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Multiple annulations of inert C(sp^2)–H bonds with alkynes

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Transition-metal catalyzed directing group (DG) assisted annulation of inert C–H bonds leads to the formation of complex molecular frameworks from readily accessible substrates. Thus, multiple annulation of less functionalized substrates with unsaturated species leads to the construction of structurally diverse fused poly(hetero)cycles. The directed inert C(arene)–H bond activation and the mode of TM-migration in this process could enabled obatining L-type [involves DG heteroatom, *o*-C(arene)–H bond, and C(arene)–H bond of aryl-motif in alkyne], Y-type [involves two heteroatoms of the DG and *o*-,*o*′-C(arene)–H bonds], and B-type [involves *o*-C(arene)–H bond and *m*-C(arene)–H bond] π-extended annulation products. The coordination preference of the DG heteroatom makes the transformation chemo- and regio-selective. This article underlines the conceptual development of unsymmetrical multiple annulation of arene C(sp^2)–H bonds with alkynes, which is exceedingly appealing and highly important.

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1. Introduction

The development of efficient synthetic methods continuously helps society in many ways. In this regard, the pioneering discovery of transition-metal (TM) catalyzed directing group (DG) assisted annulation of (hetero)arenes C–H bonds, which are ubiquitous, is certainly invaluable. The C–H annulation process is atom- and step-efficient, offering a reliable platform for the rapid construction of complex molecular entities.[1] Mostly, diverse arrays of materials as well as biologically important unnatural π-conjugated fused-(hetero)cycles that are inaccessible by conventional methods, are now being constructed using a C–H annulation strategy (Fig. 1).[2] Hence, recent years have witnessed an increase in the discovery of new catalytic C–H annulation methods.[3]

For decades, significant work has gone into addressing C–H annulation regio- and stereo-selectivity issues, and reaction proficiency. Task-specific ligands, flow systems, mechano reactors, and electrochemistry modules have subsequently been

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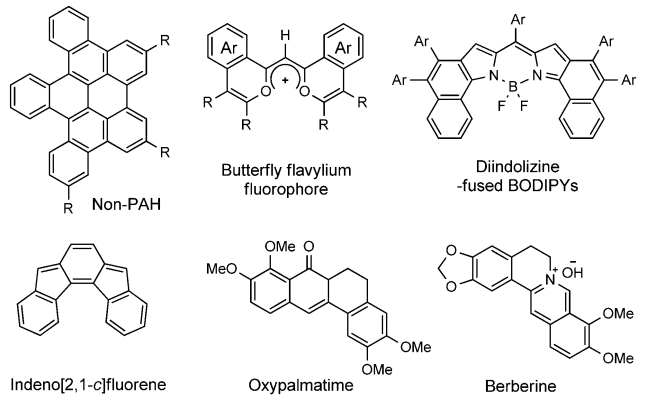

Fig. 1 Representative example of polycyclic hetero(arenes).

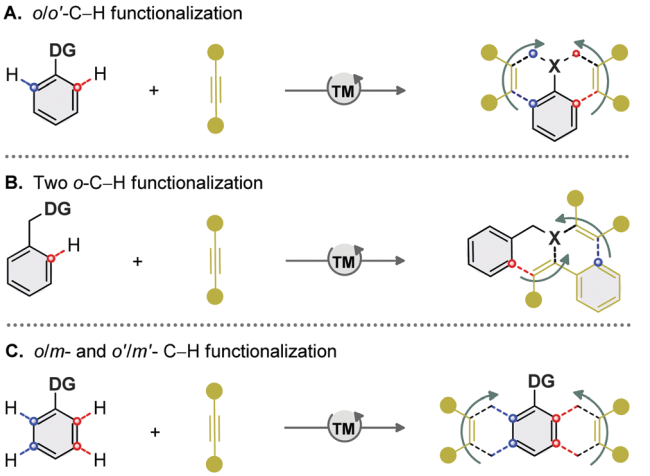

Fig. 2 Symmetrical and unsymmetrical C–H functionalization of arenes.

used that have largely benefitted C–H functionalizations.[4] Importantly, the DGs assisted in regulating the C–H annulation efficiency. Thus, π-electron-rich or heteroatoms (such as: S/N/O) involving DG promoted annulation of unactivated C(arene)–H bonds have been systematically realized and developed.[5,6] Although mono-C–H annulation processes have been widely studied, multiple annulation methods have been poorly examined.

Of note, unsymmetrical multiple annulations are challenging due to the undisputable concerns like: (i) single catalytic conditions have inferior reactivity, (ii) single DG strategies are often incapable; rather they are confined in producing mono-annulated products, (iii) chemo- and regio-selectivity issues due to the introduction of more than one directing group, (iv) the change in the stereo-electronic environment after first annulation hampers the subsequent C–H activations resulting in an unproductive process.[7] Thus, one-pot unsymmetrical multiple C–H annulations have been largely difficult and excedingly challenging.[7c,d] Of note, heteroatom directed unsymmetrical multiple C–H annulations have been recently examined.[6–8] In this regard, *o*,*o*′-C(arene)–H bonds (Fig. 2A), two *o*-C(arene)–H bonds (one from the substrate and the other from the coupling partner; Fig. 2B) and *o*,*m*- and *o*′,*m*′-C(arene)–H bonds (Fig. 2C) consecutively participate resulting in unusual π-extended complex molecules; the overall multiple annulation process is depicted in Fig. 2.

As shown in Fig. 3, the DG heteroatom coordination to the TM catalyst and the first *o*-C(arene)–H bond activation ($F_{C-H}A$) in close proximity to DG followed by insertion of unsaturated species lead to a monoannulation product (**Int-I**). Next, a second C(arene)–H bond activation ($S_{C-H}A$) of the aryl-motif in alkyne species involved in the first annulation and then annulation with alkynes yields an unsymmetrical L-type double annulation product (Path-A, Fig. 3). However, complexation of a second heteroatom in the DG of **Int-II** to the TM and second *o*′-C(arene)–H bond activation ($S_{C-H}A$) and annulation with alkyne

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Akhila K. Sahoo

Professor Akhila K. Sahoo worked with Prof. Ganesh Pandey at the National Chemical Laboratory, Pune and received a PhD. He also worked as a postdoc researcher with Prof. Hans-Joachim Gais, RWTH-Aachen, Germany; Prof. Tamejiro Hiyama, Kyoto University (JSPS); Prof. Atsuhiro Osuka, Kyoto University. His group works on metal-catalyzed C–H activation, Au-catalyzed synthetic methods, cyclization-cycloisomerization of ynamides, and difunctionalization of ynamides. He is a Fellow of the National Academy of Science (FNASc)-2019; Fellow of the Royal Society of Chemistry (FRSC)-2020; Fellow of the Indian Academy of Sciences (FASc)-2021. He received the UGC-BSR-Mid Career Award-2020. He currently serves as Associate Editor of New Journal of Chemistry, RSC.

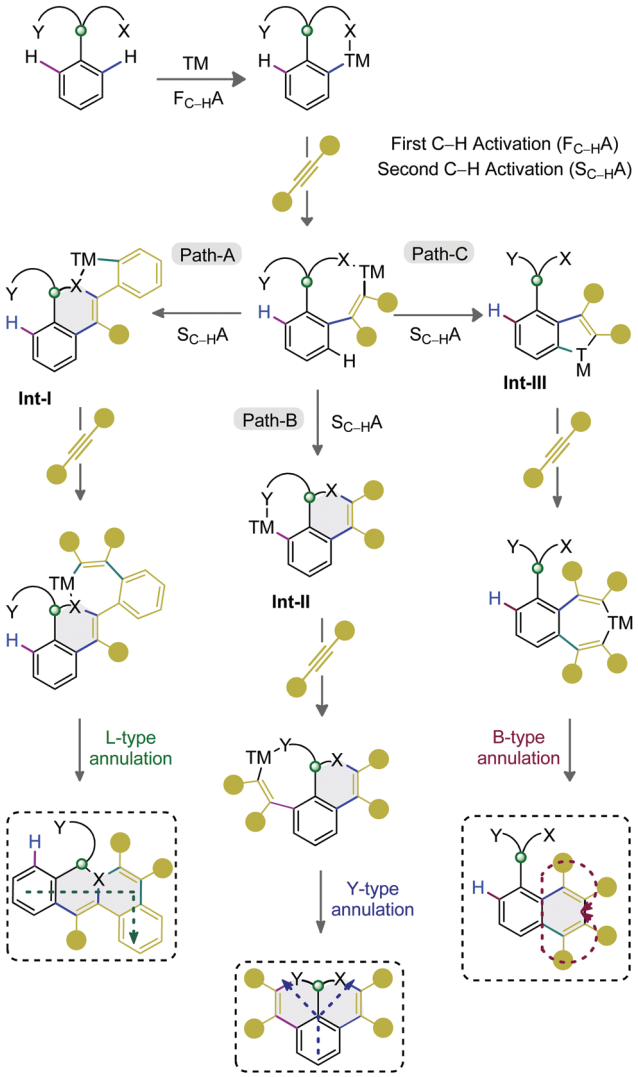


Fig. 3 BLY-type multiple C–H annulations of arenes.

provide the Y-type annulation product (Path-B, Fig. 3). In the case of the B-type unsymmetrical annulation process, the $F_{C-H}A$ of *o*-C(arene)–H bonds and alkyne insertion followed by $S_{C-H}A$ of the *m*-C(arene)–H bonds render *cis*-aryl-metalation **Int-III**. Next, alkyne insertion on **Int-III** leads to the unsymmetrical B-type double annulation product (Path-C, Fig. 3). To address cumulative challenges (shown in Fig. 2 and 3), unraveling an unsymmetrical multiple annulation of C(arene)–H bonds in a single pot is certainly thought-provoking.[6,7]

In this review, the emerging field of TM catalyzed unsymmetrical multiple annulation of inert arene-C–H bonds leading to π-extended BLY-type products is described. The conceptual development of DG-assisted multiple C–H annulation strategies for the construction of π-conjugated polycycles is illustrated. The established reaction conditions, reaction generality with illustrative examples, and mechanistic insights for all the synthetic methods have been shown in every transformation. Our aim is to highlight the progress made in unsymmetrical multiple annulations of arenes in recent years, rather than presenting an exhaustive account on this topic. Thus, not all the articles in the TM catalyzed C–H annulations are included and cited. In addition, the unusual π-extended complex molecular scaffolds fabricated through multiple C–H annulation strategies exhibit interesting optical properties. Although detailed discussion of the optical properties of the materials in this feature article would offer valuable insights to researchers, the content would be too exhaustive. We, therefore, believe a review article highlighting the optical properties of π-extended complex heteraryls would garner appropriate attention.

2. *ortho*-Selective double annulation of two different C–H bonds

The DG promoted double annulation of arene *ortho*(*o*)-C–H bonds with internal alkynes expediently produces poly fused-heterocycles. The participation of identical (hetero)atoms of DG's in the annulations of *o*,*o*′-C(arene)–H bonds with alkynes yields a Y-type-**I** symmetrical double-annulation (DA) product (Fig. 4), while the identical reaction with an unsymmetrical alkyne leads to a Y-type-**II** unsymmetrical DA-product (Fig. 4). Likewise, double-annulation sequences involving different heteroatoms of DG with dialkyl-alkynes form a Y-type-**III** unsymmetrical DA-compound (Fig. 4); in contrast, identical reaction with diaryl-alkynes leads to L-type-**IV** unsymmetrical DA-species (Fig. 4), as C(arene)–H bond activation of the alkyne-moiety in the mono-annulation product is highly facile. The complete reaction trajectory is highlighted in Fig. 4.

2.1. Linear L-type unsymmetrical double annulation

The aryl-motif in diaryl-alkynes directly participated in the C(arene)–H annulation to provide an L-type DA product. Thus, the first annulation of DG-enabled arenes with alkyne leads

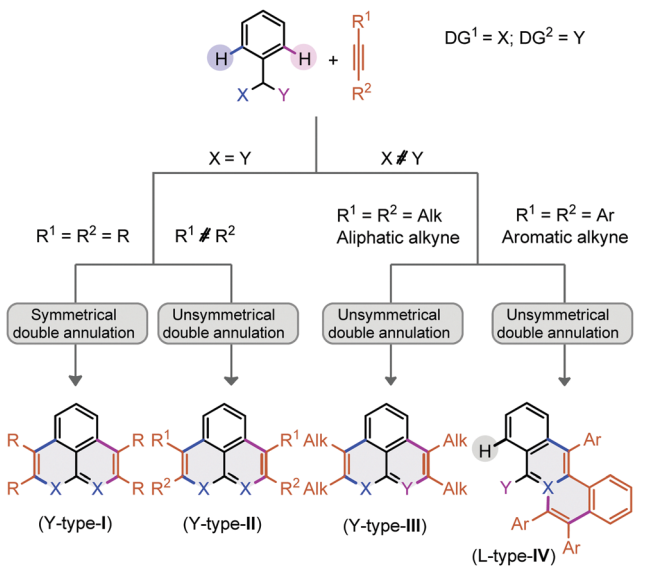


Fig. 4 Schematic presentation of symmetrical/unsymmetrical Y- and L-type double annulations.

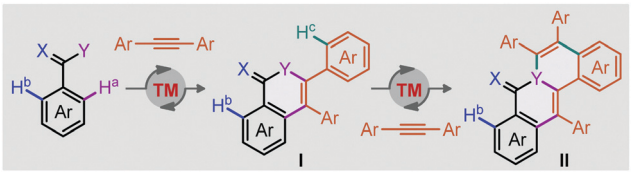


Fig. 5 Schematic presentation of L-type double annulations.

to **I** (Fig. 5). The second annulation then occurs with the C(arene)–H^c moiety in close proximity to the heteroatom Y to build **II** (Fig. 5).

In 2010, the Miura group first demonstrated an oxidative double annulation of benzamides **1** with alkynes **2** under Rh(III)-catalysis to make π-conjugated polycyclic amides **3a** (Scheme 1A-I).[9] Functionalization of both C–H and N–H bonds makes this cascade double annulation viable. Interestingly, the π-conjugated polycyclic amides exhibit bright solid-state fluorescence.

In the same year, the Li group reported an identical reaction when conducted in the presence of an Ag_2CO_3 oxidant in acetonitrile (Scheme 1A-II).[10]

The Zhao, Shi, and Dong groups have subsequently showcased the Rh(III)/Ru(II)-catalyzed L-type DA of hetero(arenes) by using oxidizable hydrazine, 2-aminoisoindoline-1,3-dione, and 1,4,2-dioxazol-5-one DGs, respectively (Scheme 1A-III–V).[11]

The identical transformation is also possible with amides, giving lower yields with a Ru(II)-catalyst (Scheme 1A-VI).[12]

In 2016, the Sahoo group reported a Ru(II)-catalyzed methylphenyl sulfoximine (MPS) assisted one-pot double annulation of heteroarylamides **7a** with alkynes to construct diverse arrays of polycyclic amides **3b** (Scheme 1B-I).[13] The oxidizing MPS DG plays a vital role, making the double annulation viable *via* the formation of multiple C–C and C–N bonds in a one-pot operation. The reaction proceeds through the formation of a mono-annulated isoquinolone intermediate followed by amidyl "N"-directed second annulation to access **3c**. This unsymmetrical annulation of heteroarenes is also showcased with two distinct alkynes.

In 2017, the Sahoo group also demonstrated an unprecedented double-annulation of MPS-enabled acrylamides **7b** with unactivated alkynes (Scheme 1B-II).[14]

The electrochemical strategy was implemented by the Tang group in 2019 to construct polycyclic amides under Ru(II)-catalysis in the absence of an extra oxidant (Scheme 1C).[15] This process is effective in providing products with high regioselectivity and therefore is synthetically viable.

In 2017, Jun and co-workers reported a Rh(III)/Cu(II) catalyzed new cascade double N-annulation of allylamine **8** and an internal alkyne to produce benzoquinolizinium salts **9** (Scheme 2).[16] The reaction begins with the Rh(III)-catalyzed vinylic C–H bond activation of allylic amine followed by the insertion of alkyne delivering intermediate **8-I**. Next, $Cu(OAc)_2$ mediated oxidation of **8-I** forms diphenylpyridine **8-II** (Scheme 2). The activation and metalation of the C(aryl)–H bond in close proximity then lead to the formation of five-membered rhodacycle **8-III**. The second annulation of **8-III** with alkynes in the presence of HBF_4 finally occurs to yield benzoquinolizinium salt **9** (Scheme 2). To understand the mechanism, the substituted pyridine **10-II** was prepared from secondary allylamine **10** and alkyne through **10-I** (Scheme 2). The N-annulation of **10-II** under the standard reaction conditions affords benzoquinolizinium salt **9d** (Scheme 2). Thus, the second N-annulation is presumably faster than the first annulation, which makes the intermediate **8-II** isolation difficult. The annulation was even successful with 1-phenylprop-2-en-1-amine (**11**; contains both a benzylamine and allylamine moiety) and 4-octyne (**2b**) to deliver benzoquinolizinium salt **12** in 98% yield (Scheme 2). This demonstration truly attests the activation of both allylic C–H and *ortho*-phenyl C–H bonds for the double N-annulation process (Scheme 2).

In 2017, the You group has developed a cascade double C–H annulation of aldoximes **13** with alkynes in the presence of $[Cp^*Rh(OAc)_2]_2$, $Zn(OTf)_2$ and oxygen as the sole oxidant, to access benzo[*a*]acridizinium salts **14** (Scheme 3).[17] The reaction at first forms a five membered rhodacycle intermediate **13-I**. Next, the insertion of an alkyne to **13-I** delivers intermediate **13-II**, which further undergoes a second annulation with another alkyne *via* intermidiate **13-III** to provide benzo[*a*] acridizinium salt **14** (Scheme 3).

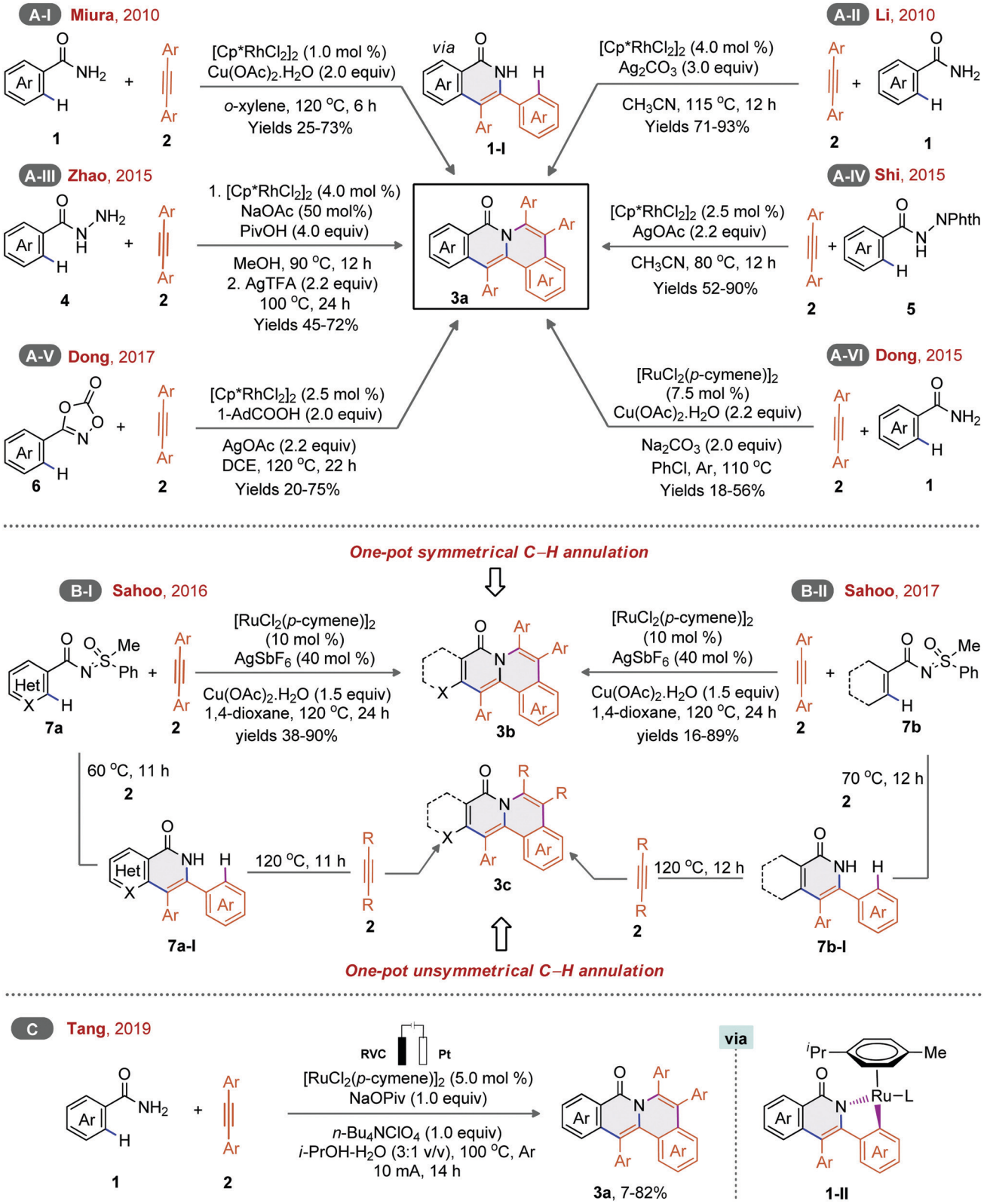
In 2017, the Sun group demonstrated a Rh(III)-catalyzed oxidative C–H annulation of 4-aminocoumarins (**15**) with unactivated alkyne **2** for the synthesis of coumarin fused polyaromatics **16** in good yields (Scheme 4).[18] Representative compounds exhibit strong fluorescence emission at 450–470 nm with broad bandwidths.

In 2018, Wang and co-workers established a Rh(III)-catalyzed cascade cyclization to produce cinnolinium salt derivatives **18** (Scheme 5).[19] This cascade annulation reaction pathway is shown in Scheme 5. To begin with, a Cu(II) mediated oxidation of N-Boc-phenylhydrazine **17** provides diazo compound **17-I**. Subsequent C–H bond cleavage of **17-I** with active Cp^*RhX_2 (X = OAc, SbF_6) delivers intermediate **17-II**. Then, alkyne **2** coordination to **17-II** forms a seven-membered rhodacycle **17-III**, which undergoes reductive elimination to make **17-IV**. Next, extrusion of carbon dioxide from **17-IV** provides **17-V**.

The Rh-catalyzed C(aryl)–H bond activation of **17-V** and insertion gives five-membered cyclometalated intermediate **17-VI**. Insertion of another alkyne **2** into the Rh–C bond of **17-VI** then affords **17-VII**. Finally, reductive elimination of **17-VII** and anion exchange with $AgBF_4$ constructs **18** (Scheme 5). The five-membered rhodacycle intermediate isolation supports the suggested catalytic cycle.

A new cascade N-double annulation that involves arylaldehydes **19**, aniline **20**, and alkynes in the presence of the Rh(III)-catalyst to access benzoquinolizinium salts **22** has been disclosed by the You group (Scheme 6).[20]

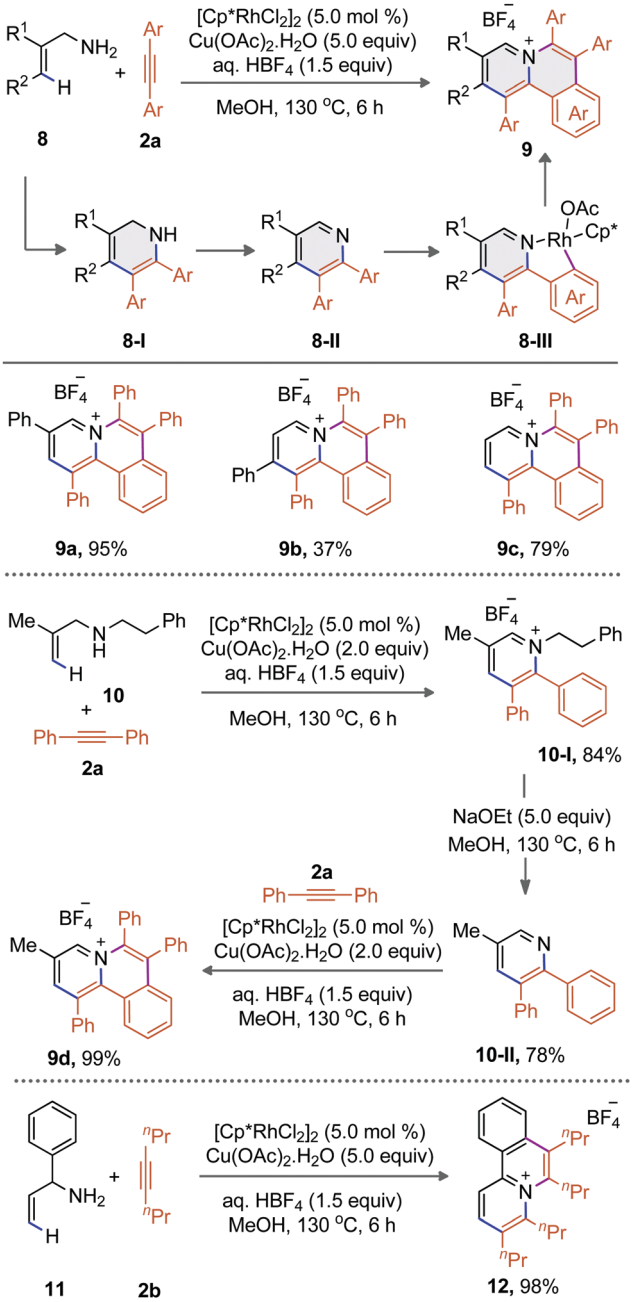
The coordination of the Rh(III) catalyst to the in-situ formed aldoxime followed by C(aryl)–H activation at first forms a five-membered rhodacycle **21**. Next, the alkyne coordination to **21**, migratory insertion, reductive elimination, and finally, the salt formation with $NaBF_4$ provides **21-I**. The activation of the



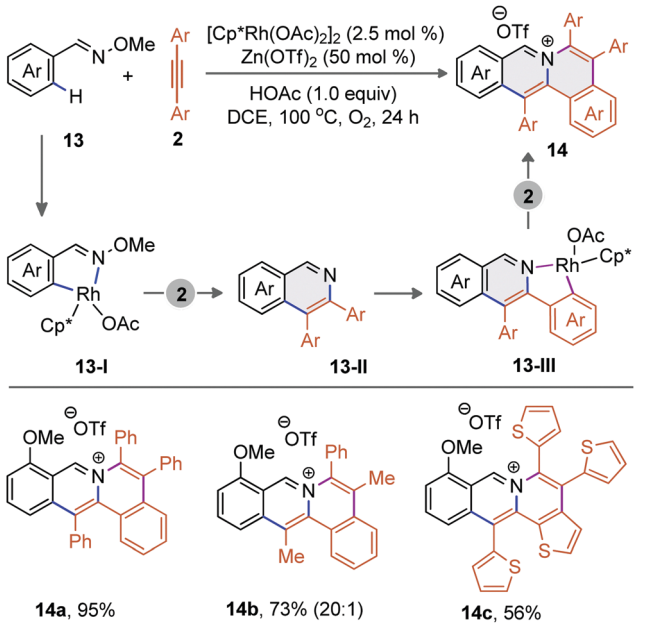
Scheme 1 Directed synthesis of π-conjugated polycyclic amides.

second C(aryl)–H bond of **21-I** by the Rh(III) catalyst and further annulation with alkyne enables the desired isoquinoline salt **22** *via* **21-II** (Scheme 6).

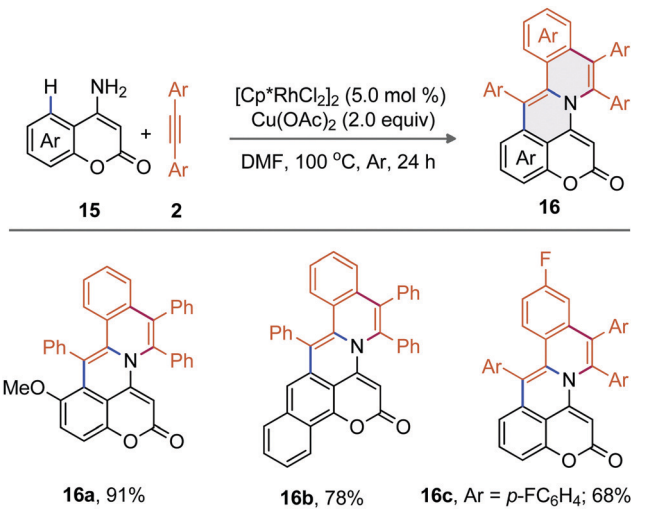
A Ru(II)-catalyzed annulation of antipyrines **23** and alkynes leading to indolo[2,1-*a*]isoquinoline scaffolds **24** has emanated from the Gogoi group, in 2019 (Scheme 7).[21] The



Scheme 2 Rh(III)-Catalyzed C–H double annulation of allyl amines.



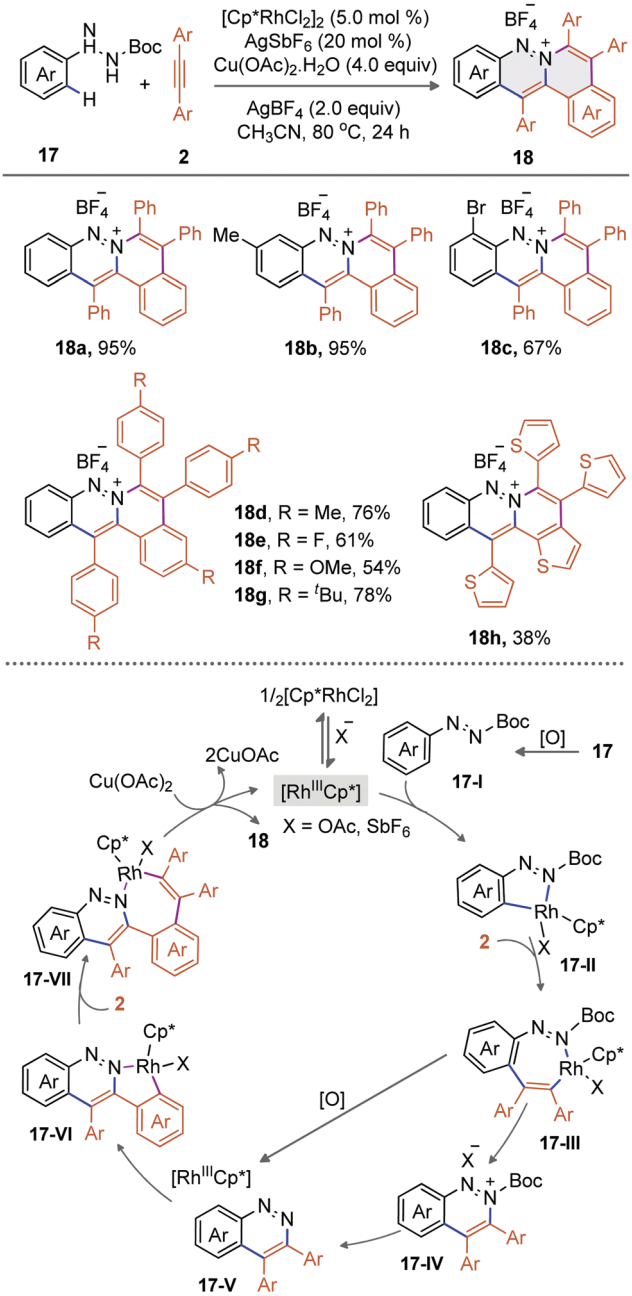
Scheme 3 Cp*Rh(III)-Catalyzed cascade double C–H annulation of aldoximes with alkynes.



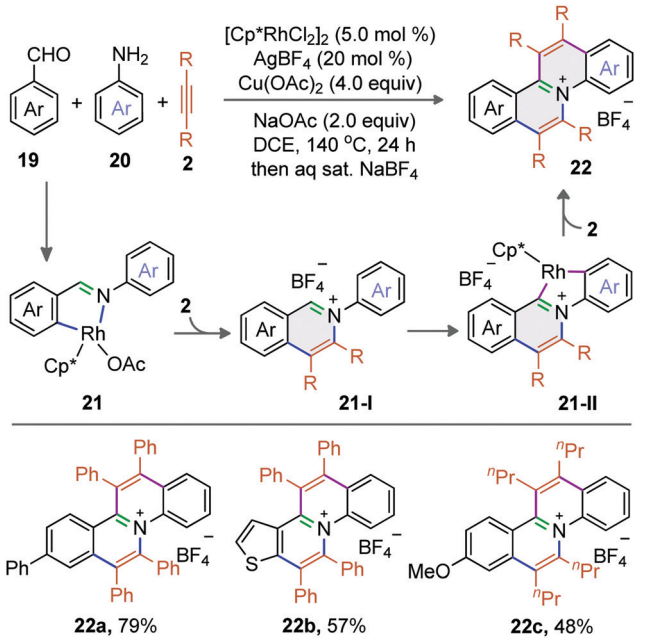
Scheme 4 Rh(III)-Catalyzed C–H double annulation of 4-aminocoumarins with alkynes.

amine-directed irreversible activation of the C(sp^2)–H bond *via* coordination of antipyrine **23** and the active Ru(II)catalyst at first forms Ru complex **23-I.** Then, alkyne coordination and migratory insertion provide a six-membered Ru(IV) complex **23-II.** Next, reductive elimination of **23-II** and further activation of the C(sp^2)–H bond form a nine-membered intermediate **23-III.** Elimination of a ketene moiety from **23-III** gives **23-IV.** Finally, insertion of another alkyne into the Ru–C bond of intermediate **23-IV** followed by reductive elimination of **23-V** delivers indolo[2,1-*a*]isoquinoline **24** (Scheme 7). Kinetic isotope effect experiments and DFT calculation studies suggest that the alkyne insertion in the second annulation step is the rate limiting step.

In 2019, the Huang group explored a Rh(III)-catalyzed C–H activation/double annulation of triazene derivatives **25** with alkynes for the synthesis of indolo[2,1-*a*]isoquinolines **26** (Scheme 8).[22] The triazene directed Rh-catalyzed C(aryl)–H activation, alkyne insertion, annulation, and N–N cleavage at first forms indole moiety **25-I** *in situ*. Next, second annulation of **25-I** N–H and C(aryl)–H bonds with alkyne occurs in same pot to obtain **26.** The transformation also worked well by stitching different alkynes (*i.e.* diphenyl acetylene **2a** followed by



Scheme 5 Rh(III)-Catalyzed synthesis of cinnolinium salt derivatives.



Scheme 6 Rh(III)-Catalyzed three component cascade N-double annulation episode of aryl-aldehydes, anilines, and alkynes.

3-octyne **2b**) to provide the unsymmetrical double annulation product **26d** (Scheme 8).

In 2020, the Ackermann group developed a step-economical Ru-catalyzed double C–H/N–H activation of naphthaquinones **27** for the synthesis of bioactive quinoidal derivatives **28** (Scheme 9).[23] The anilide assisted activation of the naphthaquinone C–H bond with the Ru-catalyst at first generates intermediate **27-I**, which undergoes annulation with the alkyne to provide pyrrole species **27-II**. Then the second annulation of **27-II** with the alkyne affords the desired π-conjugated compound **28**. The synthetic method is robust providing wide arrays of products in good yields. However, the annulation with unsymmetrical alkynes delivered a regioisomeric mixture of products (Scheme 9).

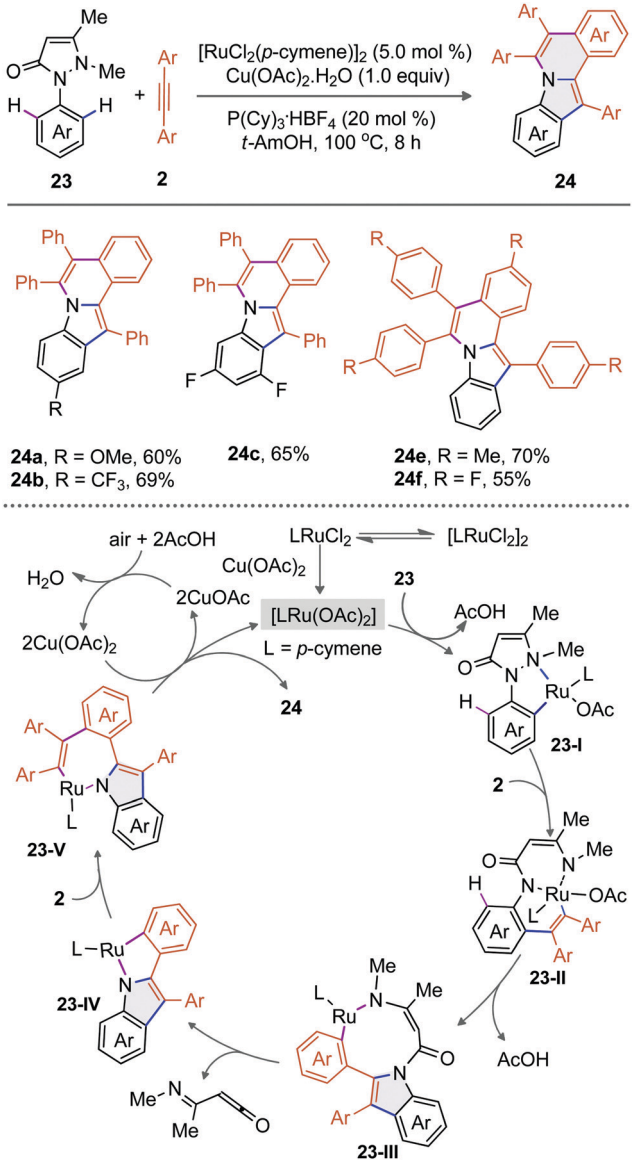
Recently, the Tadigoppula group demonstrated a one-pot Ru(II) catalyzed C–H double annulation of phenyl isocyanates **29** with unactivated alkynes for the synthesis of indole-containing polycyclic heterocycles **30** (Scheme 10).[24] The *in situ* generated carbamide (**29d-I**, urea derivatives) acts as DG and initiates the C–H annulation reaction; the control experiments support this fact (Scheme 10).

2.2. Angular Y-type unsymmetrical double annulation

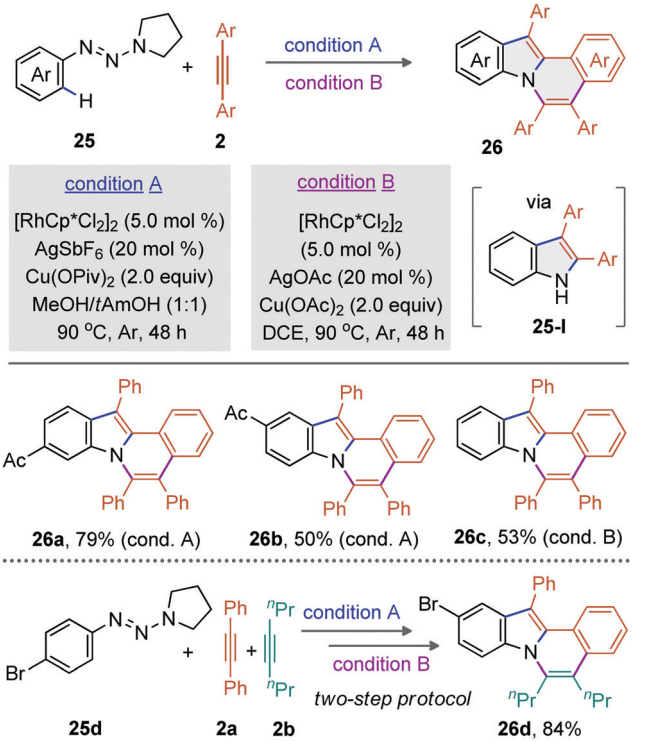
Both the *o*/*o*′-C(arene)–H bonds participate in the Y-type double annulation. The first annulation involves the heteroatom Y directed activation of the C(arene)–H^a bond and the second annulation occurs with the C(arene)–H^b moiety directed by heteroatom X (Fig. 6).

In 2012, the Wang group demonstrated a Rh(III)-catalyzed cascade oxidative double annulation of benzoylacetonitrile **31** with alkynes to produce naphtho[1,8-*bc*]pyrans **32** (Scheme 11).[25] The strong acidic methylene group could promote Rh(III)-catalyzed C(sp^3)–H activation to afford the five-membered rhodacycle intermediate **31-I**. Next, regioselective insertion of an alkyne with **31-I** gives naphthol intermediate **31-III** *via* **31-II**. Subsequent '*o*'-directed *peri*-C–H activation of **31-III** and further annulation with alkyne provide naphtho[1,8-*bc*]pyran **32** (Scheme 11). Interestingly, the π-extended functionalized naphtho[1,8-*bc*]pyran derivatives exhibit valuable solid state optical properties.

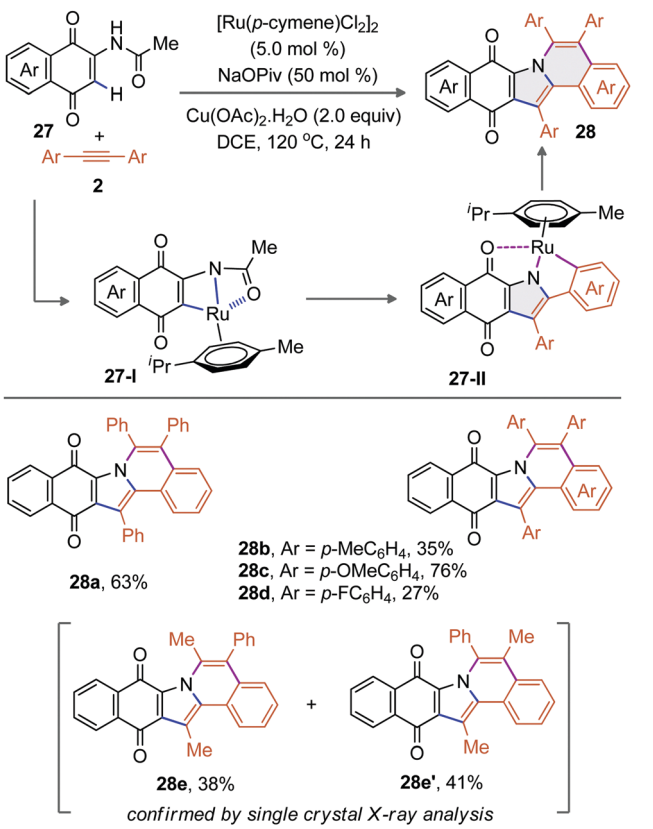
Chaudhary and co-workers developed an *N*-heterocyclic carbene (NHC) directed Rh(III)-catalyzed oxidative C–H double annulation of aryl imidazolium salts **33** with alkynes generating highly conjugated fused benzo[*ij*]-imidazo[2,1,5-*de*]-quinolizinium salt **34** (Scheme 12A).[26] The NHC ligand coordinated *o*-C–H activation in



Scheme 7 Ru-Catalyzed double annulation of antipyrines.



Scheme 8 Rh(III)-catalyzed double annulations of triazenes.

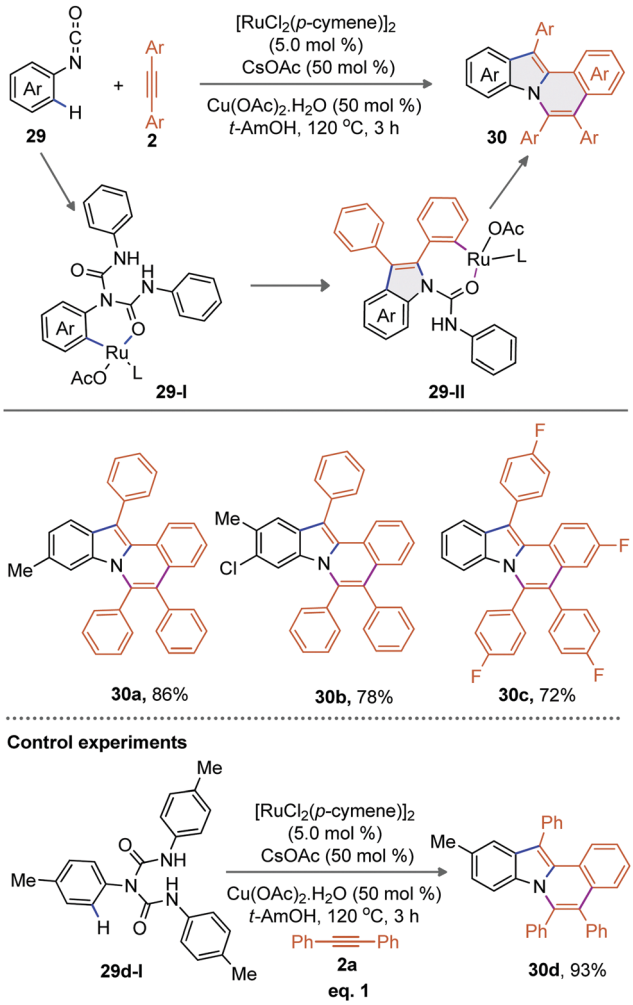


Scheme 9 Ru-Catalyzed double annulation of benzoquinones.

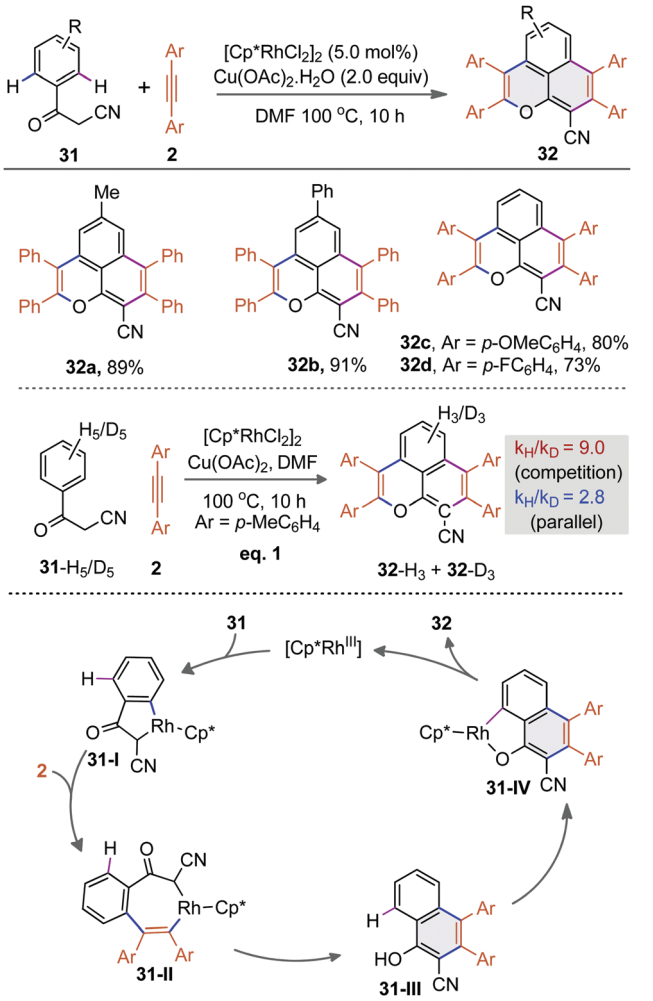
the presence of the Rh(III)-catalyst and NaOAc at first forms a 5-membered rhodacycle **33-I** (DFT studies, and other competitive experiments support this fact).

Next, halide abstraction from **33-I**, alkyne insertion, and reductive elimination affords the mono-annulation species **33-II**. The Ag^{I}-salt helps in the regeneration of the active $Cp^{*}Rh^{III}$ catalyst. Next, the second *o*′-C–H activation of **33-II** takes place with the coordination of the *in situ* formed abnormal NHC moiety to give **33-III**. Then, insertion of the alkyne on **33-III** forms a seven-membered rhodacycle **33-IV**. Finally, reductive elimination in the presence of AgOTf results in the desired product **34** along with the regeneration of $Cp^{*}Rh^{III}$ species, which keeps the catalytic cycle active.

Later, the Davies-Macgregor and Wang groups independently revealed a seminal work for the synthesis of benzo[*ij*]imidazo[2,1,5-*de*]quinolizinium salts **36** and **38** from



Scheme 10 Ru(II)-Catalyzed one-pot double annulations of phenyl isocyanates with alkynes.



Scheme 11 Oxidative double annulation of benzoylacetonitriles with alkynes.

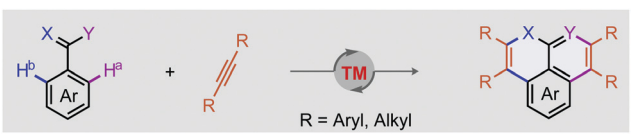


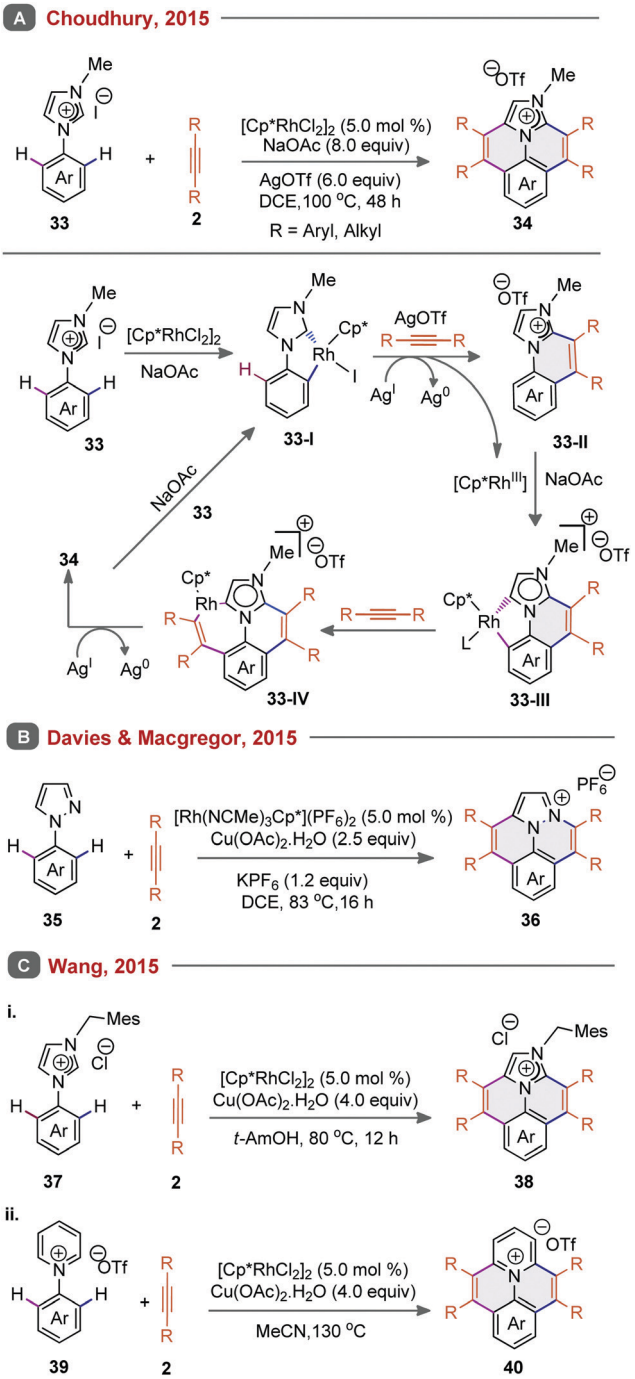
Fig. 6 Schematic presentation of Y-type double annulations.

the double annulation of **35** and **37** with alkynes, respectively (Scheme 12B and C).[27] Likewise, quinolizinium salt **40** was also constructed from **39** (Scheme 12C).[28]

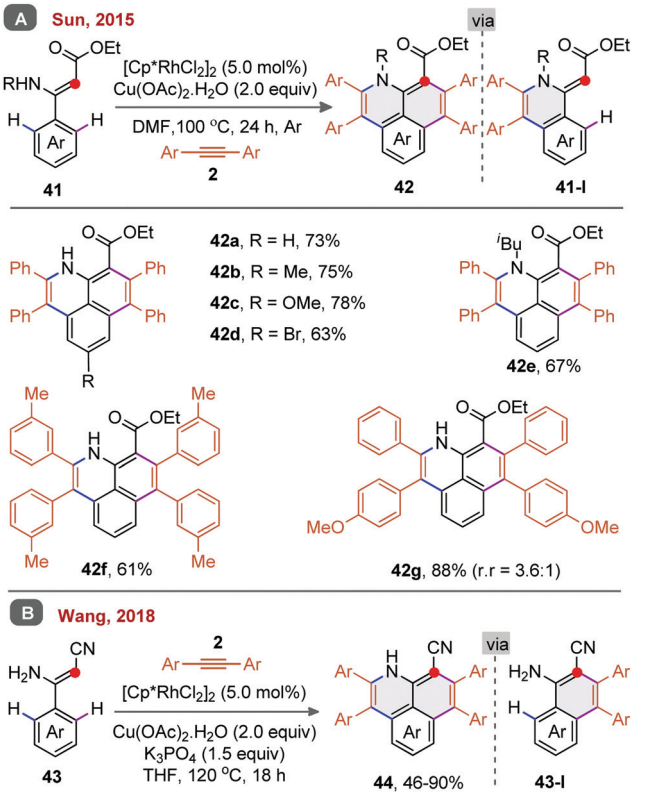
In 2015, Sun and co-workers developed an oxidative annulation cascade of β-enamino esters **41** with alkynes under Rh(III)-catalysis for the synthesis of naptho-pyridine derivatives **42** (Scheme 13A).[29a] The annulation sequence involves the enamine-N and alkynes at first followed by the annulation of vinyl-C–H, and *o*′-C–H of **41** along with alkynes; thus, the entire transformation is regiospecific (Scheme 13A). Later, the Wang group extended a similar type of cascade annulation of β-enaminonitriles **43** with alkynes under Rh(III)-catalysis to make naphtho[1,8-*bc*]pyridines **44** (Scheme 13B).[29b] Interestingly, the synthesized derivatives exhibit solid state luminescence.

In 2016, Dong and co-workers described a novel tandem Cp*Rh(III)-catalyzed one-pot cascade annulation of 1,3,4-oxadiazoles **45** with 1,4-enynes for the synthesis of decahydropyrenes **46** (Scheme 14); the diazole moiety acts as a traceless DG.[30] The transformation at first involves Rh-catalyzed *o*,*o*′-C(sp^2)–H activations and intermolecular hydroarylation with an alkyne motif of 1,4-enyne to give **45-I**. Next, the intramolecular Diels–Alder reaction/1,3-dipolar cycloaddition sequence of **45-I** affords **46** *via* the intermediates **45-II** and **45-III** (Scheme 14). This process allows the construction of three new fused rings comprising an oxygen bridged unit.

A similar type of oxidative annulation of Rh(III)-catalyzed *o*-/*peri*-C–H bonds in 3-indolylacetonitriles **47** has been demonstrated by the Wang group in 2017; this process provides access to wide arrays of novel 4H-oxepino[2,3,4,5-*def*]carbazoles **48** in moderate to good yields (Scheme 15).[31] The activation of C(sp^2)–H/C(sp^3)–H bonds of **47** by the Rh-catalyst at first



Scheme 12 Double annulation of N-heterocyclic carbene and aryl pyrazole with alkynes.



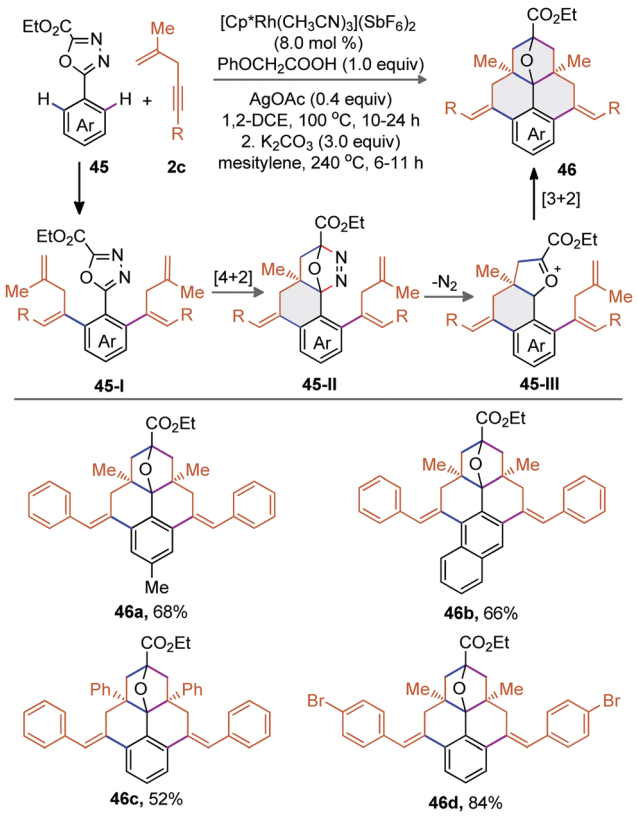
Scheme 13 Tandem double annulation of β-enamino esters/nitriles.

generates **47-I**. Next, [4+2] cycloaddition of **47-I** with an alkyne *via* migratory insertion forms substituted carbazoles **47-III**. Next, [5+2] cycloaddition of **47-III** with another alkyne occurs through Rh-catalyzed '*o*' directed *peri*-C–H activation and an annulation sequence (Scheme 15).

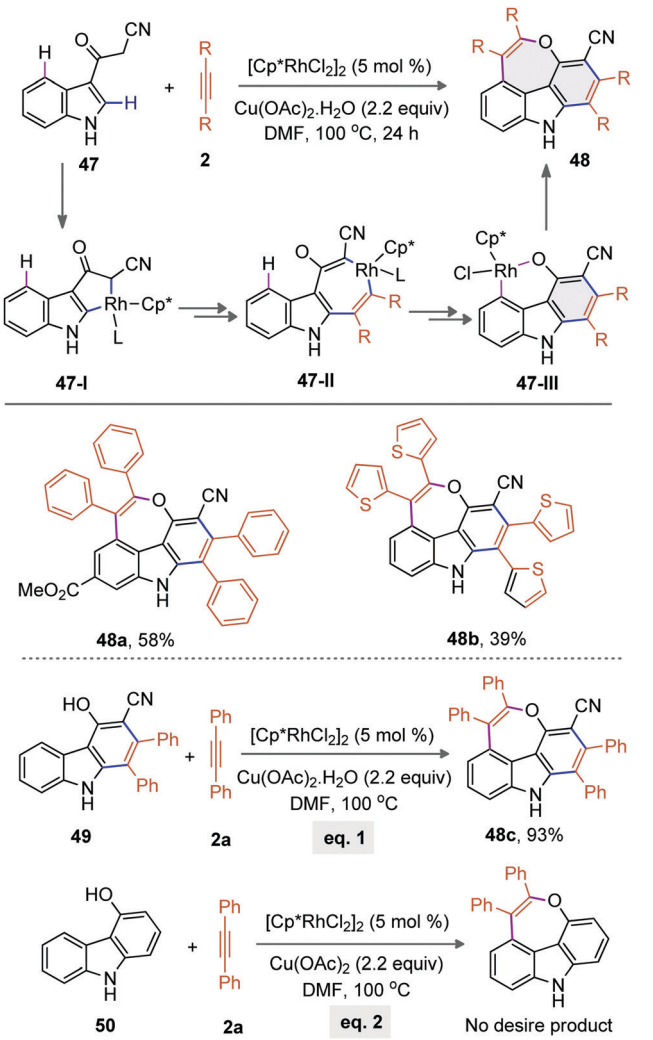
The 4*H*-oxepino[2,3,4,5-*def*]-carbazole derivatives **48** exhibit bright solid-state fluorescence. To understand the mechanistic insights, the reaction of mono annulation product **49** with diphenyl acetylene delivers **48c** in 93% yield (eqn (1), Scheme 15); this justifies the participation of carbazole intermediate **49** in this tandem double annulation. However, the annulation of 9*H*-carbazol-4-ol **50** with alkynes did not occur under the optimized conditions (eqn (2), Scheme 15); thus, the nitrile group plays a vital role in this double annulation.

The Saa group developed a novel synthetic route to access N-doped cationic PAHs benzo[*c*,*d*]fluoranthenes **52** *via* Rh(III)-catalyzed oxidative [4+2] and [4+2] double-annulation of 2-arylbenzimidazoles **51** with alkynes (Scheme 16).[32] Most of the compounds show intense fluorescence activity in the solution phase. The mono-annulation compound **51e-I**, obtained from **51e** and alkyne through C–H/N–H functionalization, undergoes second annulation to afford azafluoranthenium salt **52e** (Scheme 16). The $LiAlH_4$ mediated reduction and the addition of PhLi to **52e** were independently produced by the respective diamine derivatives **53**.

In 2017, the You group demonstrated a divergent synthetic route to fabricate four, five or six-ring-fused π-conjugated phenalenyl-fused pyrylium cations **55** from the Rh(III)-catalyzed double annulation of naphthaldehydes **54** with alkynes (Scheme 17).[33] The oxonium-doped polycycles are highly fluorescent with a high quantum yield. The aldehyde directed C–H activation and insertion of alkyne followed by nucleophilic attack on aldehyde **54** at first generates the intermediate **54-III** *via* **54-I** and **54-II**. The control experiments and ^{18}O-labelling studies support the occurrence of stepwise double annulation. The substituents in the naphthalene ring decides the fate of the second alkoxy directing group in the molecule.



Scheme 14 A diazole traceless directing group assisted Rh(III)-catalyzed double annulation with 1,4-enynes.



Scheme 15 Rh(III)-Catalyzed tandem *o*-/*peri*-C(sp^2)–H annulations of 3-indolylacetonitriles.

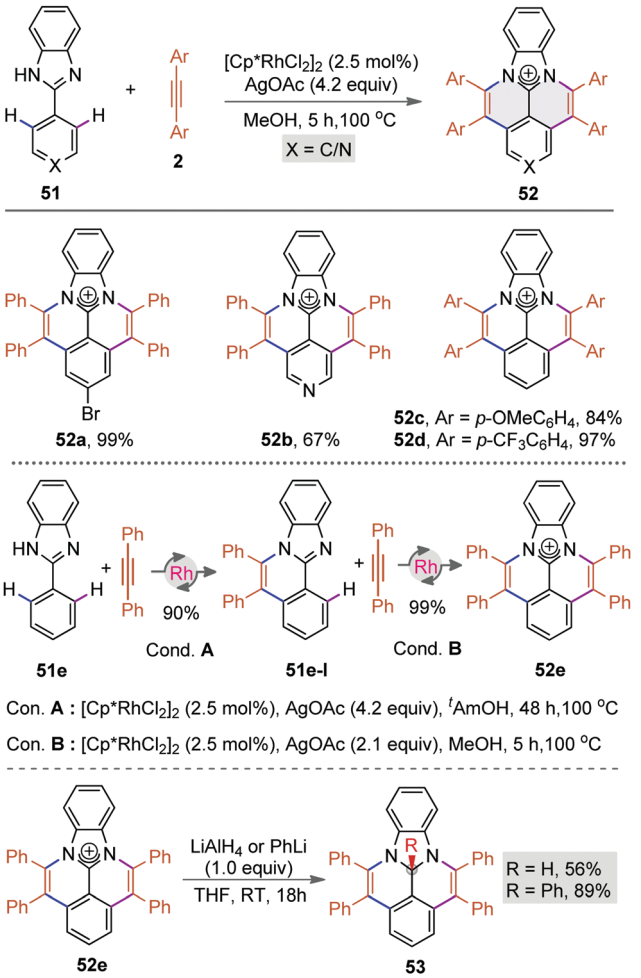
In the case of unsubstituted and 4-aryl bearing naphthaldehydes, a consecutive oxidation with Ag_2O and C_2–H cleavage of **54-III** forms a five-membered rhodacycle **54-IV**. Next, alkyne insertion to **54-IV** gives a seven-membered **54-V**, which further undergoes reductive elimination to provide the desired product **55** (path-I, Scheme 17). While the electron-rich naphthaldehydes with R = OMe or OBn, the protonation, dehydrative aromatization and oxidation of **54-III** generates **54-VI** (path-II, Scheme 17). Next, O–R bond cleavage of **54-VI** followed by carbonyl-directed C–H annulation with alkyne produces **55′** (Scheme 17). In contrast, the naphthaldehyde with a good leaving group (*i.e.*, R = Br) undergoes protonolysis and subsequent dehydration, aromatization, and nucleophilic displacement of the -Br group by the water of **54-III** then provides **54-IX** (path-III, Scheme 17). The Ag-mediated oxidation of **54-X** delivers **54-VI**, which finally undergoes annulation to construct **55′** (Scheme 17).

In 2018, the You group described the construction of structurally diverse fused [5]- and [6]-carbohelicenes **57** from α-acetyl naphthalenes **56** by merging C–H activation and radical chemistry (Scheme 18).[34] This cascade reaction proceeds through a C_2–H activation/radical approach/C_8–H activation relay comprising high chemo- and regio-selectivity.

The Miura group, in 2018, reported a Rh(III)-catalyzed unsymmetrical multiple annulation of 3,5-diarylisoxazole **58** with alkynes for the construction of highly fluorescent isoquinoline-coupled naphtho[1,8-*bc*]pyran motifs **59** (Scheme 19).[35] The coordination of 'N' isoxazole with Rh(III)-catalyst at first activates the C(aryl)–H bond to provide **58-I.** Next, alkyne addition and migratory insertion to **58-I** delivers **58-II.**

The reductive elimination of **58-II** assisted by the cleavage of an isoxazole N–O bond (acting as an internal oxidant for catalyst regeneration) gives mono-annulated-Rh-enolate species **58-III.** Furthermore, tautomerization of **58-III**, carbonyl-directed C(aryl)–H bond activation of close-proximity, alkyne insertion and annulation, and aromatization leads to **58-V** *via* **58-IV.** Finally, Rh-catalyzed annulation of α-naphthol species **58-V** with alkyne gave the desired product **59** in moderate to good yields (Scheme 19).

In 2018, the Sahoo group demonstrated a transformable methylphenyl sulfoximine (MPS) directed one-pot unsymmetrical {[4+2] & [4+2]} double annulations of hetero (arenes) **60** with alkynes under Ru(II)-catalysis (Scheme 20A).[36] This process makes unusual 6,6-fused pyranoisoquinolines **61** *via* construction of four [(C–C)–(C–N) and (C–C)–(C–O)] bonds (Scheme 20).



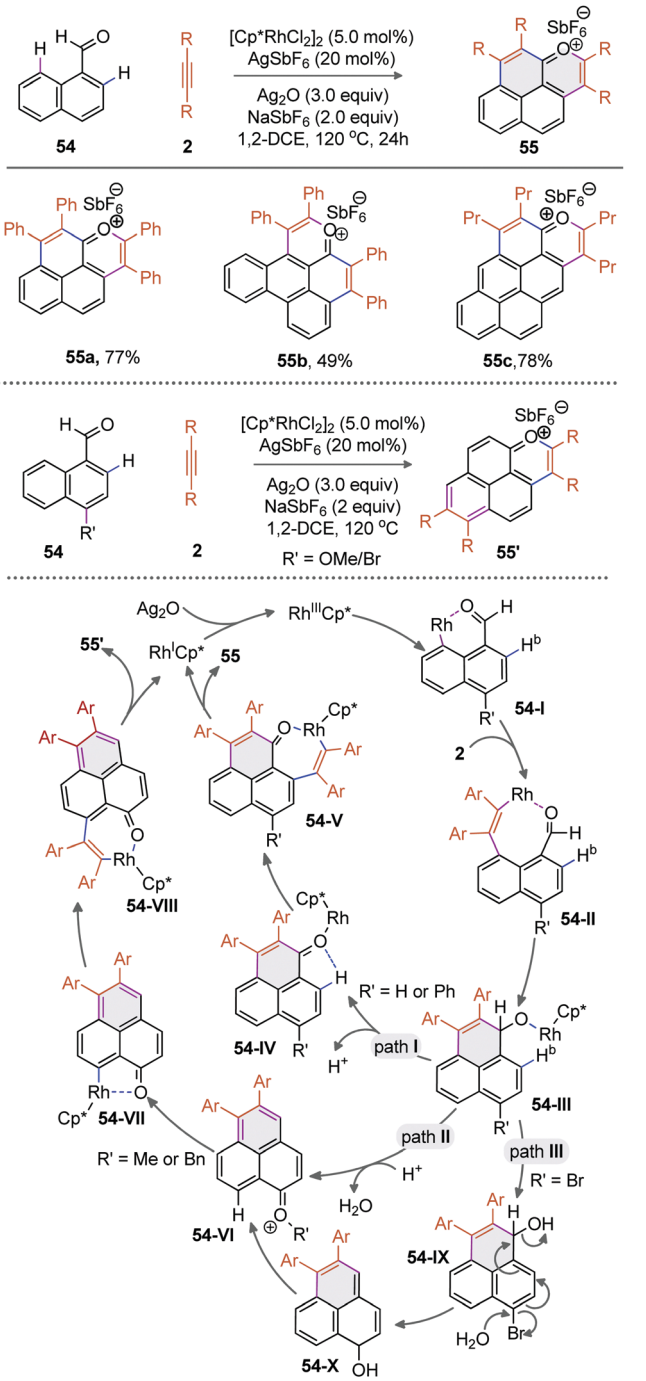
Scheme 16 Rhodium-catalyzed cationic double annulation.

The challenging unsymmetrical double annulation with two distinct alkynes is also shown. The transformation involves MPS directed *o*-C–H activation of **60** to give **60-I**, then alkyne insertion leading to **60-II**, and then annulation with concomitant expulsion of methylphenyl sulfoxide delivering isoquinolone intermediate **60-III**. Next, imide-assisted C(8)–H/C(*peri*)–H activation of **60-III** to make **60-IV** and then the annulation with alkyne delivers pyranoisoquinoline skeleton **61** (Scheme 20A).

The dual role of MPS, *i.e.*, acting as DG in the C–H activation and also involved in the annulation is significant. Interestingly, most of the **61** derivatives exhibit fluorescent properties.

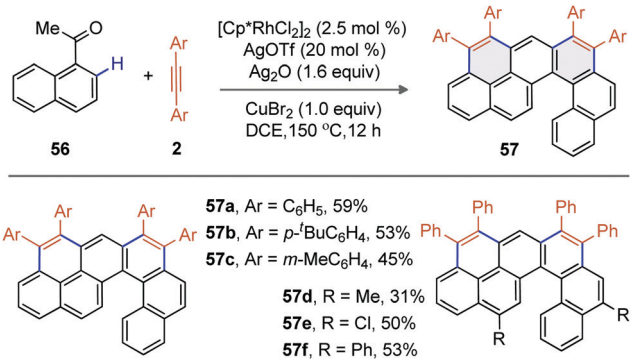
Recently, a commercially available oxidizable *N*-methoxyamine (NHOMe) has been used for the Ru-catalyzed unsymmetrical double annulation of (hetero)arenes **62** to 6,6-fused pyranoisoquinoline derivatives **61** by the Sahoo group (Scheme 20B).[37] This method successfully showcased the challenging N,O-double annulations of *N*-methoxybenzamides **61** with 1,2-dialkyl-alkynes (Scheme 20B).

In 2019, the You group addressed the challenges by successfully introducing a sterically hindered 1-methylcyclohexane-1-carboxylic acid for the double annulations of benzamides **63** with alkynes (Scheme 21).[38]

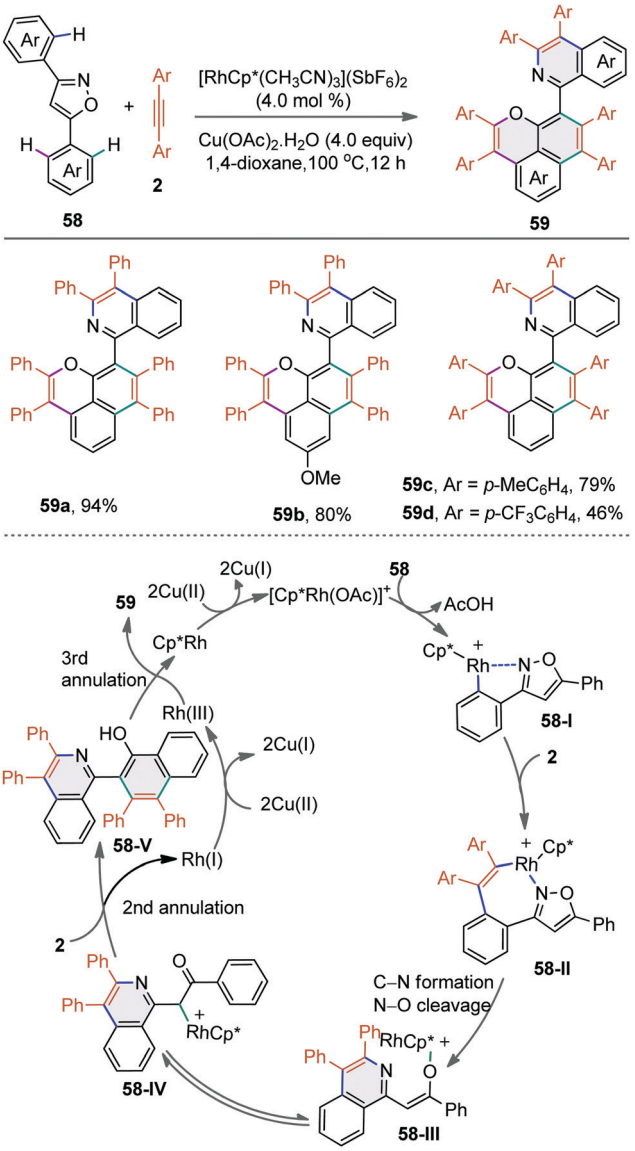


Scheme 17 Rh(III)-Catalyzed double annulation of naphthaldehydes.

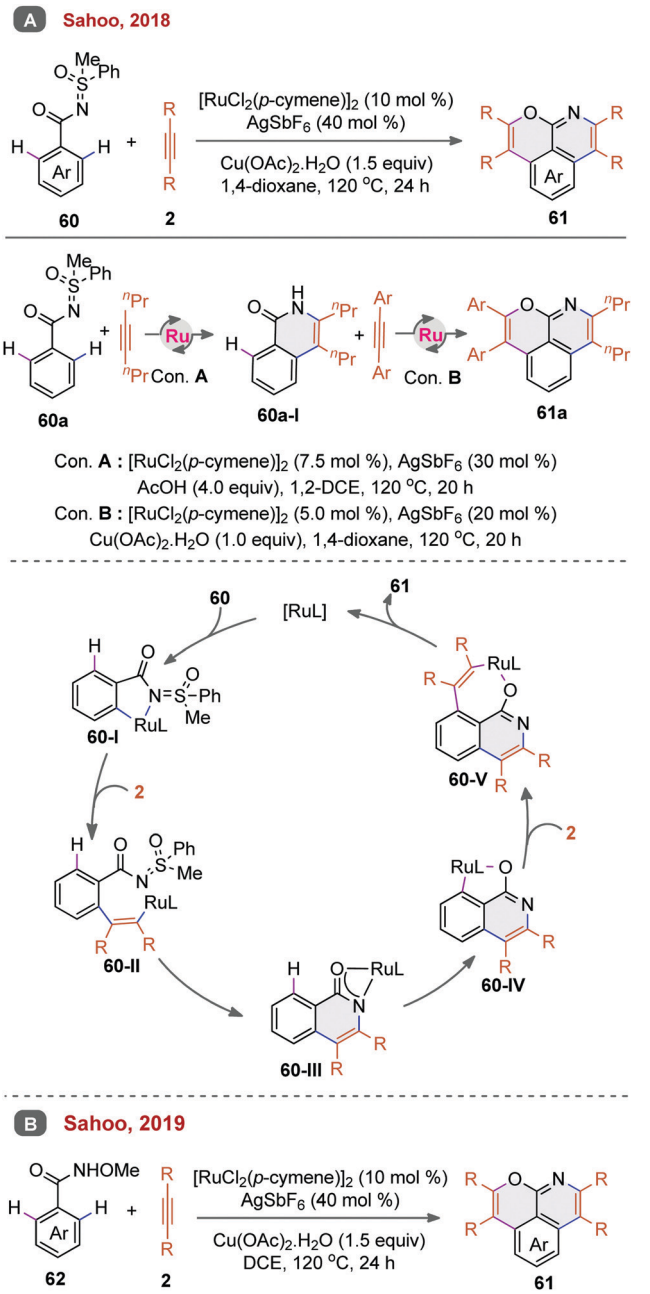
The reaction proceeds through *o*-C–H bond activation of benzamide with an Rh(III)-catalyst to provide **63-I** followed by migratory alkyne insertion to deliver **63-II**. Next, the reductive elimination of **63-II** produces the mono-annulated Rh(I)–pyridine complex **63-III**. Next, hydrogen-bonding interaction or the protonation of a pyridine-motif in the presence of 1-MeCHA helps the intramolecular migration of Rh(I) to the O centre to provide **63-IV**.



Scheme 18 Rh(III)-Catalyzed radical triggered synthesis of fused carbohelicenes.



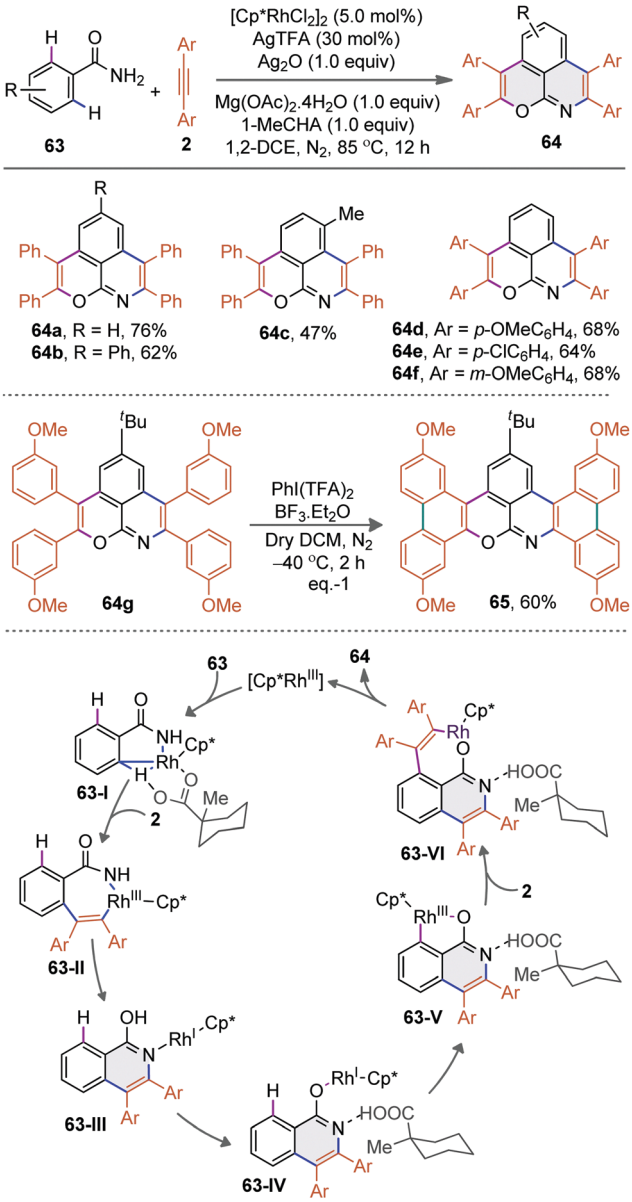
Scheme 19 Rh(III)-catalyzed cascade annulation of 3,5-diarylisoxazoles with alkynes.



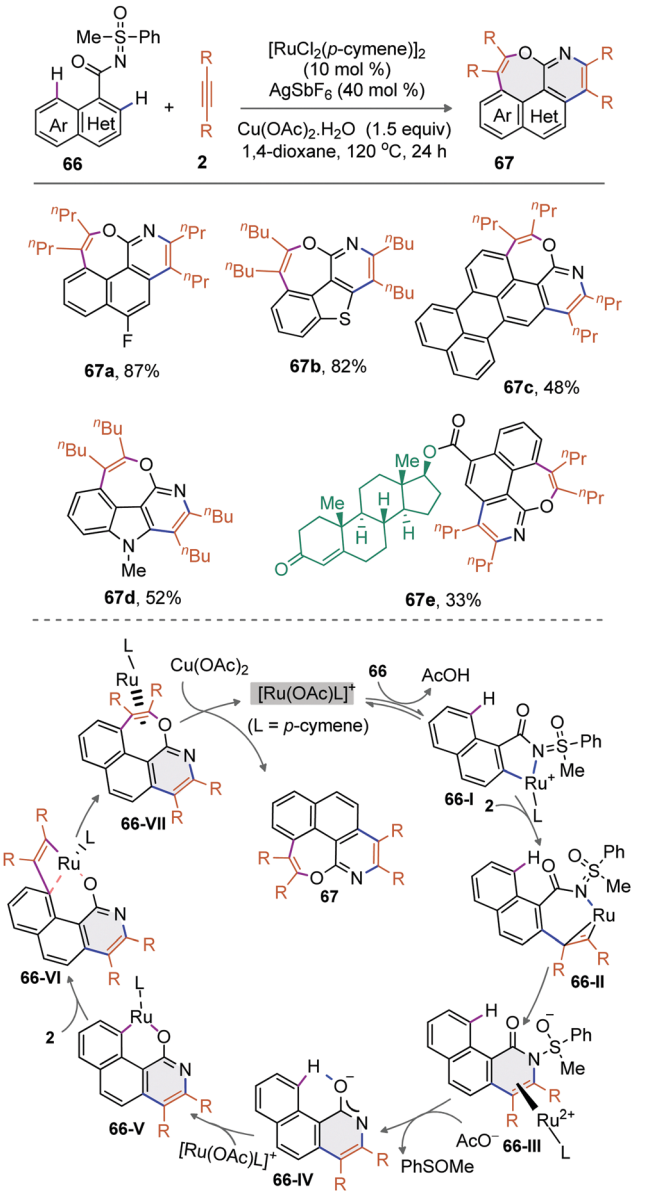
Scheme 20 Sulfoximine assisted Ru(II) catalyzed unsymmetrical cascade {[4+2] & [4+2]} annulations of hetero(arenes) with alkynes.

The second annulation of **63-IV** occurs through a silver mediated oxidation of Rh(I); subsequent activation of the *o*′-C–H bond results in **63-V**, alkyne insertion leads to **63-VI**, and reductive elimination gives the desired product **64** (Scheme 21). The Scholl oxidative C–C bond formation of electron-rich peripheral aryl-motifs in **64f** constructs double-helical extended π-conjugated polyheteroarenes **65**; importantly, these compounds are highly fluorescent.

In 2020, the Sahoo group developed an unsymmetrical double annulation of chemically distinct *ortho*- and *peri*-C–H bonds of the naphthalene system using sulfoximine as the



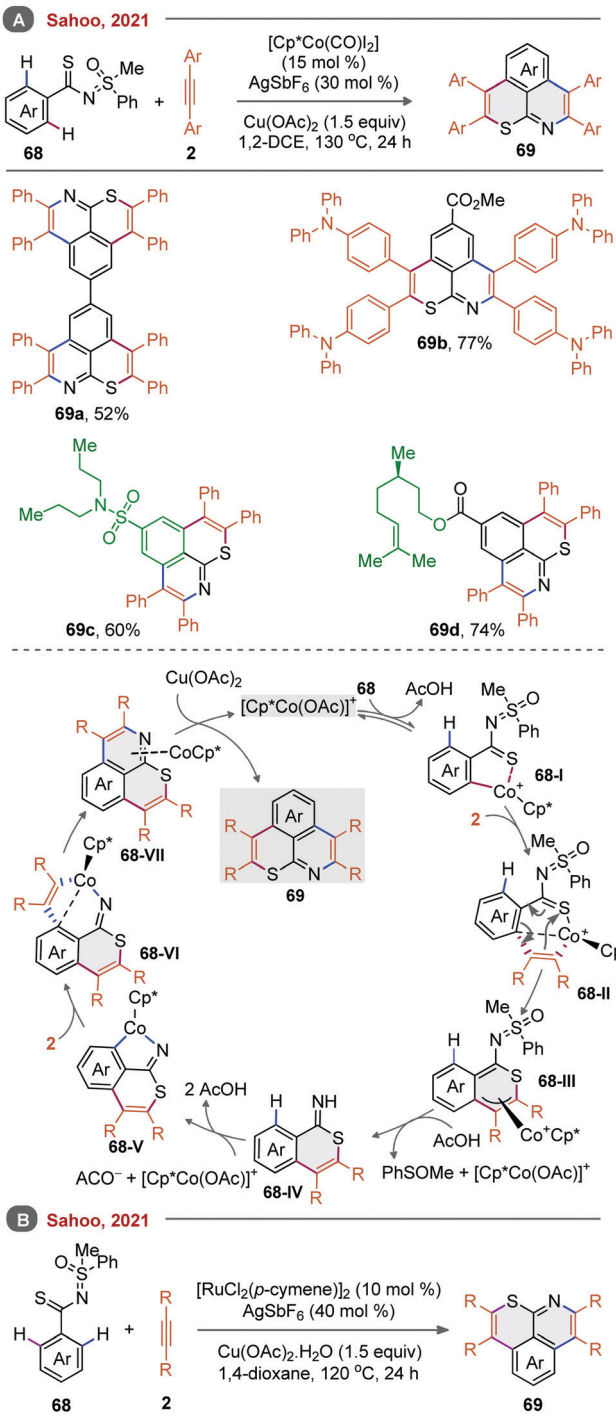
Scheme 21 Oxidative double annulation of benzamides.



Scheme 22 Ru(II)-Catalyzed MPS directed double *ortho*- and *peri*-C–H annulation of (hetero)arenes.

transformable directing group (Scheme 22).[39] This transformation involves Ru(II)-catalyzed one-pot domino {[4+2] & [5+2]} annulations of fused hetero(arenes) **66** to produce unusual [6,7]-fused oxepino-pyridines **67** *via* the formation of four [(C–C)–(C–N) and (C–C)–(C–O)] bonds. The DFT studies support the mechanistic cycle that involves Ru(II)-catalyzed MPS directed *o*-C–H activation of **66** to form **66-I** at first followed by migratory insertion of the alkyne to produce fused system **66-II**. Next, the intramolecular nucleophilic addition of the alkyne-motif to the N=S bond of **66-II** gives rise to **66-III**. The acetate-assisted removal of $[Ru(OAc)L]^+$ as well as sulfoxide from **66-III** provides mono-annulation pyridone moiety **66-IV**. The second annulation then proceeds through O-directed C(8)–H activation of **66-IV** to give **66-V**. The alkyne insertion on **66-V** involves an unusual ruthena-oxabicyclooctene complex **66-VI**. Finally, reductive elimination of **66-VI** forms the desired compound **67** (Scheme 22).

A recent demonstration of Cp*Co(III)-catalyzed directed unsymmetrical double annulation of MPS-enabled aryl thioamides **68** with unactivated alkynes has led to unusual 6,6-fused thiopyrano-isoquinoline derivatives **69** (emanated from the Sahoo group, Scheme 23A).[40] A reverse chelation of 'S' over more conventional 'N' of arylthioamides to Cp*Co(III) is significant to produce the rare Y-type N and S-bearing annulated compounds. The transformation showed broad substrate scope with good yields; moreover, direct functionalization of bioactive drug molecules makes this method noteworthy. The mechanistic pathway was authenticated by DFT studies, which involves first Co(III)-catalyzed 'S'-directed *o*-C–H activation of



Scheme 23 Cp*Co(III) and Ru(II)-catalyzed double annulation of thioamides.

68 to make **68-I** followed by migratory insertion of alkyne to produce a cyclic seven-membered Co-intermediate **68-II**. Next, 6π-electrocyclization of **68-II** produces **68-III** and subsequent acetate mediated removal of $[Cp^*Co(OAc)]^+$ and sulfoxide affords the key imine intermediate **68-IV** (Scheme 23A). Afterwards the second annulation proceeds *via* imine directed activation of the *o*′-C–H bond of **68-IV** forming **68-V** followed by alkyne insertion to provide the seven-membered cobaltacycle **68-VI**. Finally, reductive elimination of Co(III) gives thiopyranoisoquinoline derivatives **69**. Interestingly, the role of transformable masked-imine MPS-DG is significant in this strategy to regenerate the active catalyst after the first annulation as well as to provide active imine intermediate **68-IV** for the 2nd annulation process (Scheme 23A). The same reaction was also devised under Ru-catalysis mostly with dialkyl alkynes (Scheme 23B).[41]

2.2.1 Distinctive Y-type double annulation. Two directing groups assisted distinctive symmetrical and unsymmetrical Y-type double annulation *via* simultaneous involvement of two *o*-C(arene)–H bonds is depicted in Fig. 7.

In 2015, You's group explored a one-pot Rh(III)-catalyzed symmetrical double C–H annulation of 1,4-naphthoquinones **70** with alkynes (Scheme 24A).[42] The transformation constructs novel 1,8-dioxapyrenes **71** in moderate to good yields. The naphthoquinone and $Cu(OAc)_2{\cdot}H_2O$ act as the oxidant. Most of the synthesized compounds exhibit orange/red-emission and large Stokes shifts.

An interesting finding from You and co-workers demonstrate a traceless oxidizing DG assisted symmetrical double C–H annulation of *o*-methyl oxime of 5,15-dioxoporphyrins (**72**) with alkynes under the Rh(III)-catalyst (Scheme 24B).[43]

In 2019, Choudhury and co-workers described Rh(III)-catalyzed [4+2] symmetrical diannulation of pyridine and pyrazine **74** with alkynes for the construction of N-enriched π-conjugated PAHs **75**.[44] The N-PAHs display good photo physical properties; these molecules are useful as mitochondria and lysosome markers (Scheme 24C).

Ackermann and co-workers demonstrated a Ru(II)-catalyzed oxidative symmetrical double annulation of diketopyrrolopyrroles (DPPs; **76**) that involves C–H/N–H bonds with alkynes builds π-conjugated fluorogenic DPPs **77** in moderate yields (Scheme 24D).[45] Furthermore, Pd-catalyzed oxidative di C–H arylation of thiophene motifs **77** could make new π-extended DPPs with improved photophysical properties.

A series of unusual π-extended indolizine-fused BODIPY derivatives **79** were accessed through pyrrole directed Rh-catalyzed symmetrical double C–H annulation of 3,5-dipyrrolyl BODIPYs with alkynes (Scheme 24E).[47] The authors studied the electrochemical properties of the fused BODIPYs.

The Miura group revealed a distinctive Rh(III)-catalyzed unsymmetrical double annulation of 3,5-diarylisothiazoles (**80**) with alkynes for the synthesis of N- and S-fused PAH derivatives **81** (Scheme 24F).[46] This oxidative cleavage of the 3,5-diarylisothiazole N–S bond followed by N- and S-assisted C–H annulation with alkyne could yield **81**. The N–S bond of

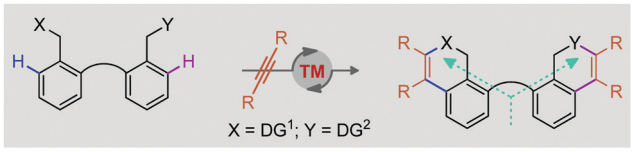
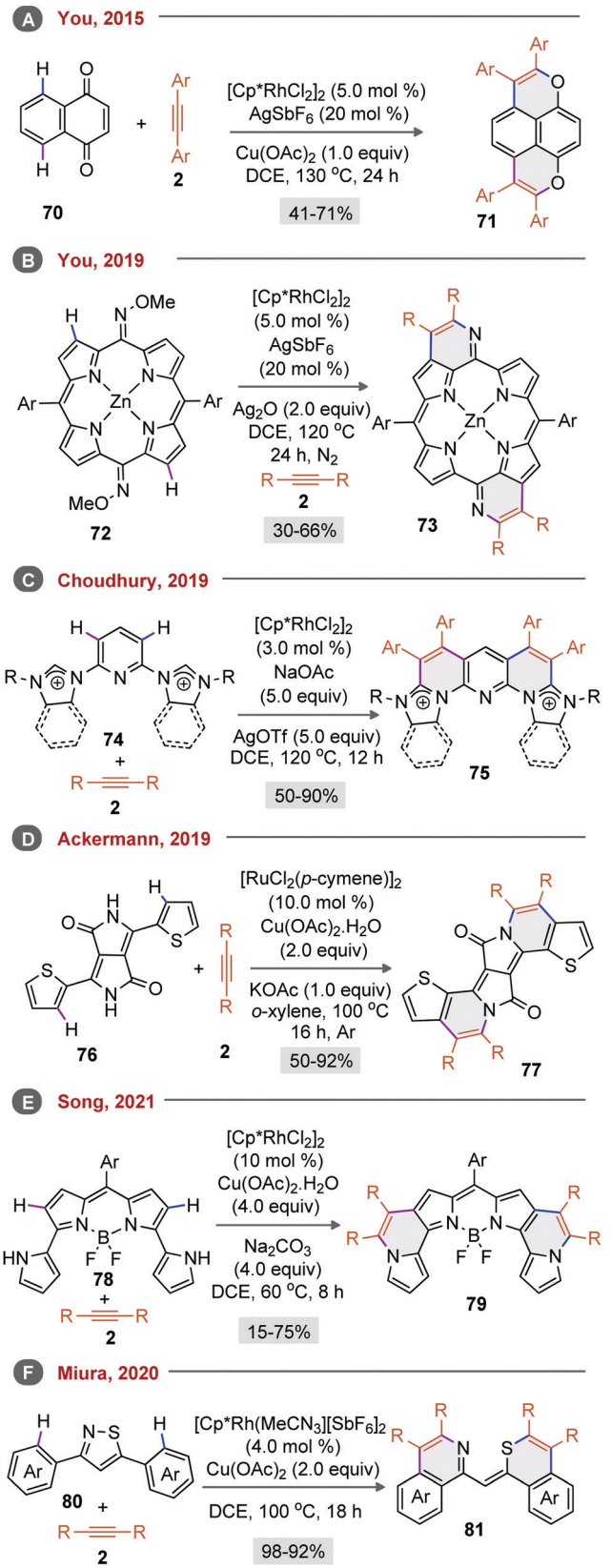


Fig. 7 Distinctive symmetrical and unsymmetrical Y-type double annulation.



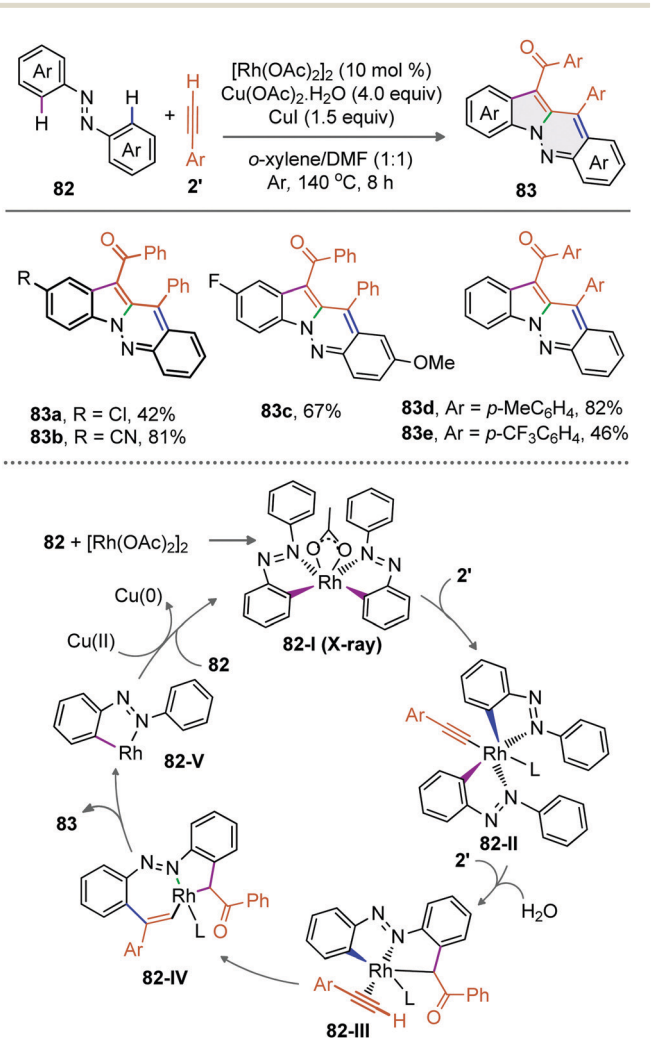
Scheme 24 Distinctive symmetrical and unsymmetrical Y-type double annulations.

isothiazole acts as the internal oxidant, while Cu(II) behaves as external oxidant that helps regenerate the active Rh(III)-catalyst (Scheme 24F).

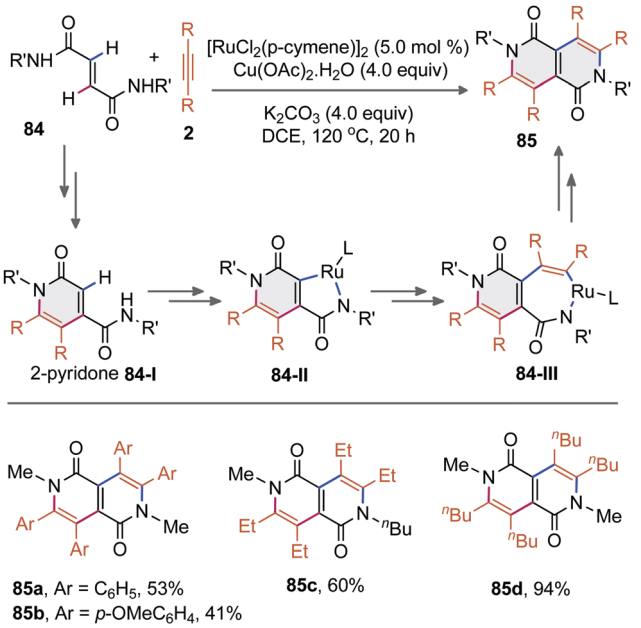
In 2019, the Yuan group reported Rh(III)-catalyzed DA of azobenzenes **82** with terminal alkynes to provide indolo[1,2-*b*]cinnolines **83** (Scheme 25).[48] The complexation of azobenzene with the Rh-catalyst at first forms intermediate **82-I.**

The structure of **82-I** has been confirmed by single crystal X-ray analysis. Next, alkyne insertion to **82-I** followed by hydration forms intermediate **82-III** *via* **82-II.** Then, complexation of another alkyne to the C(aryl)–H Rh-coordination complex of **82-III** delivers intermediate **82-IV.** Finally, alkyne slippage and reductive elimination yield **83** (Scheme 25).

Chen and co-workers have shown an interesting vinylic cascade C(sp^2)C–H annulation of fumaramides **84** with alkynes under Ru(II)-catalyst for the construction of 2,6-naphthyridine-1,5-diones **85** (Scheme 26).[49] The coordination of *in situ* generated $Ru(OAc)_2L$ to the NH- and C(alkenyl)–H moiety of **84** followed by annulation with alkyne at first gives 2-pyridone intermediate **84-I.** Subsequently, Ru-mediated C(alkenyl)–H



Scheme 25 Rh(III)-catalyzed cascade C–H annulation of azobenzenes with diphenylacetylene.



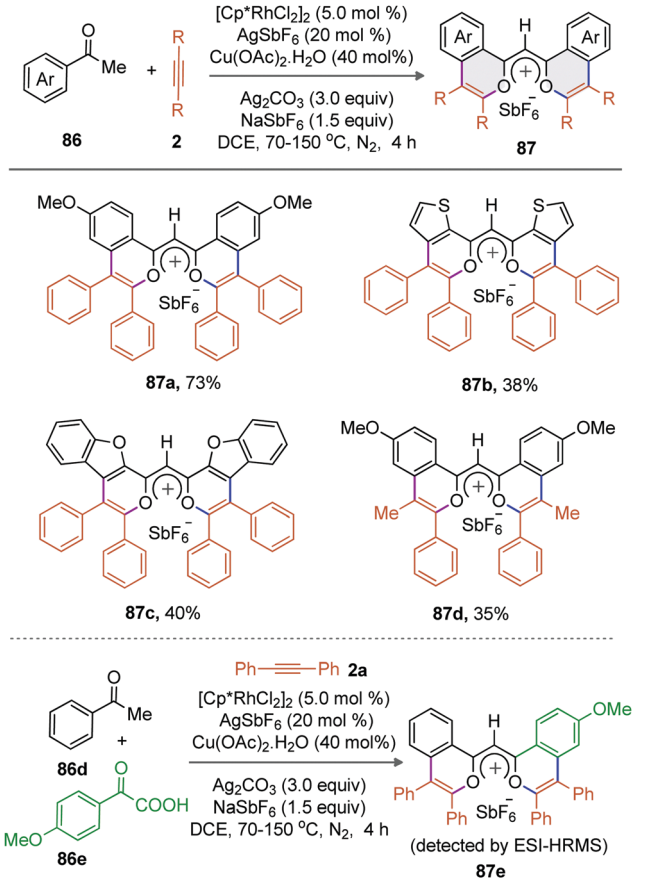
Scheme 26 Ru-Catalyzed double C–H annulation of fumaramides with alkynes.

activation of 2-pyridones **84-II** and then alkyne insertion provides seven-membered Ru-intermediate **84-III**. Finally, reductive elimination of **84-III** affords **85**.

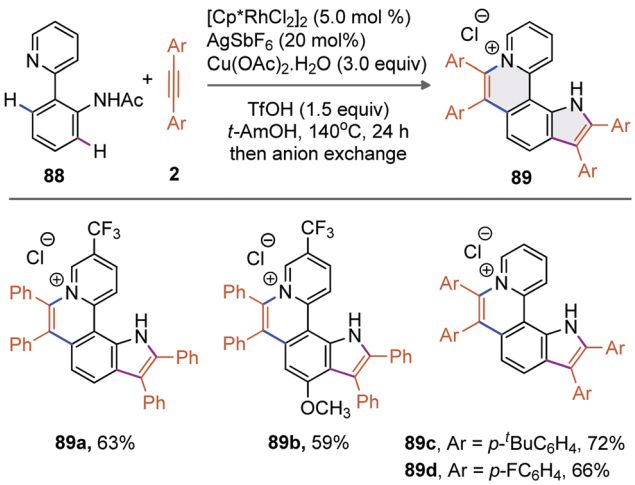
You's pioneering work in 2019 led to structurally diverse flavylium fluorophores **87** with a butterfly symmetrical configuration from (hetero)arylketones **86** and alkynes (Scheme 27).

This transformation witnessed a convergence of Rh(III)-catalyzed C–H activation and radical chemistry (Scheme 27).[50] The mechanistic studies support the reaction pathway that involves the addition of acyl radical generated from aryl ketone in the presence of a copper-catalyst to the rhodacycle formed *via* C–H activation of aryl ketone. Formation of unsymmetrical product **87**, obtained from a three-component reaction of acetophenone **86d**, diphenyl acetylene and 4-methoxybenzoyl formic acid **86e** under the standard reaction conditions, supports the participation of the intermediate benzoylformic acid in the reaction. Thus, decarboxylation of **86e** is inevitable, which helps make the annulation viable (Scheme 27). Flavylium fluorophores **87** show tunable absorption and emission with high quantum yields.

The same group in 2021 reported a synthetic method for the construction of aza[4]helicenes, pyrrolo[3,2-*k*]phenanthridiziniums **89**. The reaction involves a Rh(III)-catalyzed cascade cyclization of 2-(pyridin-2-yl)anilines **88** with internal alkynes (Scheme 28).[51] Interestingly, compounds **89** are fluorescent; consequently, they are useful as lysosome-targeted biomarkers.



Scheme 27 Rh(III)-Catalyzed cyclization and radical reaction to access butterfly flavylium fluorophores.



Scheme 28 Rh(III)-Catalyzed multiple C–H annulation of 2-(pyridin-2-yl)aniline with 1,2-diaryl alkyne.

2.3. Double alkyne insertion: B-type annulation

A site-selective annulation of arenes with alkynes makes homologated arene scaffolds; three possible ways can make this transformation viable. The transmetalation or oxidative addition of a traceless DG to the metal center could help sequential insertion of two alkynes for homologation of the aromatic motif (path-I, Fig. 8). The TM-catalyzed non-directed activation of relatively acidic C–H bonds is also useful for the site-selective conjugate double annulations (path-II, Fig. 8). Moreover, the

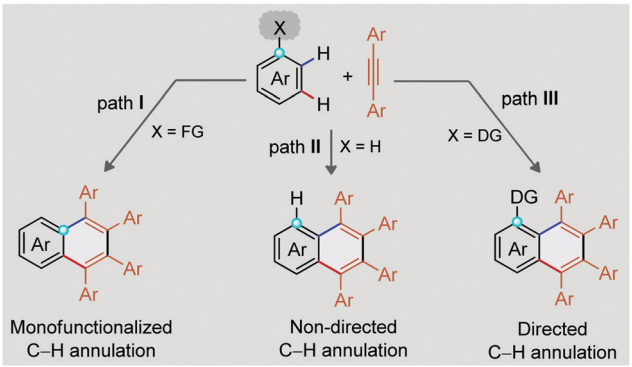


Fig. 8 Transition metal-catalyzed aromatic homologation.

DG promoted double annulation of *ortho*- and *meta*-C(arene)–H bonds with two alkynes is undoubtedly a convenient approach to form aromatic homologation scaffolds (path-III, Fig. 8).

In 2002, the Miura and Nomura groups reported the first aromatic homologation reaction of benzoyl chloride **90** with alkynes in the presence of a low valent Ir^{I} catalyst to produce peripheral substituted naphthalene derivatives **91** (Scheme 29A-I).[52]

Identical homologation of triarylmethanol **92** derivatives with alkynes in the presence of a low valent Rh^{I} catalyst has been successfully demonstrated by the Miura group in 2008 (Scheme 29A-II).[53]

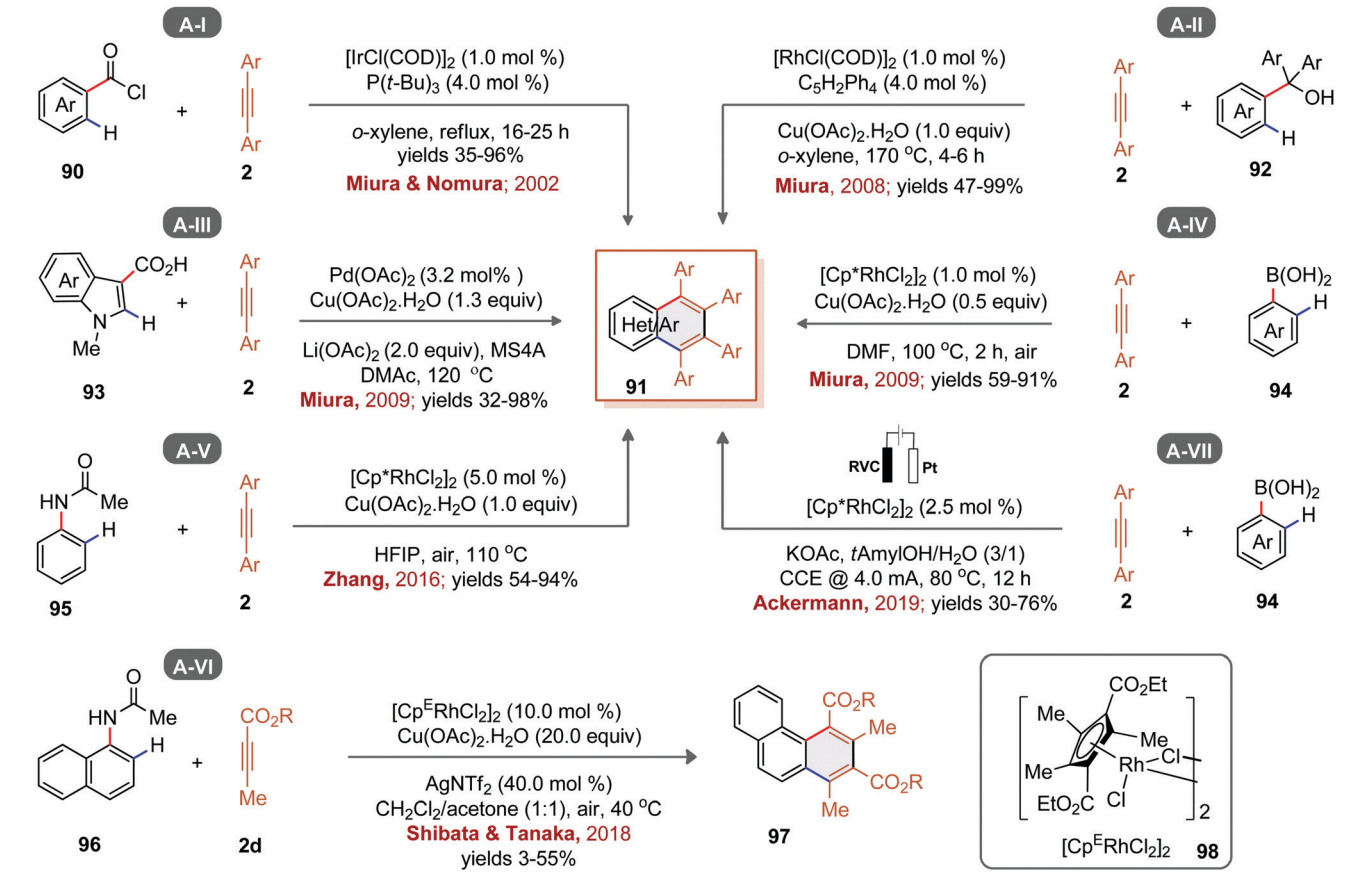
The construction of 1,2,3,4-tetrasubstituted carbazoles was realized by the Rh(III)-catalyzed decarboxylative double alkyne annulation reaction of indole-3-carboxylic acid **93** (Scheme 29A-III).[54]

In 2009, the Miura group showed the Rh(III)-catalyzed reaction of aryl boronic acids **94** with alkynes for the construction of aromatic homologation products **91** (Scheme 29A-IV).[55]

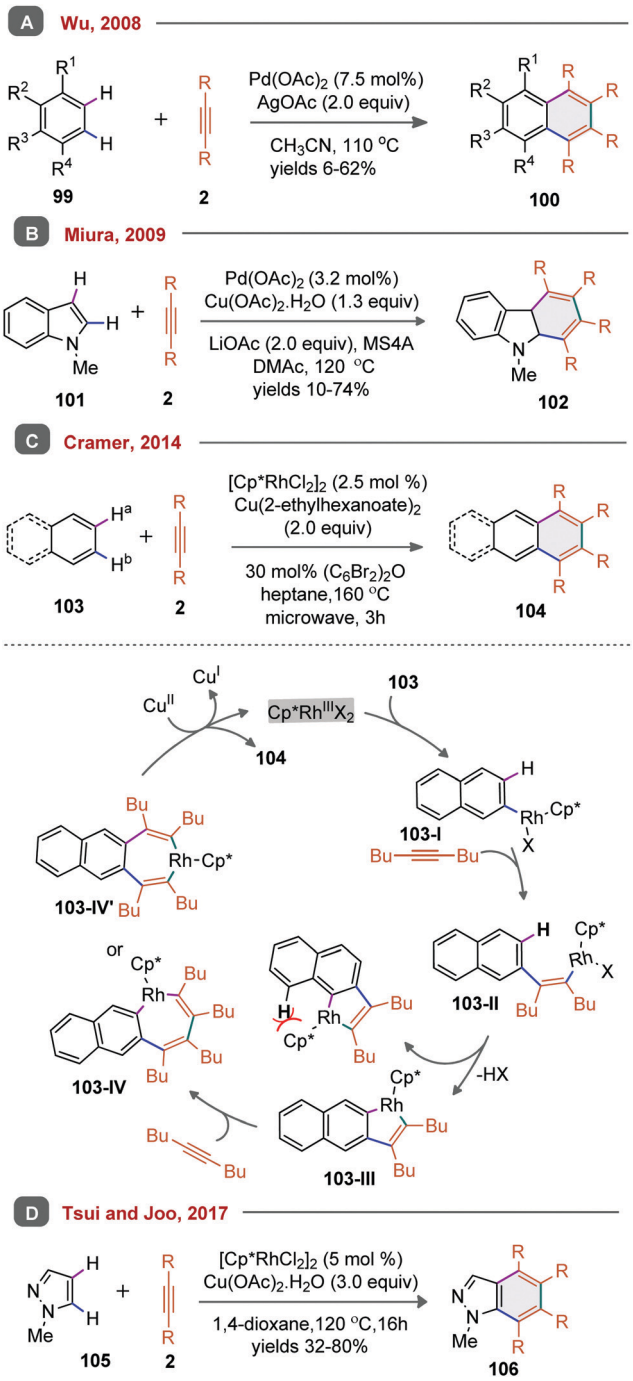
A Rh(III)-catalyzed [2+2+2]-annulation of N-acyl anilines **95** with alkynes was successfully demonstrated by the Zhang group in 2016 (Scheme 29A-V).[56] The transformation happens with the cleavage of adjacent C–H and C–N bonds and the traceless acylamino DG.

Two years later, the Tanaka group showed a non-oxidative [2+2+2] annulation of *N*-(1-napththyl)acetamide **96** with two alkynoates; the use of electron deficient Rh(III)-catalyst **98** makes the reaction successful (Scheme 29A-VI).[57] However, most of the reactions essentially require a stoichiometric or super stoichiometric amount of oxidant (a main drawback of the synthetic method).

Recently, the Ackermann group developed an elegant electrocatalytic method for the synthesis of 1,2,3,4-tetrasubstituted naphthalene derivatives **91** in the site-selective double annulation of aryl boronic acids **94** with alkynes; the Rh(III)-catalyst has been used for this transformation (Scheme 29A-VII).[58]



Scheme 29 Transition-metal catalyzed directed aromatic homologation of hetero(arenes) *via* site-selective relay double annulation.



Scheme 30 Rh(III)-Catalyzed non-directed homologation of heteroarenes.

A nondirected site selective Pd-catalyzed relay C–H annulation was first reported by the Wu group in 2008 (Scheme 30A).[59] An oxidative Pd-catalyzed two-fold aryl C–H annulation of **99** with alkynes constructs a naphthalene core **100** (Scheme 30A).

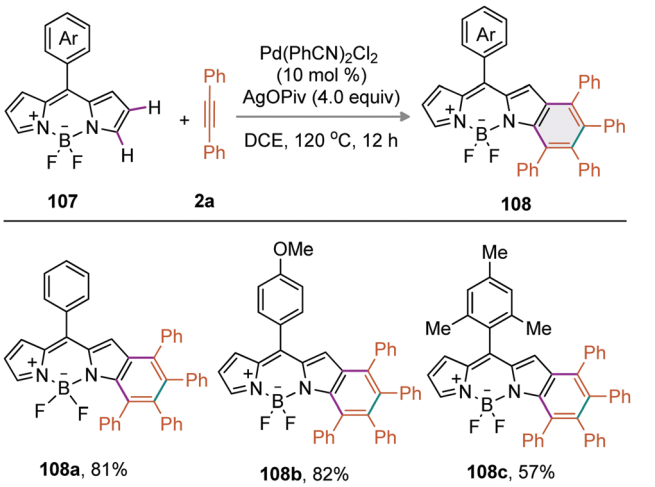
The Miura group demonstrated the synthesis of 1,2,3,4-tetrasubstituted carbazoles **102** in the Pd-catalyzed oxidative annulation of N-methyl indoles **101** with alkynes; the transformation relies on the C_2 C(aryl)–H and C_3 C(aryl)–H bond activation of **101** (Scheme 30B).[60]

In 2014, the Cramer group showcased a non-chelated two-fold C–H activation for the homologation of unbiased arenes **103** with a Rh(III) catalyst in combination with a copper(II) 2-ethylhexanoate oxidant. Besides the formation of substituted naphthalenes, this method yielded a wide range of anthracenes **104** (Scheme 30C).[61] The large polycyclic aromatic substrates like dibenzofuran, triphenylene, 9,9-spirobi[fluorene] also participated in this annulation process making complex π-conjugated molecular scaffolds. The reaction follows an identical pathway to the Satoh-Miura reaction. At first, electrophilic rhodation of sterically less hindered naphthalene **103** β-C-center forms intermediate **103-I**. Next, alkyne insertion to **103-I** followed by a second C–H activation of close proximity to vinyl-Rh species **103-II** provides **103-III**. The second alkyne insertion to **103-III** then gives a seven-membered rhodacycle **103-IV** or **103-IV′**, which finally undergoes reductive elimination to the surface homologated anthracene product **104** (Scheme 30C).

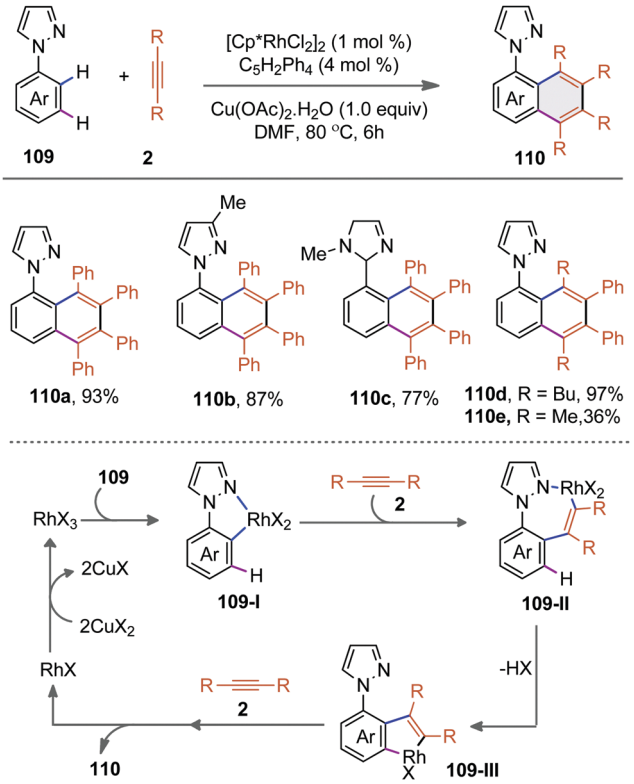
The Tsui and Joo groups used the identical non-chelation assisted C–H activation strategy for the synthesis of indazoles **106** from the direct annulation of pyrrole **105** with internal alkynes under palladium catalysis (Scheme 30D).[62]

The You and Lan groups described Pd-catalyzed double B-type C–H annulations of BODIPY's **107** with alkynes to build a series of benzo[*b*]-fused BODIPY system **108** (Scheme 31).[63] The reaction showed a broad substrate scope and good-selectivity. The annulated BODIPYs displayed red-shifted fluorescence emissions, high Stokes shifts, and fluorescence quantum yields.

In 2008, the Miura group developed a Rh(III)-catalyzed relay double annulation of *N*-phenyl pyrazole **109** with alkynes (Scheme 32).[64] The aromatic homologation for B-type annulation involves a [2+2+2]-cycloaddition of consecutive *ortho*- and *meta*-C–H bonds of **109**. The annulation makes photo physically active (1,2,3,4-tetraaryl-naphthalen-5-yl)azoles **110**. To begin with, N-assisted *o*-C–H rhodation of **109** forms a 5-membered rhodacycle **109-I**. Next, migratory insertion of alkyne to **109-I**



Scheme 31 Pd-Catalyzed C–H annulation of BODIPYs with alkynes.



Scheme 32 Rh(III)-Catalyzed relay annulations of phenylazoles.

gives *N*-anchored 7-membered intermediate **109-II**. The relay *meta*-C–H activation of **109-II** then delivers intermediate **109-III**. Finally, insertion of a second alkyne to **109-III** and then reductive elimination produces the homologation product **110** (Scheme 32). As usual, Cu-salt helps regeneration of the active Rh(III) catalyst in the final reductive elimination step.

Inspired from the pioneering Miura's discovery of directed site-selective relay annulations, a large range of one-pot arene homologation reactions have been subsequently developed for the construction of novel π-extended molecular skeletons (depicted in Scheme 33). In 2010, the Miura group revealed the anionic phenol –OH directed Rh(III)-catalyzed [2+2+2] annulation of 2-phenyl phenol derivative **111** with an alkyne to yield **112** (Scheme 33A-I).[65]

Likewise, the Wu group developed Pd(II)-catalyzed amide assisted two-fold annulations of **113** with alkynes to build highly substituted naphthalenes **112** (Scheme 33A-II).[66]

Highly substituted quinolones are accessed from the oxidative double annulation of pyridines **114a** and alkynes under the Rh(III) catalyst (developed by the Li group; Scheme 33A-III).[67]

The Carretero group reported high site-selective pyridyl directed two-fold C–H annulation of challenging picolinamides **114b** for the construction of isoquinoline derivatives (Scheme 33A-IV).[68]

The You group extended this method for the synthesis of axially chiral biaryls **115** through relay-double annulation of arenes under the directing ability of isoquinoline and 2-pyridine motifs in Rh(III)-catalyst (Scheme 33A-V).[69]

In 2016, the Miura group developed relay-double annulation of thiophen-2-carboxamides **116** with alkynes for the synthesis of benzo[*c*]thiophenes **112** (Scheme 33A-VI).[70] These compounds exhibited strong solid-state fluorescence and are attractive materials for organic field effect transistors (OFETs) as well as organic light-emitting diodes (OLEDs).

The Huang and Chatani groups have independently reported Ni-catalyzed 8-aminoquilonine (AQ) directed [2+2+2] annulation of arenes **114c** with alkynes to construct **117** (Scheme 33B).[71] In the case of Huang, the combination of $Ni(cod)_2$ and an electron rich phosphorous ligand is useful for this transformation. The high electron density on the nickel center slows down the reductive elimination for C–N bond formation; the DG dissociation from the Ni-species possibly triggers the second relay *meta*-C–H metalation and annulation. The reaction does not require an external oxidant as *ortho*-C–H nickelation *via* σ-bond metathesis forms Ni–H species. And diphenylacetylene acts as a terminal oxidant for the generation of the C–H insertion nickel intermediate. In contrast, Chatani's method uses a Ni(II)/NHC catalyst. The transformation involves an identical mechanism suggested by Huang.

The Rh(III)-catalyzed oxidative relay-double benzannulation of *N*-adamantyl-1-napththylamines **118** with alkynes has been independently reported by Zhang, Yu, and Bao groups (Scheme 33C-I).[72] The sterically hindered adamantoylamino DG restricted *peri*-C–H bond activation and annulation leading to benzoindole formation and also the *ortho*-C–H bond cleavage for the synthesis of benzoquinolines (Scheme 33C-I).

A pyridine directed Rh(III)-catalyzed relay-double annulation of N-aryl pyridone **120** with alkynes delivered peripheral extended quinolones **121** (emanated from the Patra and Samanta groups in 2017, Scheme 33C-II).[73]

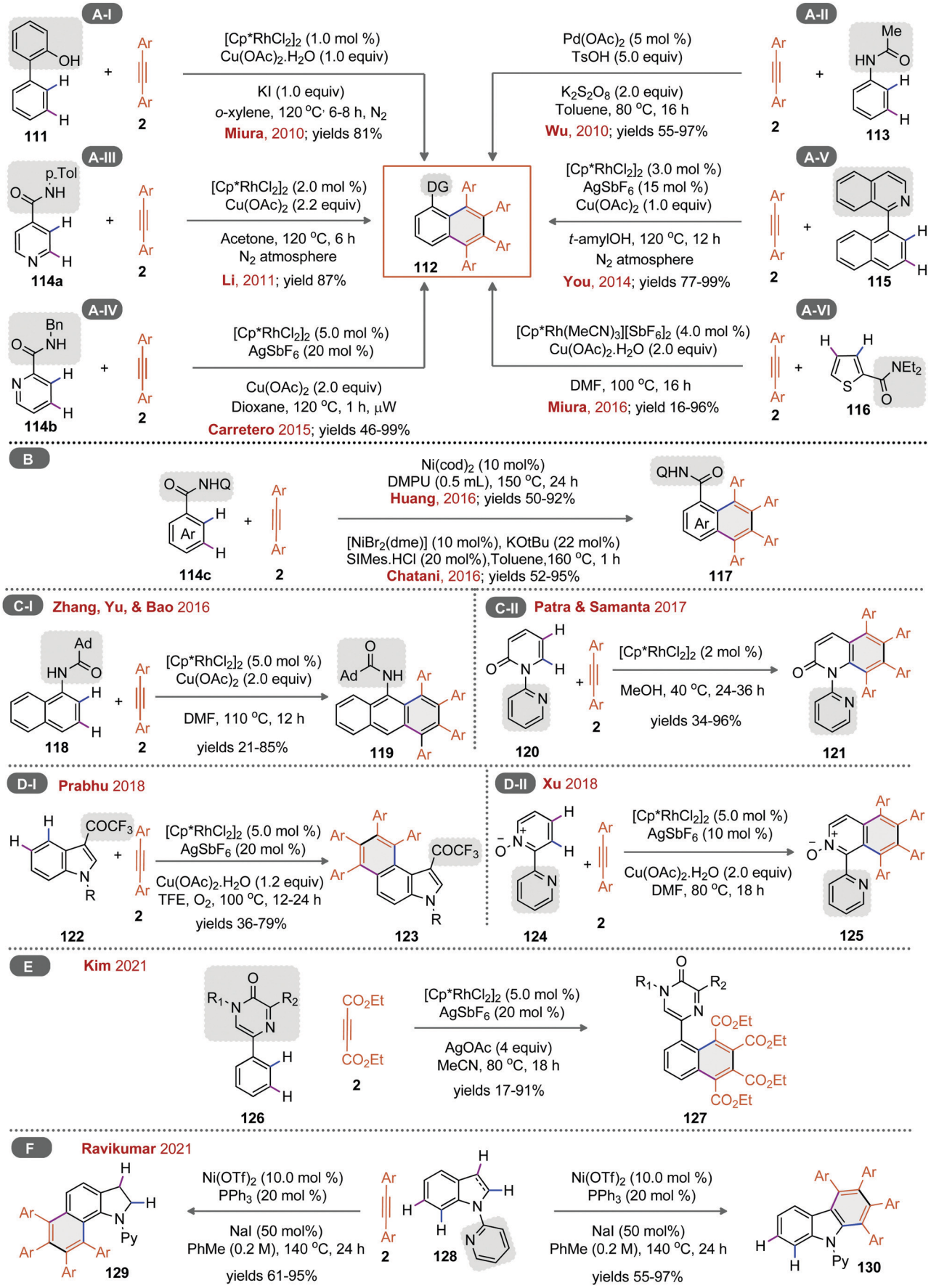
In 2018, the Prabhu group disclosed a trifluoromethyl ketone directed C4- and C5–C–H activation of indole **122** and double annulation with alkynes to produce benzo[*e*]indole frameworks **123** (Scheme 33D-I).[74]

The Xu group also reported the synthesis of 5,6,7,8-tetrasubstituted-1-(pyridine-2-yl) isoquinoline 2-oxide **125** through dual C–H bond activation of 2,2′-bipyridine *N*-oxides **124** and annulation with alkynes (Scheme 33D-II).[75]

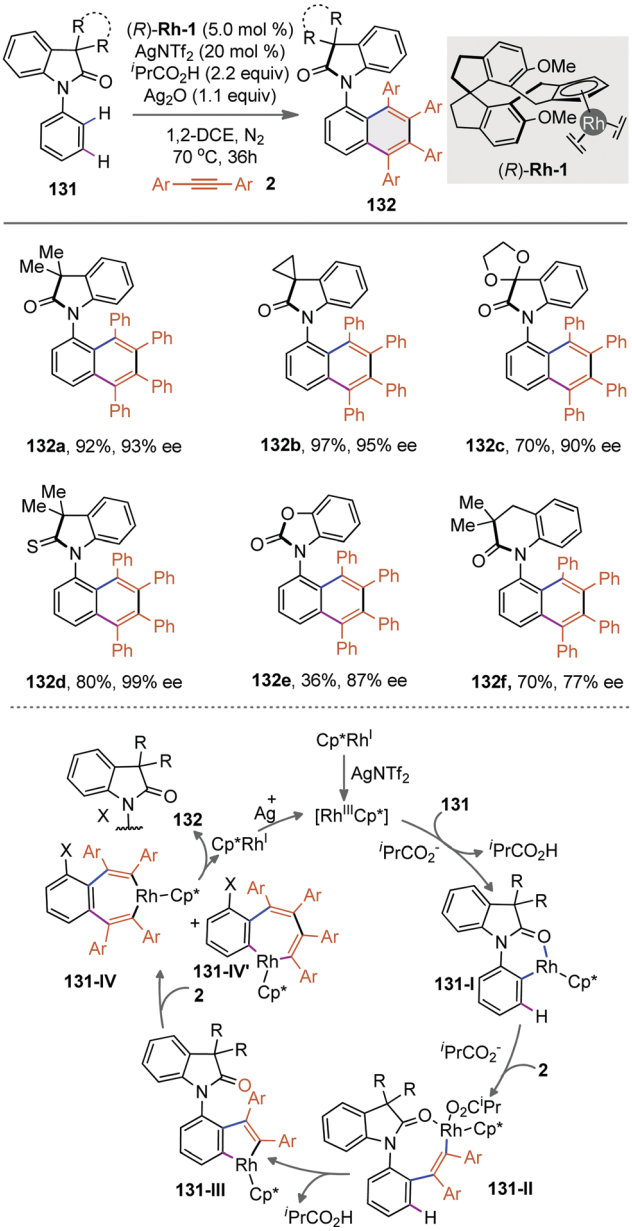
Recently, the Kim and Ravikumar groups developed an 'N'-directed similar kind of homologation of hetero(arenes) under Cp*Rh(III) [**126** → **127**] and Ni(II) [**128** → **129** and **130**] catalysts (Scheme 33E-F).[76]

The Satoh–Miura reaction was further implemented by the Wang group for the enantioselective synthesis of C–N axially chiral *N*-aryloxindoles **132** (Scheme 34). Quite good to excellent yields along with high enantioselectivity are achieved. The chiral spiro-Cp*Rh catalyst developed by the group of You is used in this transformation (Scheme 34).[77] To begin with, $AgNTf_2$ mediated oxidation of chiral $CpRh^{I}$ makes $CpRh^{III}$ an active catalyst.

Then, the amide oxygen assisted C–H rhodation of **131** forms a 5-membered diastereoselective rhodacycle **131-I**. Next, migratory insertion of an alkyne to **131-I** gives O-anchored 7-membered intermediate **131-II**. Next relay *meta*-C–H activation



Scheme 33 Transition metal catalyzed directed aromatic homologation of hetero(arenes) *via* relay annulation.



Scheme 34 Atrop-selective synthesis of C–N axially chiral *N*-aryloxindoles *via* aromatic homologation.

of **131-II** then delivers intermediate **131-III**. Finally, insertion of a second alkyne to **131-III** forms **131-IV**/**131-IV′** and then enantioselective reductive elimination produces the C–N axially chiral homologation product **132** (Scheme 34). As usual, Cu-salt helps to regenerate the active Rh(III) catalyst in the final reductive elimination step.

2.4. Double B-type annulation

The double aromatic homologation by four-fold C–H activation is also possible in the presence of a suitable directing group and catalyst. Both *o*/*o′* and *m*/*m′* C(arene)–H bonds could be activated in this 1 : 4 annulation reaction for the synthesis of anthracene derivatives (Fig. 9).

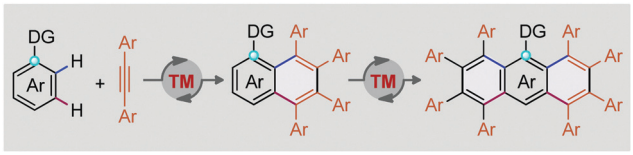


Fig. 9 Transition metal-catalyzed double aromatic homologation.

The Miura group for the first time discovered a double homologation reaction by four-fold C(aryl)–H activation with the insertion of four alkynes (1 : 4 coupling) in 2008. Thus, Rh(III)-catalyzed oxidative four-fold annulation of 1-phenylazole (**133**) with alkynes delivered anthrylazoles **134** in moderate yield (Scheme 35). An identical strategy has been further implemented for the construction of π-extended anthracene derivatives. These compounds exhibit solid state fluorescence and intense luminescence properties (Scheme 35).[78]

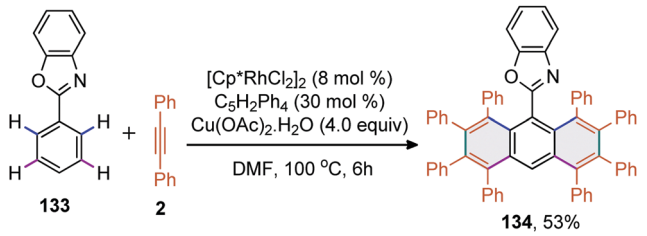
Recently, Matsunaga and co-workers demonstrated Ir(III) catalyzed four-fold annulation of benzamides **135** with alkynes to provide enlarged aromatic homologation anthracene products **136** (Scheme 36).[79] Various amide-bearing cyclopentadienyl anchored Ir(III) catalysts were prepared and screened. Interestingly, the catalyst **Ir-I** was found to be suitable for providing densely substituted unusual anthracene derivatives in good yields. Moreover, successive first and second aromatic homologation reactions using different alkynes have been achieved for the synthesis of unsymmetrically substituted anthracene derivatives (Scheme 36).

A new cascade of consecutive B-type annulations of picolinamide derivatives **137** with 1,3-diynes **138** under Rh(III)-catalysis has been developed by the Carretero group in 2019 (Scheme 37).[80] This annulation uses two 1,3-diyne units to assemble π-extended heterocycles. The reaction involves a double alkyne insertion intermediate **137-I** followed by reductive elimination *via* electron transfer between two metals and electrophilic cyclization (intermediate **137-II**) sequences.

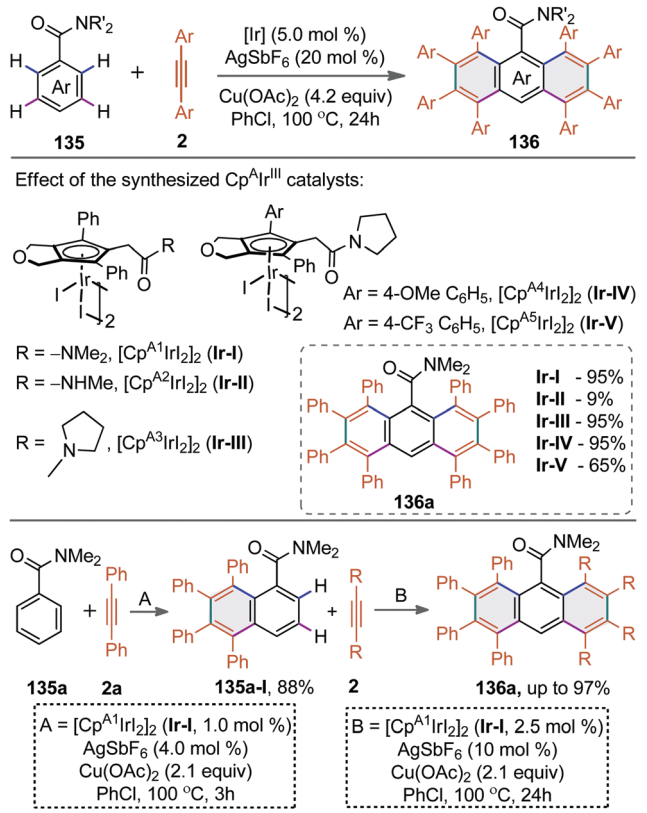
3. L–Y type unsymmetrical multiple annulation

The unsymmetrical multiple annulations *via* three-fold C–H activation in a L–Y type fashion is also possible in the presence of a suitable directing group and catalyst. In such cases, first, o/*o′*-C–H annulation provides the Y-type DA product as an active intermediate **I** (Fig. 10). Subsequent annulation of the *o*-C(arene)–H bond of close proximity with the heteroatom of the Y-type DA product delivers the desired L–Y type triannulation product (Fig. 10).

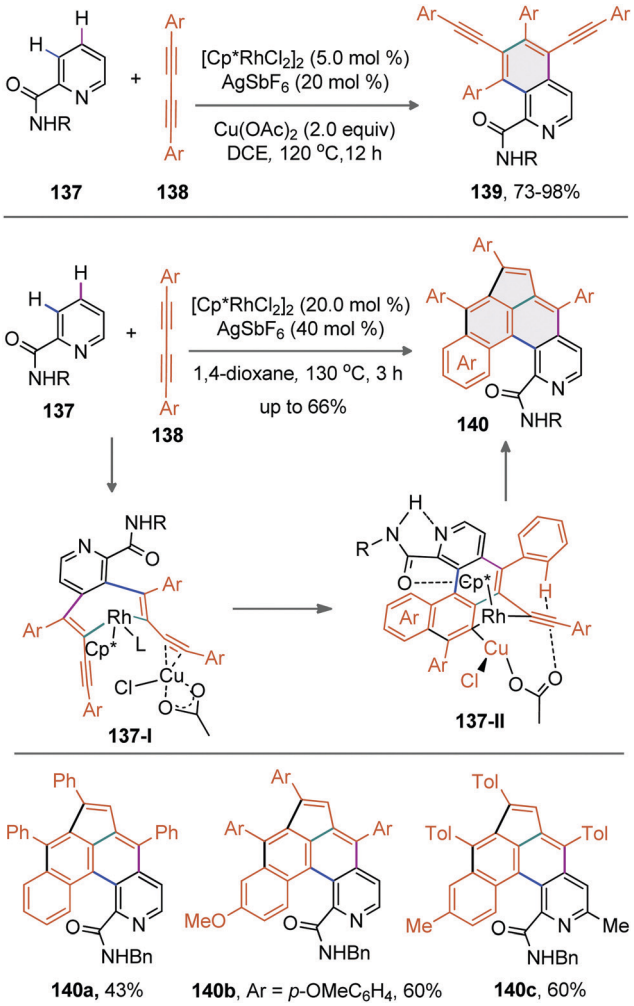
In 2014, Cheng and co-workers developed a pioneering approach to access highly functionalized and π-conjugated naphthyridine-based polyheterocycles *via* Rh(III)-catalyzed multiple C–H annulation of *N*-hydroxybenzamidines **141** in a single-pot (Scheme 38).[81] The annulation of *N*-hydroxybenzamidines **141** with unactivated alkynes begins with the coordination of oxime nitrogen with Rh(III)-species to provide five-membered rhodacycle



Scheme 35 Synthesis of anthrylazoles *via* Rh(III)-catalyzed 1 : 4 coupling of phenylazoles with alkynes.



Scheme 36 Ir(III)-Catalyzed double aromatic homologation of benzamides with alkynes.



Scheme 37 Rh(III)-Catalyzed cascade C–H annulation of picolinamides with 1,3-diynes.

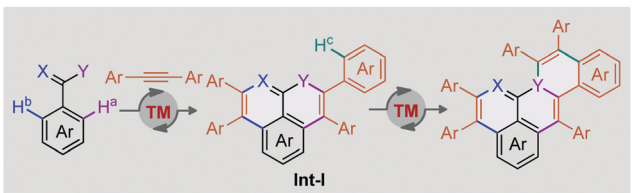
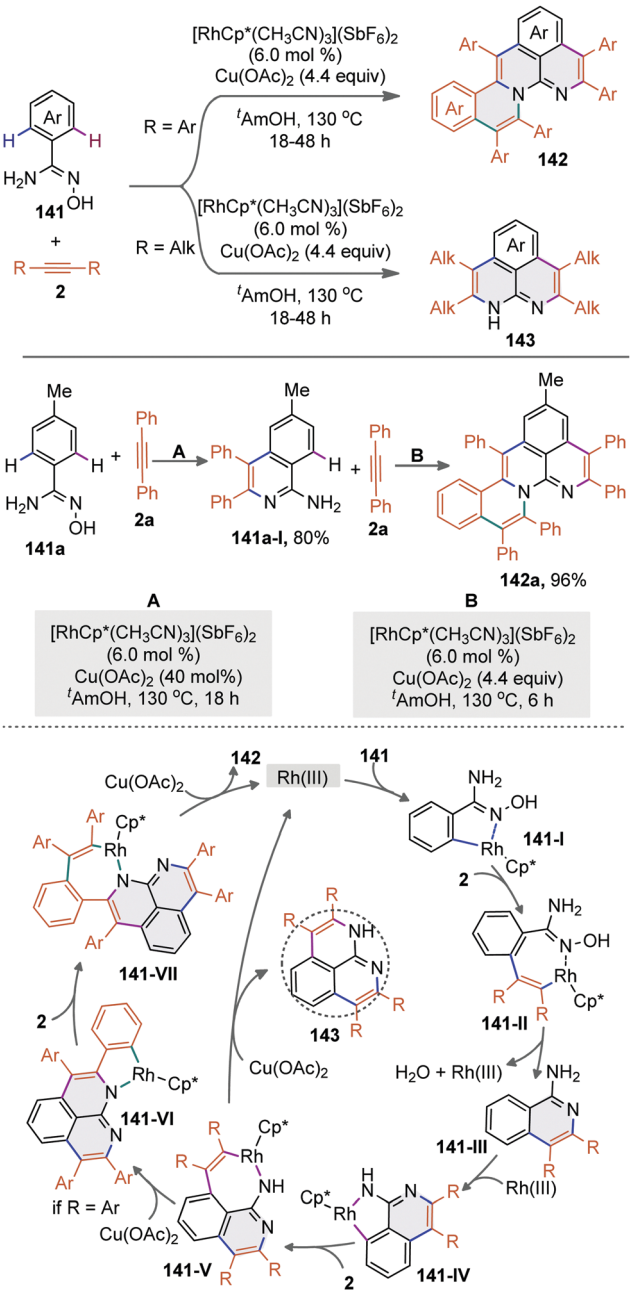


Fig. 10 Design for the synthesis of the L–Y type triannulation product.

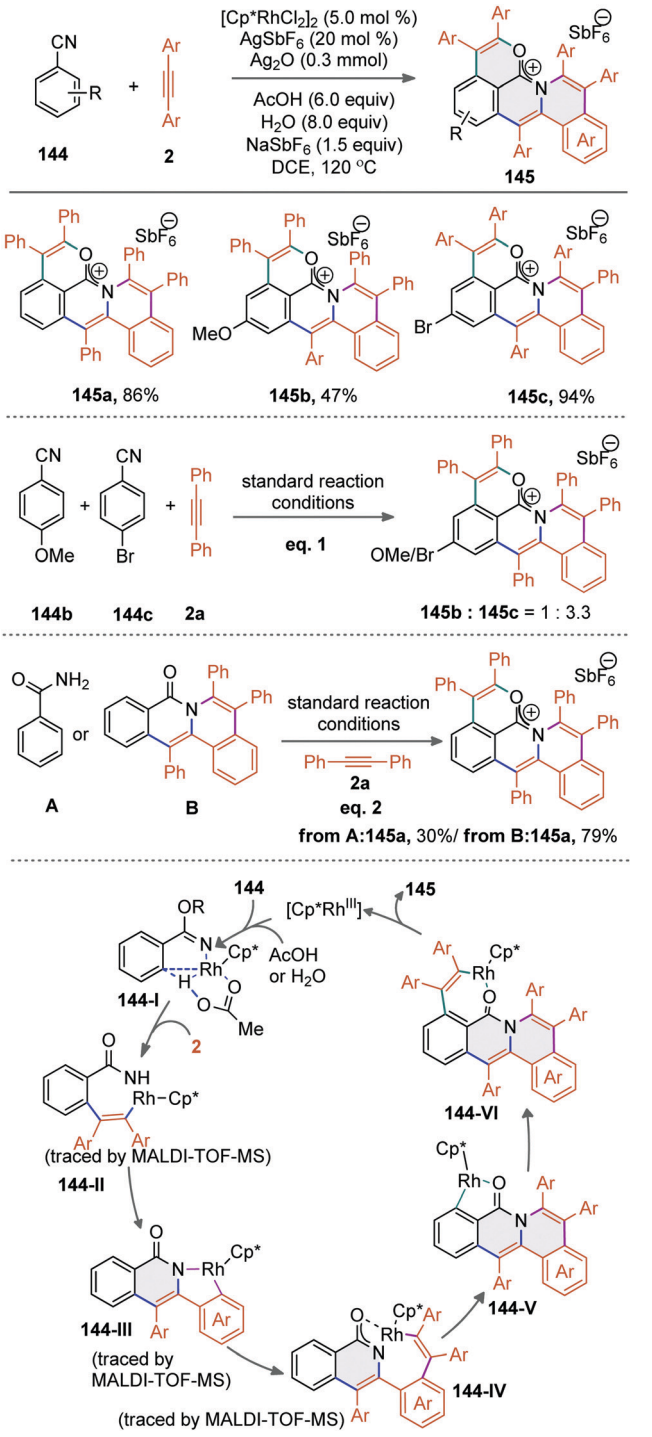
intermediate **141-I.** Next, the migratory insertion of alkyne to **141-I** followed by reductive elimination gives rise to the mono-annulated intermediate **141-II.** The concurrent oxidative cleavage of the oxime N–OH bond in **141-II** then regenerates the Rh(III)-catalyst. Next, coordination of Rh(III)-species with amine "N" of intermediate **141-III** and *peri*-C–H activation generates **141-IV.** Alkyne insertion to **141-IV** and $Cu(OAc)_2$ mediated reductive elimination of **141-V** provides double annulated intermediate **141-VI.** The third annulation of **141-VI** with alkynes follows a similar pathway; thus, "N"-chelation to Rh(III)-catalyst, C(arene)–H bond activation of close proximity, alkyne migratory insertion, and $Cu(OAc)_2$ promoted reductive elimination builds L–Y-type triannulation manifold **142** (Scheme 38). The isolation of Y-type DA product **143** from the reaction of **141** with dialkylalkyne justifies the reaction pathway detailed in Scheme 38.

In 2018, the You group demonstrated a multi-fold C–H activation/annulation cascade of **144** to access structurally diverse PAH carbocations *via* an intramolecular Rh migration sequence (Scheme 39).[82]

Thus, a Rh(III)-catalyzed three-fold C–H activation followed by the [4+2] annulation cascade of arylnitriles with alkynes provided structurally diverse heteroatom stabilized PAH carbocations. The transformation was general; a wide range of arylnitriles (irrespective of substituents on different positions of arene) even heteroaryl thienylnitriles successfully participated (Scheme 39).



Scheme 38 One-pot di/tri-annulation of *N*-hydroxybenzamidines with alkynes.

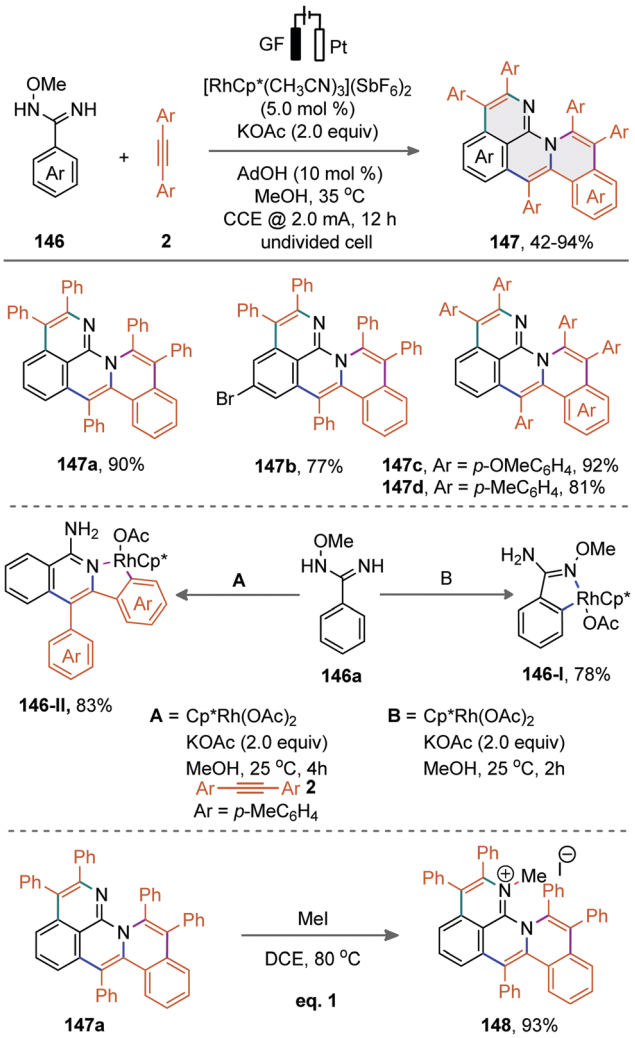


Scheme 39 Rh(III)-Catalyzed three-fold annulation of arylnitriles.

Identical reaction pathways for the Y and L-type annulation process are independently involved as detailed in (Scheme 38). The carbenium manifolds show tunable fluorescence emission, low cytotoxicity, and the ability to specifically target lysosomes.

An electrocatalytic Rh-catalyzed three-fold C–H annulation of *O*-methylamidoxime **146** with alkyne has been emanated from Ackermann and co-workers (Scheme 40).[83] The sensitive functional groups, *i.e.* iodo, azide, trimethylsilyl (TMS), *etc.* were well tolerated and did not affect the reaction outcome. The isolation of C–H-activated rhodacycle intermediates **146-I** and **146-II** confirms the cascade C–H activation, L-type and Y-type annulation sequence; (Scheme 40). Furthermore, the desired product **146a** upon treating with iodomethane afforded a cationic nitrogen doped nanographene **148**. The compound **148** exhibited reversible redox behaviour and could be applicable as a novel anolyte material in organic redox-flow batteries due to its low $E_{1/2}$ value (−1.72 V *vs.* ferrocene).

In 2014, the Shi group reported Rh(III)-catalyzed oxidative multiple annulations of aryl ketoximes **149** with diarylacetylene

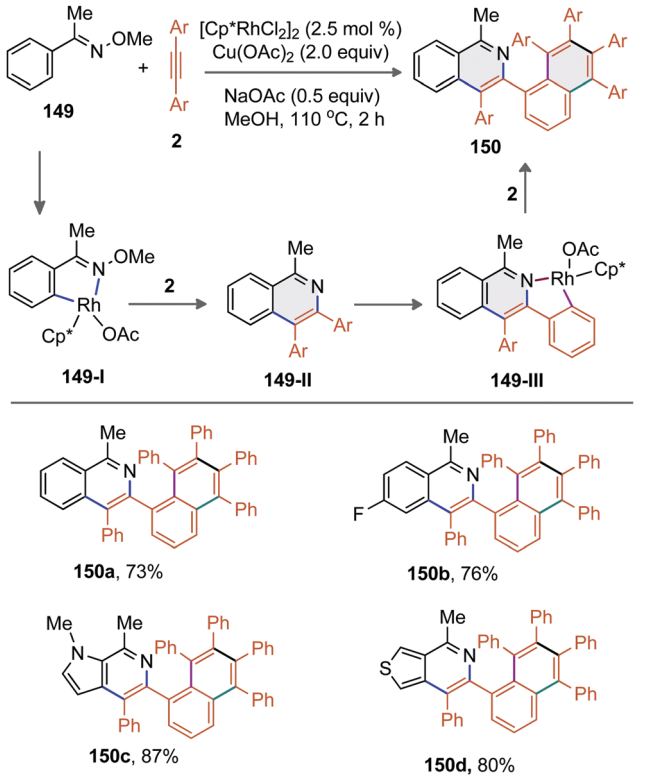


Scheme 40 The electro-catalyzed domino C–H annulations of arenes ('GF' means graphite felt anode).

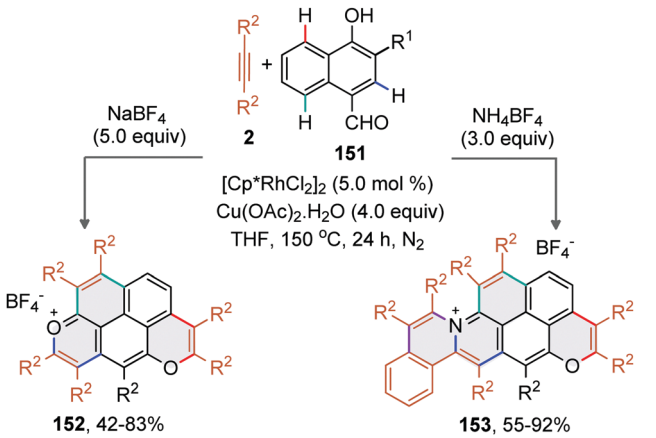
(**2**) to construct highly congested 1-methyl-4-phenyl-3-(5,6,7,8-tetraphenyl-naphthalen-1-yl) isoquinolines (**150**) (Scheme 41).[84] The reaction involves oxime directed Rh(III)-catalyzed monoannulation of **149** to produce isoquinoline intermediate **149-II** *via* **149-I**. Next, a B-type double annulation of the phenyl-moiety in **149-II** with two molecules of alkyne delivered **150**. The coordination of the isoquinoline N-moiety to the Rh(II)-species plays a vital role. The reaction efficiency, better functional group compatibility, and scalability make the transformation synthetically viable.

4. Miscellaneous BLY-type multiple annulation

A recent elegant demonstration by the You group unveils the synthesis of complex polycyclic pyrylium **152** and pyridinium **153** fluorophores (Scheme 42). A one pot triple C–H annulation of 4-hydroxy-1-naphthaldehydes (**151**) with alkynes worked under the influence of an Rh-catalyst.[85] This strategy could



Scheme 41 Rh(III)-Catalyzed cascade oxidative multiple annulation of aryl ketoximes with diphenylacetylene.



Scheme 42 BLY-type divergent multiple annulations.

successfully construct unusual O-/N-doped PAH salts **152** and **153** (Scheme 42). These π-conjugated PAHs exhibited strong fluorescence emissions 550–623 nm and are used for the HepG2 cell labelling phenomenon.

5. Conclusions

In this review, the importance of multiple C–H annulation processes for the synthesis of unusual structurally diverse π-conjugated polycycles has been discussed. The systematic

development of DG assisted TM catalyzed unsymmetrical multiple C–H annulations of arene moieties has been narrated. Based on the directed inert C(arene)–H bond activation and the mode of TM-migration, the multiple unsymmetrical C–H annulation process has been categorized into L-type, Y-type, and B-type.

Detailed investigation and insights are necessary to address the undisputed challenges in the unsymmetrical annulations. Most of the investigations are confined to developing 6-membered fused skeletons; the synthesis of 5-, 7-, and even large-rings warrants further research. Regio- and stereoselective multiple annulation strategies with unsymmetrical alkynes are rare and therefore, unconditional efforts are needed in this direction. The development of a domino annulation process for the C(sp^3)–H bonds has remained unsuccessful; thus, attention in this area is essential. The asymmetric versions of identical transformations that allows assembling optically active carbo- and hetero-cycles have so far been poorly displayed. We believe this comprehensive review of unsymmetrical multiple annulation of C(arene)–H bonds will encourage researchers to discover novel synthetic methods in this challenging area.

Author contributions

A. S., M. S. and S. S. contributed to conceptualizing the contents in the manuscript. Editing and supervision were done by A. K. S.

Conflicts of interest

There are no conflicts to declare.

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