was achieved to synthesize priolines, a class of alkaloid isolated from the roots of *Salvia prionitis* (Scheme 31).[32]



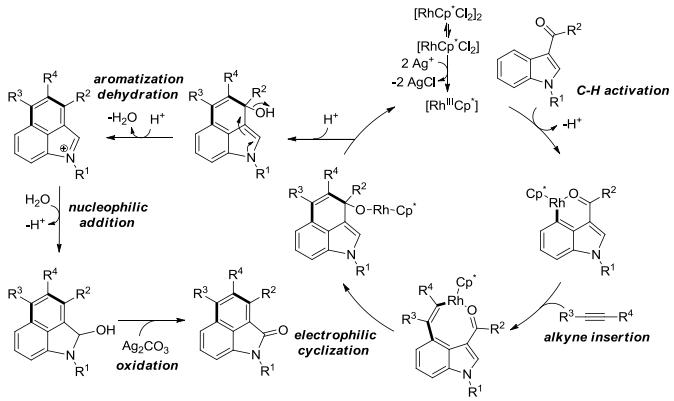
A: $[RhCp^*Cl_2]_2$ (3.5 mol%), $AgSbF_6$ (14.0 mol%), Ag_2CO_3 (1.2 equiv), THF, 120 °C, 24 h.
B: $[RhCp^*Cl_2]_2$ (5.0 mol%), $AgSbF_6$ (20.0 mol%), Ag_2CO_3 (2.0 equiv), H_2O (10.0 equiv), THF, 120 °C, 24 h.

Scheme 30 Rh(III)-catalyzed annulation of indolyl-3-aldehydes and ketones with alkynes.

A plausible mechanism is shown in Scheme 32. Coordination of the carbonyl oxygen atom to an electrophilic [Rh(III)Cp*] species gives a six-membered rhodacycle via selective cleavage of the C4−H. Then, alkyne insertion and electrophilic cyclization afford a rhodium alkoxide intermediate. Through sequential protonolysis and aromatization dehydration, an iminium intermediate is generated, which then might undergo nucleophilic addition with H_2O and oxidation to form a benzo-fused oxindole.

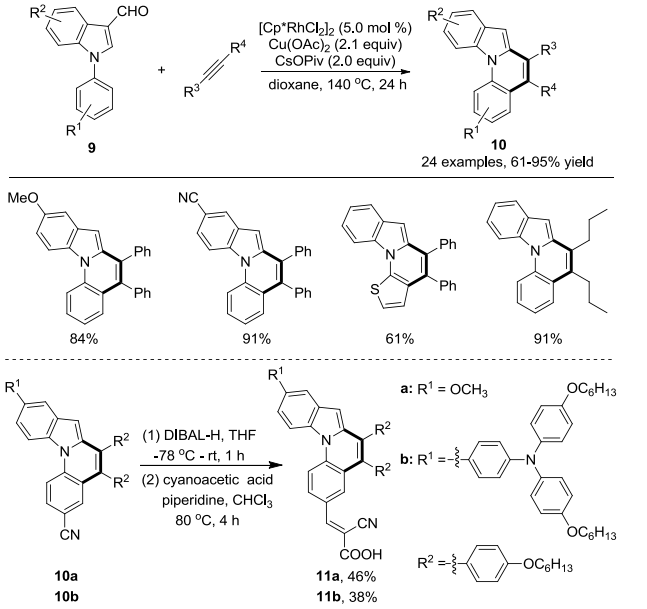


Scheme 31 Construction of the benzo-fused oxindole scaffolds in the synthesis of priolines.



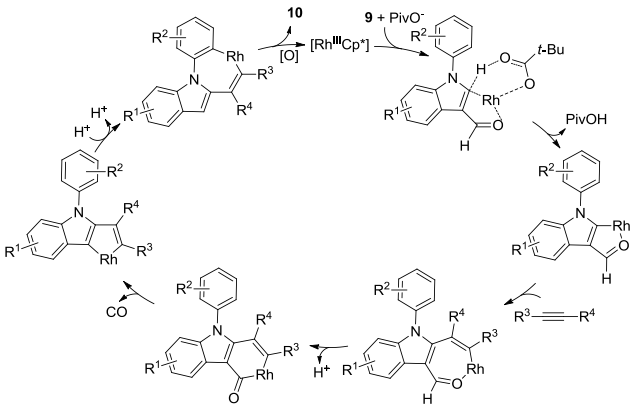
Scheme 32 Proposed catalytic cycle for the annulation of indolyl-3-aldehydes or ketones with internal alkynes.

Interestingly, when cesium pivalate was used as an additive, indolo[1,2-*a*]-quinolines was obtained instead of benzo-fused oxindoles (Scheme 33).[33] Under slightly modified conditions comprising $[RhCp^*Cl_2]_2$ (5.0 mol%), $Cu(OAc)_2$ (2.1 equiv), and CsOPiv (2.0 equiv), indolyl aldehydes with both electron-withdrawing and electon-donating groups reacted with internal alkynes to give the corresponding indolo[1,2-*a*]-quinolines in good to excellent yields. Under simulated AM 1.5G irradiation, compounds **11a**- and **11b**-based dye-sensitized solar cells (DSSCs) exhibited moderate photo-to-current conversion efficiencies (For 5a, η = 4.6%, J_{sc} = 9.51 mA cm^{-2}, V_{oc} = 0.717 V, *FF* = 0.676; for 5b, η = 5.8%, J_{sc} = 11.64 mA cm^{-2}, V_{oc} = 0.765 V, *FF* = 0.650), suggesting indolo[1,2-*a*]quinolines may be promising candidates for applications in DSSCs.

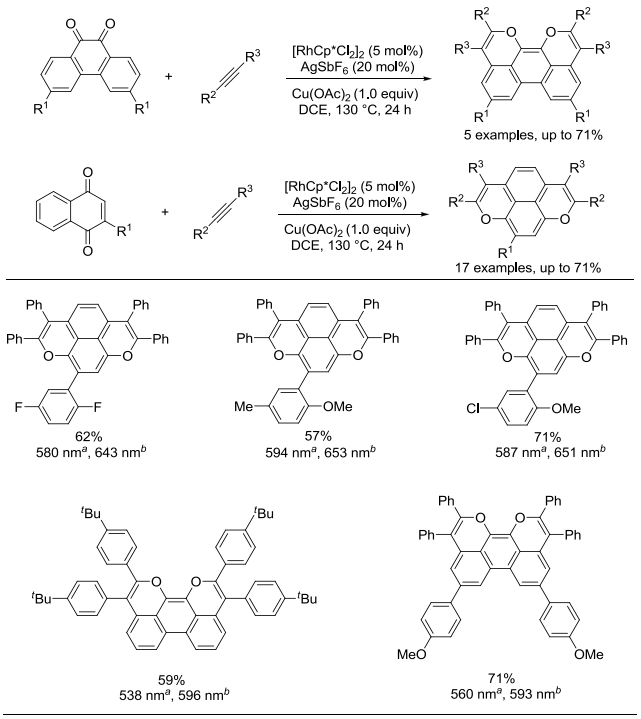


Scheme 33 Oxidative annulation of indolyl aldehydes with alkynes for the synthesis of indolo[1,2-*a*]-quinolines.

The primaryl kinetic isotopic effect experiment (KIE = 1.13) indicated that the C2−H bond cleavage of indole might not be involved in the rate-determining step. In a plausible catalytic cycle, coordination of the carbonyl oxygen atom to Rh(III) and subsequent pivalate-assisted C2−H activation deliveres a five-membered rhodacycle, which sequentially undergoes migratory insertion of alkyne, decarbonylation, protonolysis, recyclorhodation with the phenyl ring and reductive elimination to afford the final product (Scheme 34). CsOPiv is proposed to facilate the cleavage of C2-H instead of C4-H via a six-membered transition state, thus leading to a distinct regioselectivity from the aformentioned transformation.[31]



Scheme 34 Proposed catalytic cycle for the oxidative annulation of indolyl aldehydes with alkynes.



[a] Emission maximum in CH_2Cl_2 (5.0×10^{-5} M). [b] Emission maximum in solid state.

Scheme 35 Oxidative annulation of 1,4-naphthoquinones and 9,10-penanthraquinones with alkynes.

Recently, using 1,4-naphthoquinones and 9,10-penanthraquinones as the substrates, 1,8-dioxapyrenes and 1,12-dioxaperylenes were successfully achieved through Rh-catalyzed oxidative cyclization (Scheme 35).[34] Most of these synthesized compounds exhibited large Stoke shifts, high thermal stability and orange/red-emitting performance, which

might originate from good planarity and strong intermolecular π-π stacking of the dioxapyrene cores.

3. Conclusions

In conclusion, rhodium-catalyzed chelation-assisted annulation of aromatic compounds with internal alkynes has become a promising and expedient tool to construct cyclic compounds. The convetional "weakly coordinating directing groups", including ketones, aldehydes, and carboxylic acids, have been demonstrated as viable directing groups for the C–H activation/annulation to afford a variety of carbocycles and heterocycles. Notably, this strategy greatly streamlines accesses to a variety of π-extended (hetero)aromatic compounds appealing in optoelectronic, fluorescent materials and natural products. In addition, in most cases, the directing groups are completely merged into the newly generated products, which obviates troublesome extra steps for removal of an external directing group. Thus it is also highly atom- and step-economic.

As for transtition metal catalysts, Cp*Rh complex is the most widely used and powerful catalyst for chelation-assisted annulation of aromatic compounds with internal alkynes. The rhodium catalysis features broad substrate scope, excellent regioselectivity, relatively mild reaction conditions and good functional group tolerance and sometimes exhibits much higher reactivity than the corresponding iridium and ruthenium analougues.

Despite great progress, this type of transformations are limited to C(sp^2)–H bond activation. Extension of the chemistry to the cleavage of inert C(sp^3)–H bonds should be next pursued. On the other hand, catalytic annulation with terminal alkynes, unsymmetrical diaryl and dialkyl alkynes in a highly regioselective manner remains another formidable challenge to be resolved.

Acknowledgements

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Notes and references

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