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Advances in transition-metal catalyzed C–H bond activation of amidines to synthesize aza-heterocycles

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Amidine compounds, as important nitrogen analogues of isoelectronic carboxylic acids, are found throughout biologically active molecules and serve as the most attractive precursors for the synthesis of *N*-containing compounds. In this review, the advancements in the synthesis of aza-heterocycles *via* transition-metal catalyzed C–H bond activation of amidines have been summarized through diverse annulation reactions. Amidines act as two-electron donors *via* the more basic and less sterically crowded imino lone pair and coordinate with transition-metals, in which N–H imine could act as both directing group and intramolecular nucleophile, electrophile or proton acceptor. The mechanisms of different annulation pathways will be highlighted in this review along with a discussion of more recent developments in the field.

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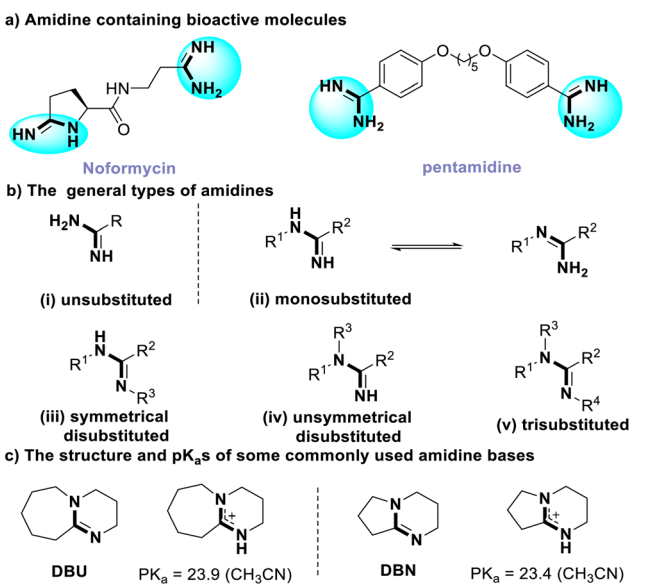
1 Introduction

Aza-heterocycles, as common fragments of the vast majority of clinical drugs and candidates of medicinal targets, have made notable contributions to the quality of human life.[1,2] Therefore, the diversity of aza-heterocyclic structures, as well as the important biological and pharmaceutical applications, motivated researchers to develop efficient, atom economical and selective transformations to access aza-heterocycles. Amidines, as important nitrogen analogues of isoelectronic carboxylic acids, are found throughout biologically active molecules and among the most attractive precursors for the synthesis of *N*-containing compounds (Scheme 1a).[3] The molecular structure confirmation of amidines dates back to 1858, reported by Gerhardt, through the reaction of aniline with *N*-phenylbemimidyl chloride and named.[4] Subsequently, Shriner noted that there were five general types of amidines classified according to the number and distribution of the substituents at the nitrogen atoms, including (i) unsubstituted, (ii) monosubstituted, (iii) symmetrical disubstituted, (iv) unsymmetrical disubstituted and (v) trisubstituted (Scheme 1b).[5] Especially, amidines contain an amino nitrogen atom with a free electron pair, which conjugate with the π-electrons of the C=N double bond. It combines the properties of an azomethine-like C=N double bond with an amide like C–N single bond with a partial double bond character as indicated by the resonance form (Scheme 1b(ii)).[6] For more than 160 years, amidines have proven to be irreplaceable building blocks and ranked as one of the most important classes of nitrogen reagents in organic chemistry because of their versatile chemical properties.[7] For example, they are strongest neutral organic bases due to the ability of their protonated forms to delocalise charge over two nitrogen atoms.[8] These bases, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) have been



Scheme 1 Examples of drug molecules containing amidine, bases and the general types of amidines.

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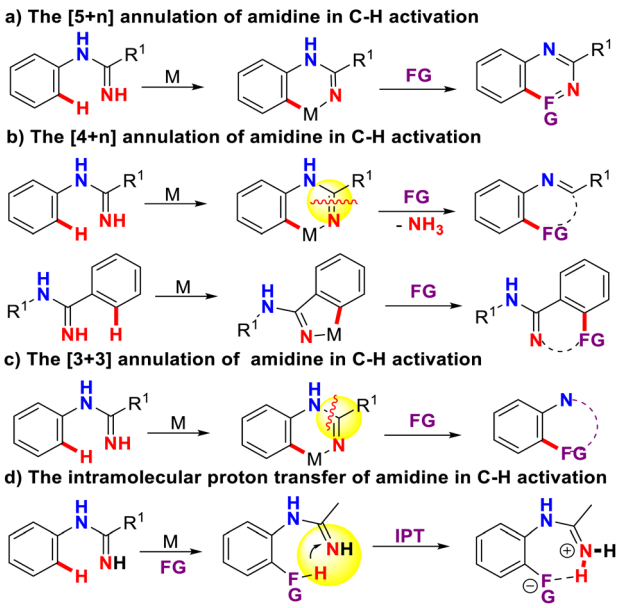
widely used in numerous organic reactions and have often been shown to be advantageous when compared with other organic bases (Scheme 1c).

Transition-metal catalyzed C–H bond activation has gained great attention in the past decade and become one of the most reliable tools for synthesis of *N*-heterocycles.[9,10] Among this family, the directing groups (DGs) are generally required to resolve the regio-selectivity and improve the catalytic activity of metal.[11] For example, the pyridines[12] and oximes[13] are used as DGs to realized C–H bond activation through coordinating with transition-metal. However, a single reaction sits will bring chemical trace left in the products, which leads to undesired waste-products. Based on that, the commercially available amidines have attracted intensive interest as DGs to synthesize *N*-heterocycles, because amidines act as two-electron donors *via* the more basic and less sterically crowded imino lone pair and coordinate with transition-metal, in which N–H imine could act as both directing group and intramolecular nucleophile or electrophile. However, multiple activity reaction sites of different substitutive amidines not only presented a challenge for the synthetic chemistry but also offered the opportunity to obtain an array of different *N*-heterocyclic compounds. Generally, according to the principal resonance structures of amidines, the transition-metal catalyzed C–H bond activation of amidines takes the following mainly four chemical transformations (Scheme 2): (a) the N–H imine acts as intramolecular nucleophilic group to promote the [5 + *n*] annulation progress; (b) the metal-X (X = C, N) or nucleophilic reagent undergoes migratory insertion into the C=N bond (acting an electrophilic group) or the N–H imine acts as intramolecular nucleophilic group, leading [4 + *n*] annulation progress; (c) nucleophilic reagent undergoes migratory insertion into the C=N bond, resulting in [3 + 3] annulation and the cleavage of C–N bond; (d) the N–H imine is used as the proton acceptor to promote intramolecular proton transfer (IPT) process. Based on its recent advances, it would be timely to provide a comprehensive review of the plethora of transformations in the field of C–H functionalization.

The previous reviews[14] mainly summarized the preparation, structural studies and synthetic application of amidines. In this review, we summarize and unify the development of the transition-metal catalyzed C–H bond activation of amidines to synthesize heterocyclic compounds since 2008. The critical goal of our review is to draw attention to this burgeoning research area, and stimulate further interest from the synthetic community in discovering novel reactivities as well as multidisciplinary application. We feature the recent development of transition-metal catalyzed C–H bond activation of amidines to synthesize *N*-heterocycles through diverse annulation models.

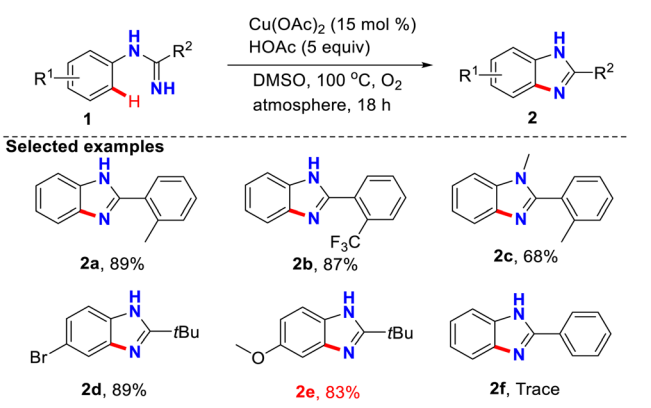


Scheme 2 The strategies of C–H bond activation of amidines.

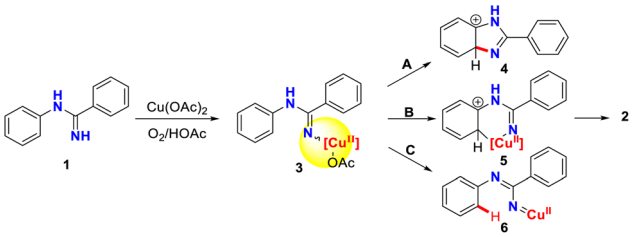
2 The [5 + *n*] annulation of amidines in C–H activation

2.1 The [5 + 0] annulation of amidines

The earliest [5 + 0] annulation of amidines developed in the 1960s was a milestone in organic synthesis chemistry, which has been successfully applied in the selective synthesis of benzimidazoles.[15] Then, organic chemists have made significant efforts to gain insight into the mechanism of this transformation[16,17] until C–H activation comes into view. As early as 2008, Buchwald group[18] firstly reported an efficient copper-catalyzed C–H functionalization/C–N bond-forming approach, providing benzimidazoles in good yields from *N*-phenylbenzamidines (Scheme 3). Various benzimidazoles could be easily obtained with high step economy. This method could be extended to the preparation of *N*-methylated 2-phenylbenzimidazoles. Meanwhile, the bulky *tert*-butyl group was also compatible in this transformation, affording the corresponding products in 83–89% yields. However, the functionalized amidines without *ortho* substituents showed less reactivity to give the desired benzimidazole, primarily underwent decomposition, which seemed to inhibit the catalytic cycle.



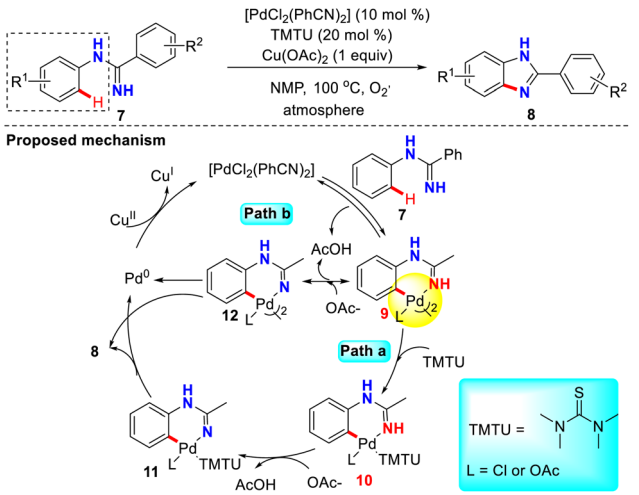
Scheme 3 Cu-catalyzed intramolecular annulation of *N*-phenylbenzamidines.



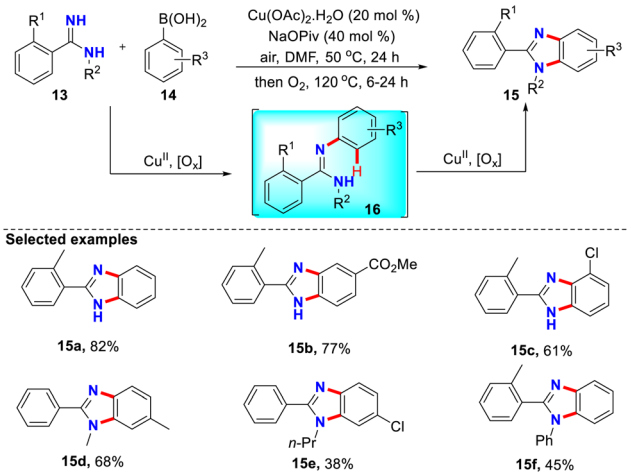
Scheme 4 The possible reaction pathways for the conversion of **1** into **2**.

On the basis of the previous reports,[19] the possible reaction pathways were proposed in Scheme 4. First, the $Cu(OAc)_2$ presumably led to a Cu–N adduct **3** with copper either in oxidation state II or III. Subsequently, the *N*-aryl ring attacked the amidine moiety in a fashion similar to an electrophilic aromatic substitution to form **4** with concurrent release of a reduced copper species in pathway **A**. The rearomatization of intermediate **4** provides the product **2**. In pathway **B**, the *N*-phenyl ring attacks the copper center in **3** to give a metallacycle **5**, which underwent rearomatization and reductive elimination of the metal to form **2**. Pathway **C** involves a copper nitrene. A concerted insertion of the nitrogen into a C–H bond or an electrocyclic ring closure and a final [1,3]-shift of a hydrogen would then lead to **2**.

One year later, Shi and co-workers[20] developed a novel method to construct the core structure of 1*H*-benzo[*d*]imidazole through Pd^{II}-catalyzed C–H activation of *N*-phenylbenzamidines under mild reaction conditions (Scheme 5). This transformation contains a broad substrate scope, with various functional groups being well-tolerated. The detailed mechanism studies indicated that a palladacycle monomer or dimer is the key intermediate for this transformation and thiourea (tetramethylthiourea, TMTU) was first used to prompt the efficiency of C–H activation. Based on a series of control experiments, a possible reaction mechanism was depicted in



Scheme 5 Pd-catalyzed intramolecular C–H activation of *N*-phenylbenzamidines.



Scheme 6 Cu-catalyzed *N*-arylation of amidines with aryl boronic acids.

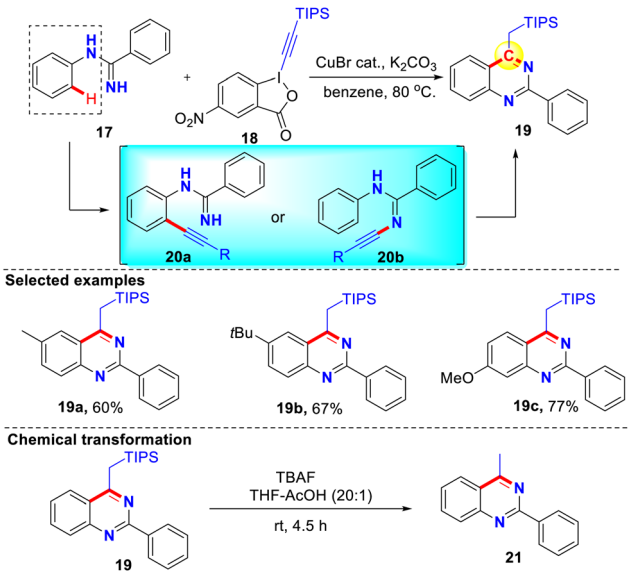
Scheme 5. Initially, the Pd^{II} coordinated with imino-group to deliver the palladacycle intermediate **9**. In Path **a**, after the decomposition of the dimeric palladacycle to produce the monomer **10** in the presence of TMTU, the acetate played a role as a base to in removing the proton of the imine group to generate intermediate **11**. The intermediate **11** underwent reductive elimination to yield the desired product **8** and Pd^0 specie, which was oxidized to the Pd^{II} by copper salt for the next catalytic cycle. In Path **b**, the palladacycle dimer **9** may also go through the direct deprotonation and reductive elimination to finish this catalytic cycle according to its observed weak reductive elimination activity.

In 2012, Zhu group[21] discovered a novel Cu-catalyzed *N*-arylation of amidines with aryl boronic acids to synthesis of benzimidazoles (Scheme 6). Unprotected amidines were compatible in this transformation, affording the corresponding products in moderate yields. Meanwhile, the *N*-arylated amidine **16** was generated *in situ* in a one-pot manner to carry out annulation reactions avoiding prefunctionalization of amines prior to the reaction.

2.2 The [5 + 1] annulation of amidines

Inspired by Wasers work,[22] Ohno group[23] deduced that the amidine group in *N*-phenylbenzamidine not only serves as a directing group for copper-catalyzed C–H alkynylation, but also forms substituted quinazoline through [5 + 1] cyclization as a nucleophilic group (Scheme 7). Otherwise, nitrogen alkynylation[24] might promote tautomerization–electrocyclization cascade[25] of **20b** to give the same quinazoline **19**.

The challenges of this strategy include predominant alkyne introduction over benzimidazole formation and and regioselective cyclization or alkynylation in the presence of two nitrogen atoms. After exploring appropriate alkyne sources for the reaction, they successfully developed a novel synthesis of quinazolines through copper-catalyzed alkynylation and [5 + 1] cyclization of *N*-phenylbenzamidine in 2010 (Scheme 7). This reaction was synthetically useful since functionalized



Scheme 7 Cu-catalyzed [5 + 1] annulation reactions of *N*-phenylbenzamidines with alkyne.

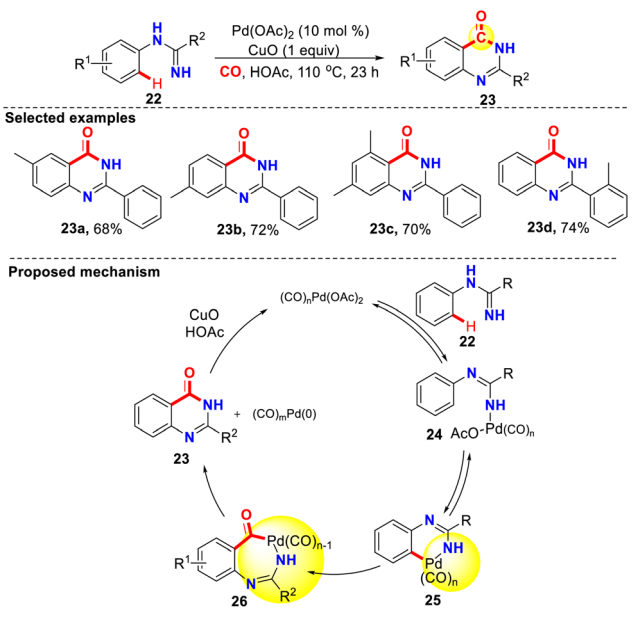
quinazolines can be directly constructed from *ortho*-unsubstituted amidines, readily prepared from commercially available anilines. Meanwhile, the reaction of **19** with TBAF in THF–AcOH (20 : 1) at room temperature led to efficient cleavage of the TIPS group to give known quinazoline **21** in 76% yield.

Subsequently, the transition-metal catalyzed C–H bond activation/[5 + 1] annulation of amidines has been made significant progress. In 2011, Zhu group[26] developed an efficient synthesis of quinazoline-4-(3*H*)-ones from *N*-phenylbenzamidine through palladium-catalyzed intramolecular C(sp^2)–H carboxamidation (Scheme 8). No atoms except protons in substrates were lost during the process. In addition, the control experiments suggested that the C–H bond activation was reversible and deuterium–hydrogen exchange occurred during the reaction. In this reaction, initial chelation of the amidine nitrogen with palladium(II) forms intermediate **24**, followed by reversible cyclopalladation. The coordinated CO inserts into the C–Pd bond in intermediate **26**, generating a seven-membered palladacycle **26**. Reductive elimination leads to the product **23** and releases Pd(0), which is reoxidized by CuO under the aid of HOAc.

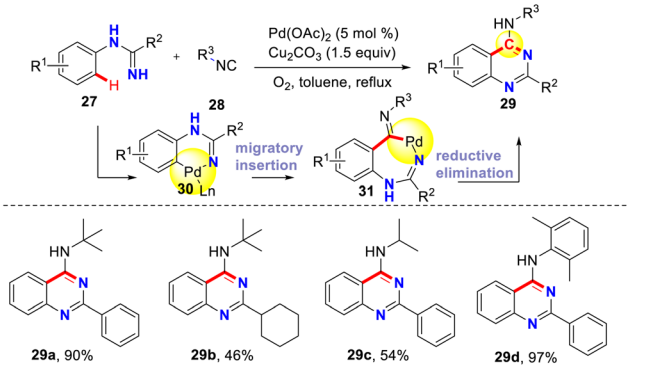
At the same year, they[27] found that the similarity of CO and isonitriles in terms of their coordination to transition metal suggested that an equivalent C–H isonitrile insertion process should be viable. Based on that, they achieved palladium-catalyzed intramolecular C–H amidination by isonitrile insertion provided direct access to 4-aminoquinazolines (Scheme 9).

After these work, various kinds of C_1 synthons were applied to this system to construct nitrogen-heterocycle derivatives. In 2013, Zhang group[28] used solvents (including DMSO, DMF, DMA, NMP, TMEDA) as methyl one carbon synthons to synthesize quinazolines through direct oxidative amination of N–H bonds and methyl C(sp^3)–H bonds followed by intramolecular C–C bond formation reactions (Scheme 10). In this reaction, the oxidation of CuX with the oxidant (such as selectfluor) provided the Cu(III) complex **34**, which underwent a C–N bond formation reaction *via* nitrene insertion into the C(sp^3)–H bond of DMSO to give the intermediate **35**. Finally, in the present of H^+, the cleavage of the C–S bond gave an iminium species **36**, which underwent an electrophilic addition reaction or electrocyclization with the aromatic ring to provide dihydroquinazolines. Subsequently, aromatic aldehydes or benzyl alcohol were found to be one carbon synthon for the synthesis of quinazoline derivatives *via* reactions of *N*-phenylbenzamidines by Zhang.[29] The CuO nanoparticles were used as efficient catalysts, and reaction showed high generality and functional group tolerance (Scheme 11).

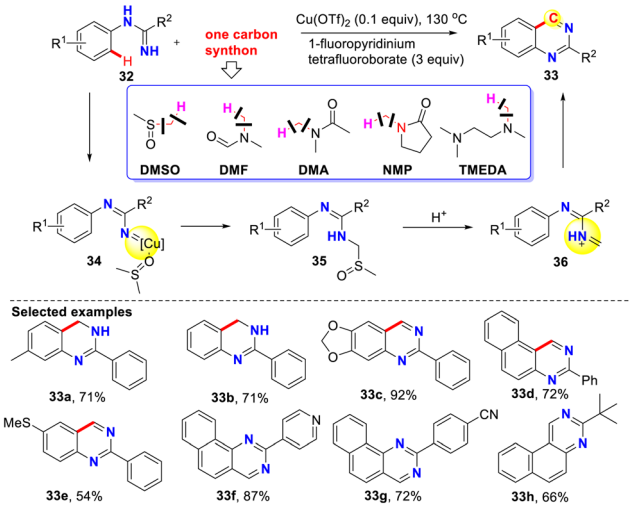
Besides Cu and Pd, the [5 + 1] annulation reaction with *N*-phenylbenzamidine could also occur through Rh(III)-catalyzed C–H activation. However, this required an appropriate C_1 synthon in reaction system and avoided the metal-X (X = C, N)



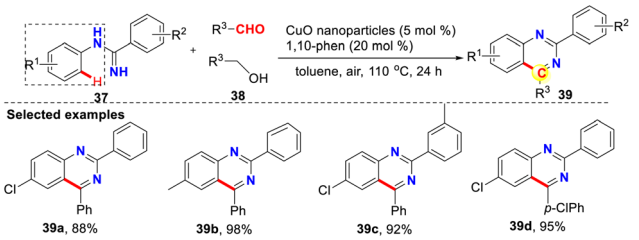
Scheme 8 Pd-catalyzed intramolecular C–H carboxamidation of *N*-arylamidines.



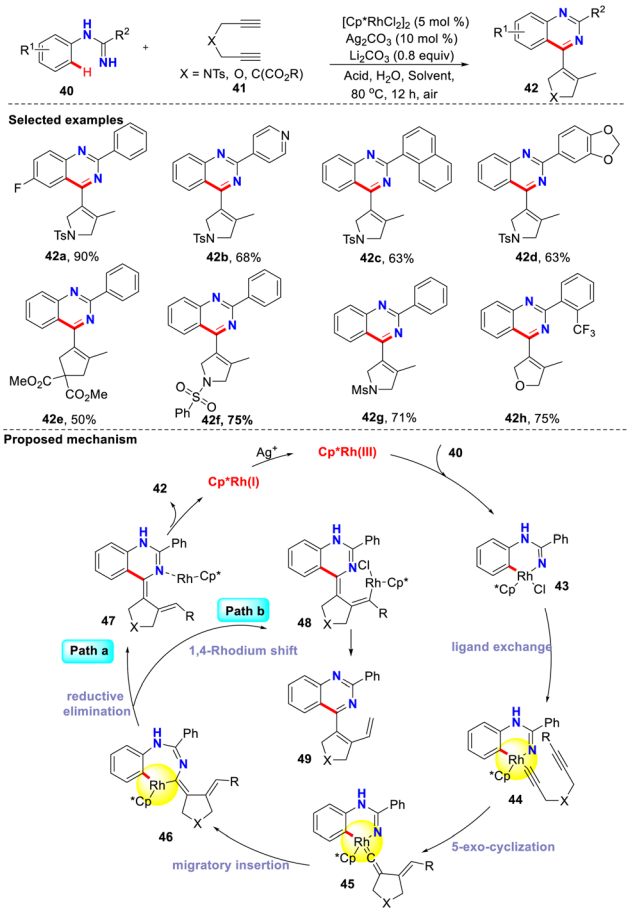
Scheme 9 Pd-catalyzed intramolecular C–H amidination of *N*-arylamidines.



Scheme 10 Cu-catalyzed [5 + 1] annulation reactions of amidines with various one carbon synthons.



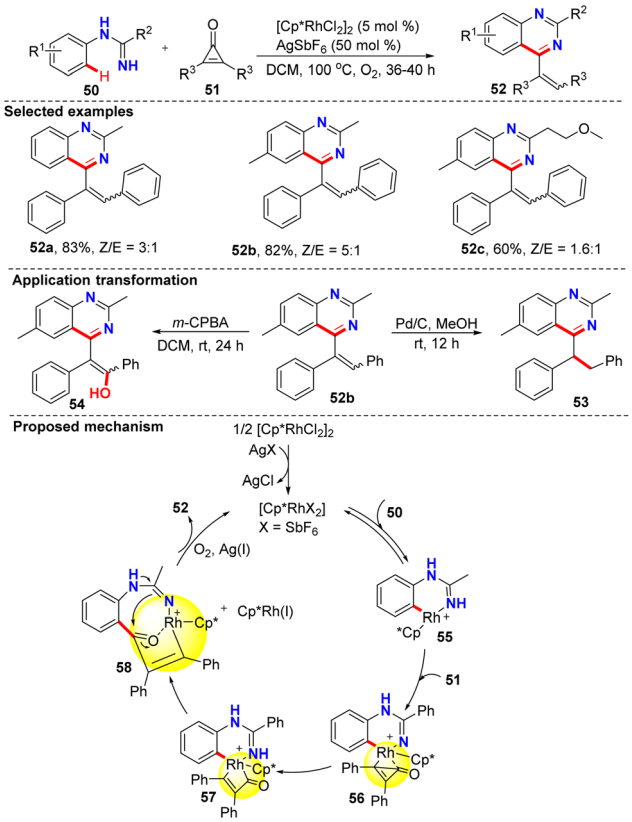
Scheme 11 Cu-catalyzed oxidative coupling of amidines with aromatic alcohols.



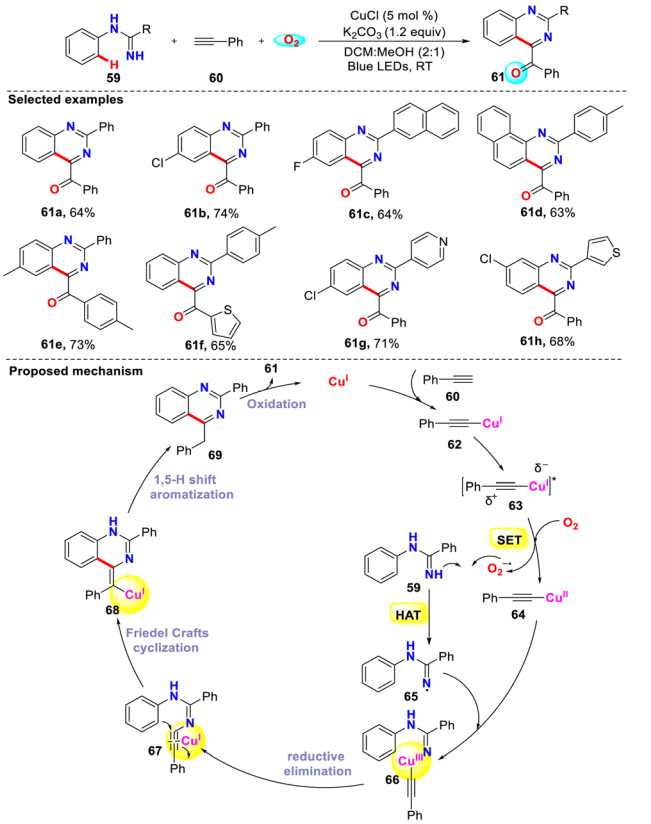
Scheme 12 Rhodium(III)-catalyzed cascade [5 + 1] annulations of amidines with diynes.

undergoing migratory insertion into the C=N bond (acting an electrophile), causing NH to be removed through subsequent elimination. In 2018, the catalytic [5 + 1] annulation/5-exocyclization reaction of amidines with diynes was reported by Du (Scheme 12).[30] Significantly, this reaction represented the first example of using diyne as a one-carbon reaction partner in C–H functionalization. The diynes were employed as new one-carbon units that efficiently enable insertion of six-membered metallacycles *in situ* and accelerate implementation of subsequent cascade reactions by another alkyne group, thereby providing a favorable driving force for resisting well-established [*n* + 2] annulations. Initially, the C–H activation at the amidine led to six-membered **43**, which then would undergo ligand exchange to deliver the intermediate **44**. The intermediate **44** generated **45** has a lower barrier, and migratory insertion of **45** generated intermediate **46**. Two distinct pathways can be speculated after the formation of intermediate **46**. In path **a**, reductive elimination of intermediate **46** gave the intermediate **47** with release of the Cp*Rh(I). Then demetalation of intermediate **47** led to the formation of desired products, which proceeded with isomerization to yield the final [5 + 1] products. Alternatively, for unsymmetrical diynes bearing the Me-group at one alkyne terminus, continuous migration insertion and a 1,4-rhodium shift of **46** followed by the subsequent β-H elimination generates dehydrogenation product in path **b**.

In 2020, Wu group[31] used cyclopropenone as coupling partner to realize rhodium-catalyzed [5 + 1] annulation reaction of *N*-arylamidines (Scheme 13). The reaction featured mild reaction conditions, wide substrate scope and high atom-economy. Cyclopropenones were employed as appealing reaction partners with the release of the ring strain being the driving force. Interestingly, *C*-benzyl imidamides underwent not only the C–H activation/annulation, but also the attached oxidation to develop 2-benzoyl quinazolines. In addition, the synthetic practicality has been highlighted in several derivatization reactions, including the alkene functionalizations by reduction and oxidation. A plausible mechanism was proposed by author. First, a six-membered rhodacyclic intermediate **55** was generated *via* coordination of **50** to the active catalyst and following cyclometalation. Subsequently, oxidative addition for the C–C bond cleavage in cyclopropenone occurs through the transition state **56** to form the Rh(v) intermediate **57**. The followed reductive elimination led to the formation of acyl arene in intermediate **58**. The final product **52** was obtained by way of cyclocondensation with the release of H_2O and the rhodium(I)



Scheme 13 Rhodium(III)-catalyzed [5 + 1] annulations of *N*-arylamidines with cyclopropenones.



Scheme 14 Visible light-initiated copper-catalyzed aerobic oxidative C_{sp^2}–H annulation of amidines with terminal alkynes.

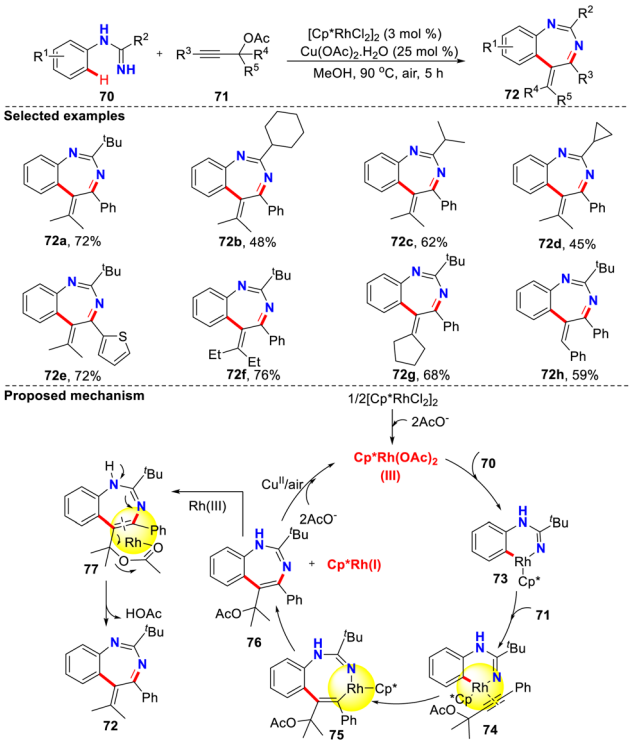
species can be reoxidized by the action of Ag(I) and/or O_2 to complete the catalytic cycle.

Different from the conventional transition metal-catalyzed thermal annulation reactions, metal photocatalysis oxidative C_{sp^2}–H annulation at room temperature (RT) is very challenging and complementary, which has been proven to follow the principles of green chemistry. In 2021, Hwang group[32] reported the visible light-initiated copper-catalyzed oxidative C_{sp^2}–H annulation of amidines with terminal alkynes to form 2,4-disubstituted quinazolines using molecular O_2 as an oxidant at RT (Scheme 14). This method was applicable for the synthesis of anticancer compounds from simple commercially available starting materials. The green metrics and eco-scale evaluations signify that the current photochemical process was simple, cost-effective and environmentally benign.

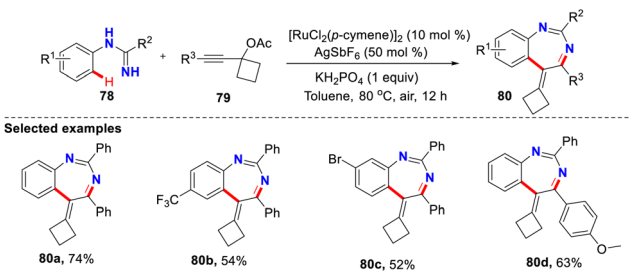
Based on the mechanistic investigations, a possible reaction mechanism was depicted. Under visible light irradiation, *in situ* generated Cu(I)-phenylacetylide **62** absorbed blue light and become photochemically excited triplet state **63**. This photoexcited state **63** then underwent a SET process by donating an electron to molecular O_2 and generated a Cu(II) complex **64**, as well as a superoxide anion radical. In the next stage, the basic nature of the copper-superoxo radical anion had propensity to abstract acidic NH proton **59** to form a nitrogen-centered radical **65**, which further reacts with Cu(II)-phenylacetylide complex **64** and forms Cu^{III}-complex species **66**. This intermediate Cu^{III}-complex **66** underwent reductive elimination and generated Cu(I)-coordinated ynamine intermediate **67**. Intermediate **67** then underwent Friedel–Crafts-type cyclization (6-exo-dig cyclization) to form cyclized intermediate **68** and subsequent aromatization to form compound **69**, which upon photo-oxidation by Cu(II) superoxo forms product **61**.

2.3 The [5 + 2] annulation of amidines

Compared with the C–H activation/[5 + 0] or [5 + 1] annulation reactions with the amidines, the [5 + 2] annulation reaction is more hard to achieve due to the fact that the formation of an eight-membered metallacycle intermediate required in the envisioned [5 + 2] annulation is energetically unfavorable. Meanwhile, the substrate is requested to provide C_2 synthon in reaction. With these challenges in mind, an efficient approach for the synthesis of 1,3-benzodiazepines has been developed *via* rhodium(III)-catalyzed annulative coupling between *N*-aryl amidines with propargylic esters by Fan group[33] in 2020 (Scheme 15). Of note, this was the first example in which *N*-aryl amidines serving as a C_5 synthon underwent a regioselective [5 + 2] annulation with propargyl esters acting as a C_2 synthon to afford valuable seven-membered heterocyclic system. This protocol featured broad substrate scope, good tolerance of a wide range of functional groups and facile operation process. In addition, the cytotoxicity of selected products against several human cancer cell lines was tested, which demonstrated their



Scheme 15 Rh(III)-catalyzed [5 + 2] annulation of *N*-aryl amidines with propargylic esters.



Scheme 16 Ru(II)-catalyzed [5 + 2] annulation of *N*-aryl amidines with alkynyl cyclobutyl acetates.

good potential for pharmaceutical applications. In this reaction, the insertion of the triple bond into the C–Rh bond generated an eight-membered rhodacycle **75**, which underwent a reductive elimination to give the intermediate **76** and released the Rh(I) species. The Rh(I) species was then oxidized back to the active Rh(III) catalyst by Cu(II)/air. Finally, the intermediate **76** took part in a deacetylation process, most likely under the promotion of Rh(III) as a Lewis acid catalyst *via* the formation of intermediate **77** to give product **72**.

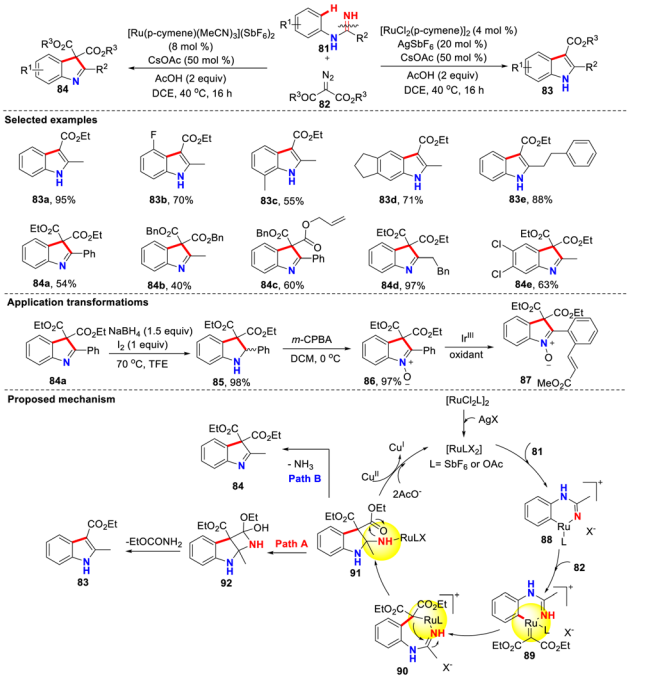
In 2023, Cui group[34] developed Ru(II)-catalyzed regioselective [5 + 2] annulation of *N*-aryl amidines with alkynyl cyclobutyl acetates to construct 5-cyclobutylidenebenzo[*d*][1,3] diazepines (Scheme 16). The method featured excellent regioselectivity, high step economy and good functional group tolerance. In this reaction, cheaper and earth abundant ruthenium was used as catalyst and the introduced cyclobutyl group would facilitate the subsequent biotransformation.

3 The [4 + *n*] annulation of amidines in C–H activation

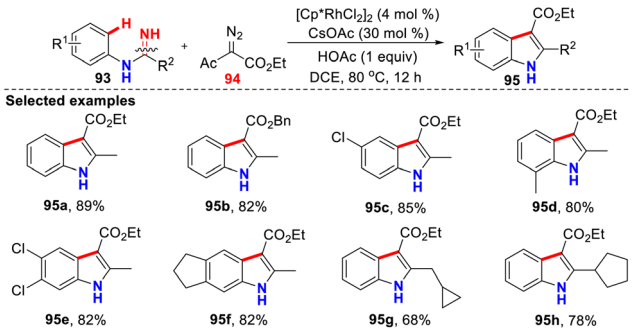
3.1 The [4 + 1] annulation of amidines

Recently, the metal-catalyzed annulation reaction has been increasingly employed for synthesis of nitrogen-heterocycles, especially by Rh^{III},[35] Ru^{II},[36] Co^{III},[37] and Ir^{III}-catalyzed[38] C–H activation in the presence of a DG. For these metals, amidines exhibited different chemical properties from copper and palladium-catalyzed C–H activation reactions, which afforded the opportunity to manipulate an array of different heterocyclic compounds. The amidines were used in a series of [4 + 1] annulation reactions, in which the metal-X (X = C, N) or nucleophilic reagent underwent migratory insertion into the C=N bond (acting an electrophilic group) and the cleavage of C=N bond.

In 2016, Li group[39] developed the firstly ruthenium(II)-catalyzed intermolecular coupling between aryl imidamides and diazo compounds by C–H activation, which enabled the synthesis two classes of indole derivatives by [4 + 1] annulation under mild conditions (Scheme 17). Derivatizations of 3*H*-indole **84a** were performed to further showcase the synthetic utility of these compounds.[40] Interestingly, the intermediate **91** was formed by Ru–C(alkyl) migratory insertion into the C=N bond. In path **A**, the intermediate **91** underwent protonolysis, intramolecular nucleophilic addition and subsequent elimination of one molecule of amide to generate product **83**. In path **B**, the intermediate **91** underwent elimination of ammonia with



Scheme 17 Ru(II)-catalyzed C–H activation of imidamides and divergent couplings with diazo compounds.



Scheme 18 Rh(III)-catalyzed C–H activation/[4 + 1] annulation of imidamides with α-diazo-β-ketoesters.

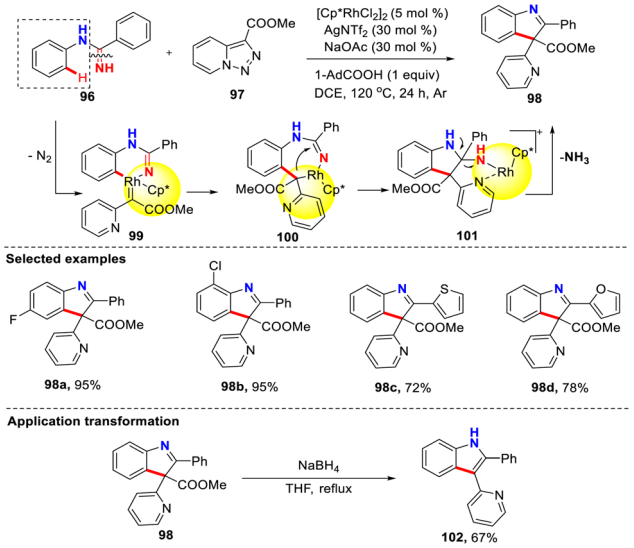
assistance of Ru^{II} or acetic acid, furnishing 3*H*-indole **84** as the final product. This change in selectivity was likely caused by the reduced electro-philicity of the ester carbonyl group.

At the same year, they reported[41] a redox-neutral approach to synthesize unprotected indoles *via* Rh(III)-catalyzed C–H activation in similar reaction system (Scheme 18). This reaction proceeded under relatively mild conditions with broad substrate scope. The metal–C underwent migratory insertion into the C=N bond (acting an electrophile), causing NH to be removed through subsequent elimination in the case of HOAc. Meanwhile, a rhodacyclic intermediate was isolated to favor the plausible mechanism.

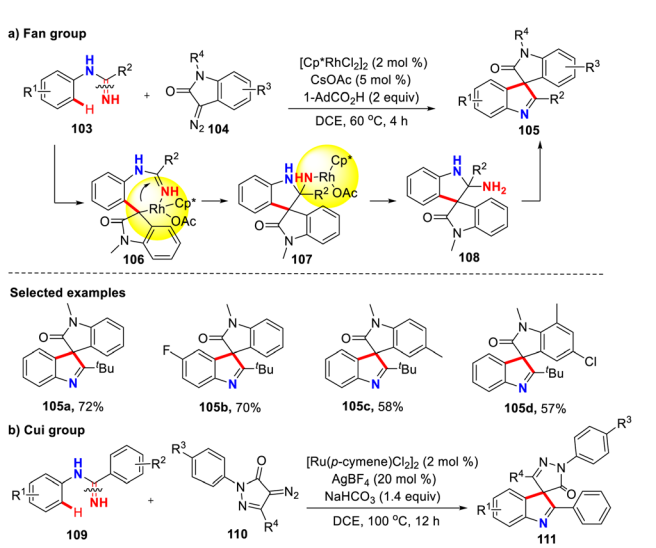
Subsequently, Dong group[42] revealed an efficient approach for the synthesis of unique 3*H*-indole derivatives from *N*-phenylamidines with pyridotriazoles *via* a rhodium-catalyzed highly selective C–H bond activation and annulation reaction (Scheme 19). In this transformation, the pyrido-triazoles were employed as a powerful carbene precursor coordinating with the metal by releasing of N_2 to afford the rhodium carbene **99**. The intermediate **99** provided seven-membered rhodacyclic species **100** by migratory insertion. Thereafter the Rh–C(alkyl) bond underwent migratory insertion into the C=N bond to intermediate **101**, which underwent elimination of the active Rh(III) catalyst and one molecule of NH_3 with the assistance of acid upon protonolysis and intramolecular protonolysis to afford product **98**. The reaction tolerated diverse functional groups and conveniently afforded various 3*H*-indoles in moderate to excellent yields. In addition, the ester group could be removed in the present of $NaBH_4$ to afford 2,3-disubstituted indole **102**, which suggested that this current protocol could be a practicability synthetic method and a late-stage modification tool.

In 2021, Fan group[43] developed Rh(III)-catalyzed coupling and spirocyclization of *N*-aryl amidines with diazo oxindoles to construct 3-spiroox-indole 3*H*-indoles (Scheme 20a). In this reaction, the newly formed C(sp^3)–Rh bond underwent a nucleophilic addition onto the C–N double bond of the amidine moiety to accomplish spirocyclization to form intermediate **107**. The protonation of **107** with HOAc afforded intermediate **108**, which underwent the elimination of ammonia to afford product. This novel spirocyclization features easily accessible substrates with a broad scope and generality, and formation of multiple bonds with high efficiency. Subsequently, Cui group[44] developed the Ru(II)-catalyzed selective C–H bond activation/[4 + 1] spirocyclization starting from easily available *N*-aryl amidines and diazopyrazolones (Scheme 20b). A series of spiropyrazolones could be easily obtained under mild reaction conditions with high step and atom economy.

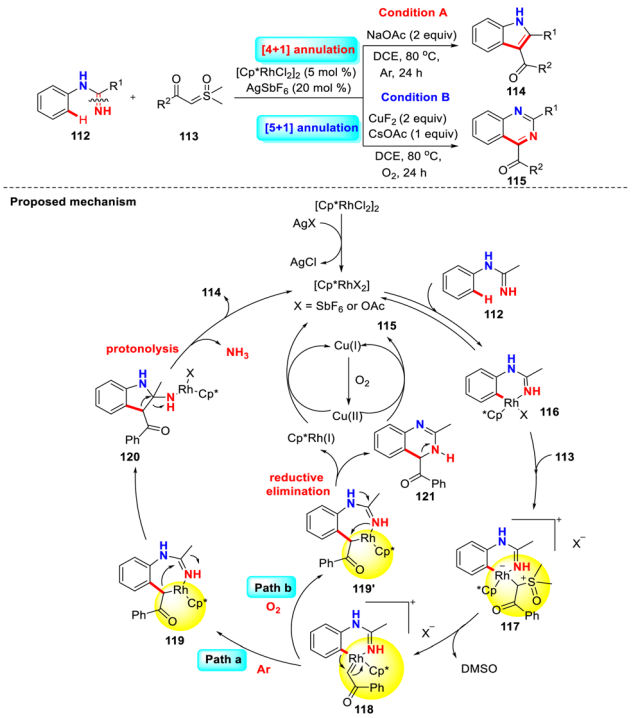
In addition, sulfoxonium ylides as a convenient and safe carbene precursor reagent, have been widely used in transition-metal-catalyzed C–H activation.[45] Interestingly, the sulfoxonium ylided can be used as the C_2 (ref. 46) unit or C_1 (ref. 47) unit according to the different reaction conditions. In 2019, Wu group[48] reported their work on additive-controlled selective synthesis of indoles and quinazolines by using *N*-arylamidines and sulfoxonium ylides as the starting materials (Scheme 21). In



Scheme 19 Rh(III)-catalyzed cascade annulation between *N*-phenylbenzimidamides and pyridotriazoles.



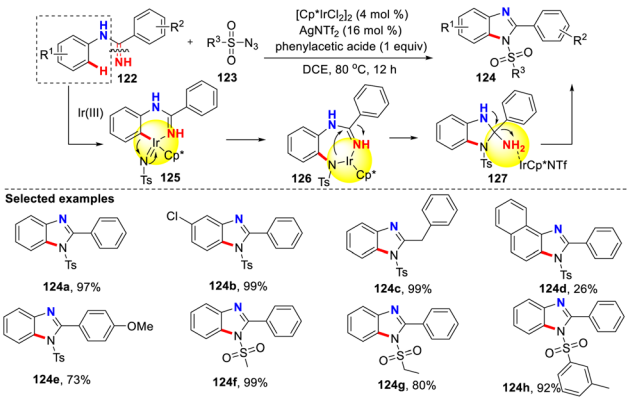
Scheme 20 Transition metal-catalyzed [4 + 1] spirocyclization of *N*-aryl amidines with diazo compounds.



Scheme 21 Rh(III)-catalyzed selective C–H activation/annulation of *N*-arylamidines and sulfoxonium ylides.

this process, the oxidants were shown to play a key role in selectively controlling the [4 + 1] and [5 + 1] annulation. In Ar atmosphere, the reaction predominantly gave the indoles through [4 + 1] annulation because sulfoxonium ylide was used as internal oxidant. Changing to O_2 and copper salt system, the preference of the annulation was switched to [5 + 1] annulation because the Cp*Rh(I) need to be reoxidized for catalytic cycle. Initially, the rhodacyclic intermediate **116** coordinated of sulfoxonium ylides **113** to generate a Rh(III) alkyl species **117**, and the α-elimination of DMSO from **117** afforded a reactive rhodium α-oxo carbene species **118**. Subsequently, in pathway **a**, the intermediate **118** was proposed to undergo migratory insertion of the Rh–C bond to generate a seven-membered rhodacyclic intermediate **119**, which undergo Rh–C(alkyl) migratory insertion into the C–N bond to afford intermediate **120**. Finally, the product **114** was released from **120** by elimination of the active Rh(III) catalyst and one molecule of ammonia from **120** upon protonolysis and intramolecular protonolysis. In pathway **b**, the reductive elimination from intermediate **119′** formed partially reduced quinazoline **121**. Subsequently, the oxidation of **121** afforded the quinazoline product **115**. On the other hand, the resulting Cp*Rh(I) can be reoxidized to the starting Rh(III) species by the action of Cu(II) and/or O_2 to complete the catalytic cycle.

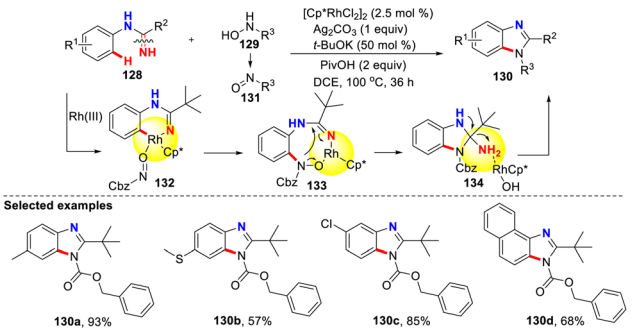
Subsequently, Cui group found that Ir(III)-catalyzed C–H activation of arens bearing a protic directing group preferred to couple with carbene compounds occurred under redox-neutral conditions to furnish various heterocycles. Different from ionic radius and catalytic activity of Ru and Rh, it can improve the selectivity of reaction of *N*-phenylbenzamidine and promote



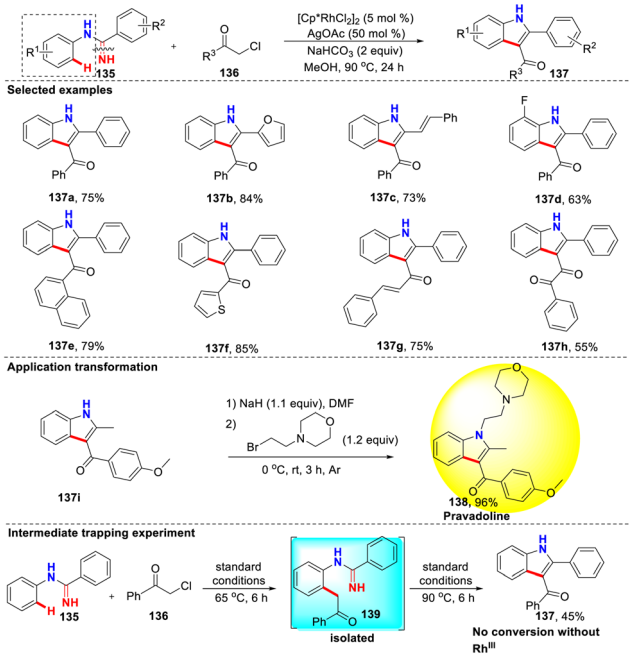
Scheme 22 Ir-catalyzed [4 + 1] annulation of imidamides with sulfonyl azides.

the reaction to occur. Hence, they[49] reported a convenient and straightforward approach to synthesis 1,2-disubtituted benzimidazoles *via* Ir(III)-catalyzed C–H activation of *N*-phenylbenzamidine and organic azides in 2017 (Scheme 22). The TsN_3 took part in the reaction by removing N_2 as the precursor of the nitrogen carbene, which coordinated with metal to generate iridium carbene species **125**. The Ir–Ar bond was proposed to undergo migratory insertion into the carbene unit to generate intermediate **126**. The Ir–N(TsN_3) bond then underwent migratory insertion into the C=N bond to afford amide species **127**. Finally, the product **124** was eventually formed from **127** by elimination of the active Ir(III) catalyst and one molecule of NH_3 from **127** upon protonolysis and intramolecular protonolysis. The products could be easily obtained in up to 99% yield and with good functional group tolerance.

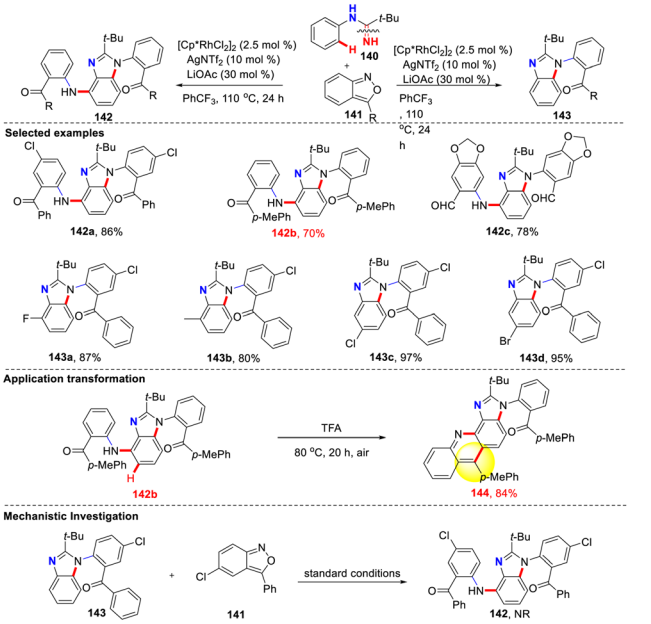
However, the organic azide was unstable chemical reagent. To solve this limitation, Cui group used *N*-hydroxycarbamates instead of organic azides as amination reagents. Soon after, they[50] successfully developed a novel method to synthesize 2-alkylbenzimidazole through the direct C–H amination of imidamides with hydroxylamines catalyzed by Rh(III) (Scheme 23). Various 2-alkylbenzimidaoles were conveniently afforded in good to excellent yields under relatively mild conditions employing readily available *N*-hydroxycarbamates as a nitrogen source.



Scheme 23 Rh(III)-catalyzed [4 + 1] annulation of imidamides with hydroxylamines.



Scheme 24 Rh(III)-catalyzed [4 + 1] annulation of *N*-phenylamidines with α-halogenated ketones.



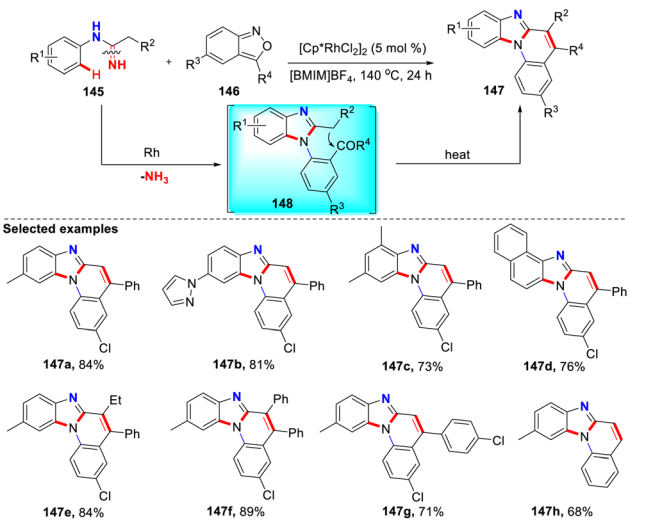
Scheme 25 Rh(III)-catalyzed sequential C–H amination/annulation cascade reactions of imidamides with anthranils.

According to the property of C=N bond of imidamides (acting an electrophile), causing NH to be removed through subsequent elimination, various cyclization reactions of imidamides involving different nucleophiles were reported. In 2018, Liu group[51] demonstrated that the easily accessible α-halogenated ketones could be used as one-carbon reaction partners for direct construction of 3-acylindoles *via* Rh(III)-catalyzed annulation of *N*-phenylamidines (Scheme 24). This strategy featured high regioselectivity and wide substrate tolerance. In particular, the methodology could provide a short synthesis route for pravadoline **138**, which demonstrated the practicability of this protocol. Meanwhile, the intermediate **139** was isolated and characterized, suggesting that C–H alkylation took place before C=N bond cleavage. The key intermediate **139** could be further converted into the desired product **137** under standard conditions with Rh-catalyzed system.

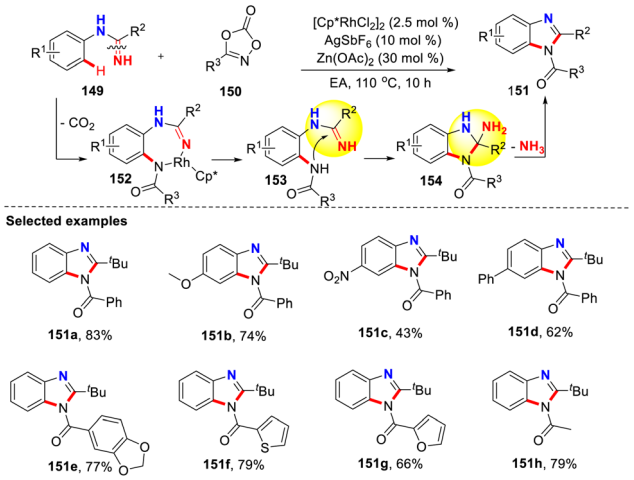
Soon afterwards, Cui group[52] developed an efficient and practical method to construct benzimidazole derivatives *via* Rh(III)-catalyzed sequential C–H amination by using anthranil[53] as bifunctional aminating reagent (Scheme 25). This procedure could proceed smoothly with a low catalyst loading, avoid the external oxidants, and offer high-value products as versatile building blocks for further transformation, especially for heterocycle synthesis. In addition, the title product **142b** could be easily further converted into imidazo[4,5-*c*]acridines **144**, which was observed with unique fluorescent properties. According to the result of the control experiment, the NH of *N*-phenyl pivalimid amide might play as a directing group to sequential C–H aminations in the catalytic cycle, and compound **143** was a byproduct, but not the key intermediate in this reaction.

In 2020, an efficient and practical Rh(III)-catalyzed C–H activation/annulation to construct benzimidazo[1,2-*a*]quinolines from readily imidamides and anthranils in [BMIM]BF_4 was reported by Wu group (Scheme 26).[54] Anthranils were as a new type of bifunctional aminating agent to expose carbonyl group after breaking the N–O bond. Subsequently, the product was obtained from the intramolecular Knoevenagel condensation of intermediate **148** at high temperature without extra additives.

Based on that, Fan group[55] achieved a Rh(III)-catalyzed [4 + 1] annulation of *N*-arylpivalimidamides with dioxazolones (Scheme 27). It was the first example in which *N*-acylbenzimidazoles were synthesized through simultaneous formation of



Scheme 26 Rh(III)-catalyzed C–H activation cascade reaction between imidamides and anthranils.



Scheme 27 Rh(III)-catalyzed C–H activation/[4 + 1] annulation reaction of *N*-arylpivalimidamides with dioxazolones.

the imidazoyl moiety and introduction of the *N*-acyl group. The dioxazolone as a masked amidating reagent followed by an intramolecular *N*-nucleophilic addition and ammonia elimination to afford product. In addition, the chemistry transformations illustrated the synthetic utility of the products.

3.2 The [4 + 2] annulation of amidines

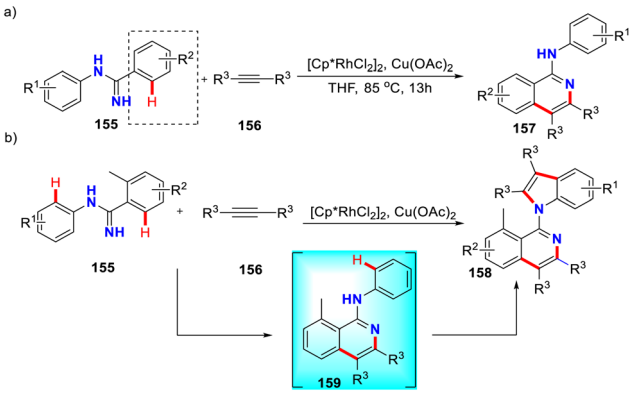
Different from other DGs, the *N*-phenylbenzamidine is essentially bifunctional with two N–H bonds. In addition, the low thermostability of benzamidines might cause complications, which is difficult to achieve the C–H activation at the *C*-phenyl ring. In 2011, Li group[56] firstly achieved the synthesis of *N*-substituted 1-aminoisoquinolines *via* Rh(III)-catalyzed oxidative coupling of *N*-aryl and *N*-alkyl benzamidines with alkynes (Scheme 28). C–H activation occurred at *C*-phenyl ring with excellent regio-selectivity. The exposed amino group avoided the use of other ammoniation reagent, which provided a new strategy for synthesis of amino heterocyclic compounds.

Interestingly, they unconsciously discovered the incorporation of two alkynes units with *N*-phenylbenzamidine, even though only 1.05 equiv alkyne was provided (Scheme 28b). Simple optimization by providing an excess of alkynes and $Cu(OAc)_2$ afforded this product in 73% yield. They reasoned that the isolation of the 2-fold oxidative coupling product is due to steric assistance. After the formation of the 1-(phenyl-amino) isoquinoline intermediate, the steric repulsion between the *o*-Me and the *N*-phenyl group renders these two groups distal to each other, leading to a conformation that is exactly favorable for C–H activation. With this conformational assistance, the isoquinoline ring nitrogen coordinated to the Rh(III) to give an intermediate in which the *ortho* C–H bond in the *N*-phenyl ring is pointed favorable to the metal center, leading to cyclometalation and eventually C–C and C–N formation.

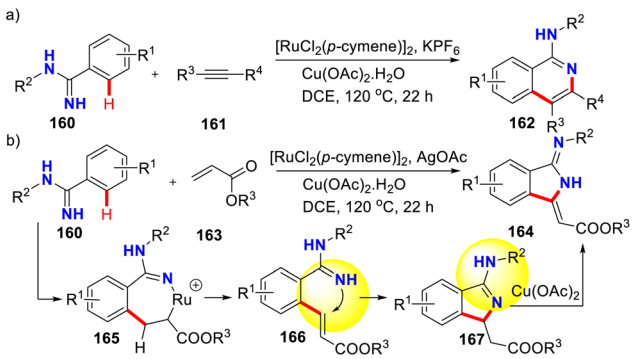
Subsequently, in order to improve the selectivity, Ackermann group[57] changed the *N*-aryl to *N*-alkyl benzamidines, and reported a ruthenium(II)-catalyzed oxidative C–H-bond functionalization on easily accessible *N*-alkyl benzamidines with alkynes and alkenes (Scheme 29). Notably, this strategy proved to be widely applicable and enabled annulations of alkynes and alkenes to provide expedient access to diversely substituted 1-aminoisoquinolines and novel 1-iminoisoindo-lines, respectively. The desired product **164** was obtained through an intramolecular aza-Michael addition of intermediate **166**, followed by dehydrogenation of the thus obtained intermediate **167**.

Under this strategy, a cobalt(III)-catalyzed C–H/N–H bond functionalization for the synthesis of 1-aminoisoquinolines from amidines and diazo compounds was developed by them in 2016 (Scheme 30).[58] The byproducts of N_2 and H_2O in the reaction made the process environmentally benign and the *in situ* formed cationic cobalt(III) catalyst provided access to structurally diverse isoquinolines under the assistance of carboxylates cobalt intermediate.

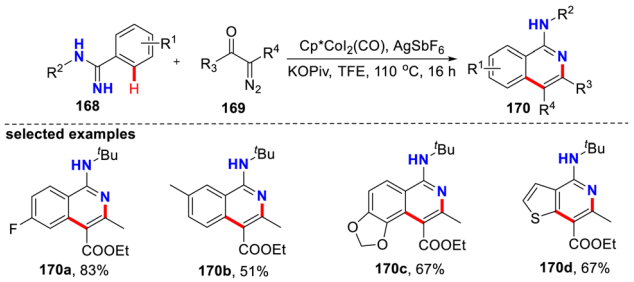
It was not difficult to find that the Rh was more inclined to react with *N*-phenylbenzamidine than other metals, and the experimental results also confirmed this. For example, Shang[59] and Li group[60] developed a Rh-catalyzed annulative coupling between *N*-phenylbenzamidine with cyclic 2-diao-1,3-diketones or sulfoxonium ylides to synthesize 1-aminoisoquinoline derivatives (Scheme 31a and b). These methodologies featured a broad substrate scope, and involved the formation of two new σ bonds (C–C and C–N) in a single operation under redox-neutral conditions.



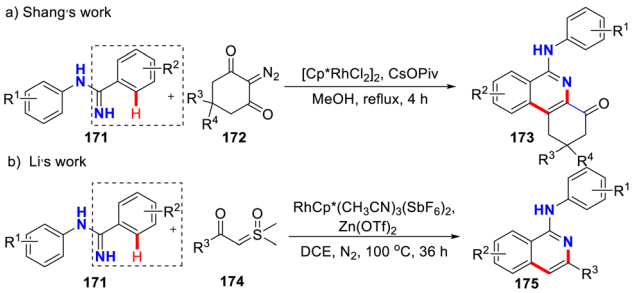
Scheme 28 Rh(III)-catalyzed oxidative coupling of *N*-aryl benzamidines with alkynes.



Scheme 29 Ruthenium(II)-catalyzed oxidative C–H bond functionalization of aryl amidines with alkynes and alkenes.

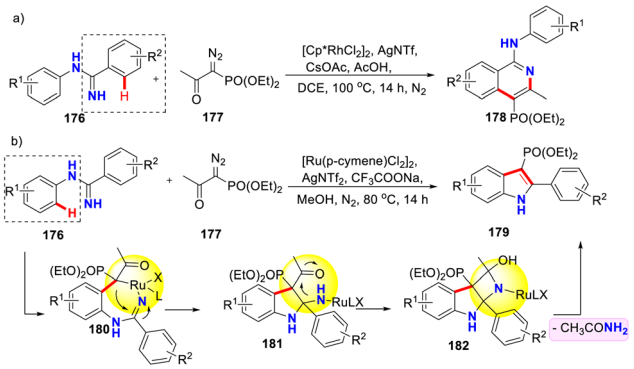


Scheme 30 Cobalt(III)-catalyzed synthesis of isoquinolines through C–H functionalization with diazo compounds.



Scheme 31 Rh(III)-catalyzed annulative coupling between *N*-aryl amidines with cyclic 2-diazo-1,3-diketones and sulfoxonium ylides.

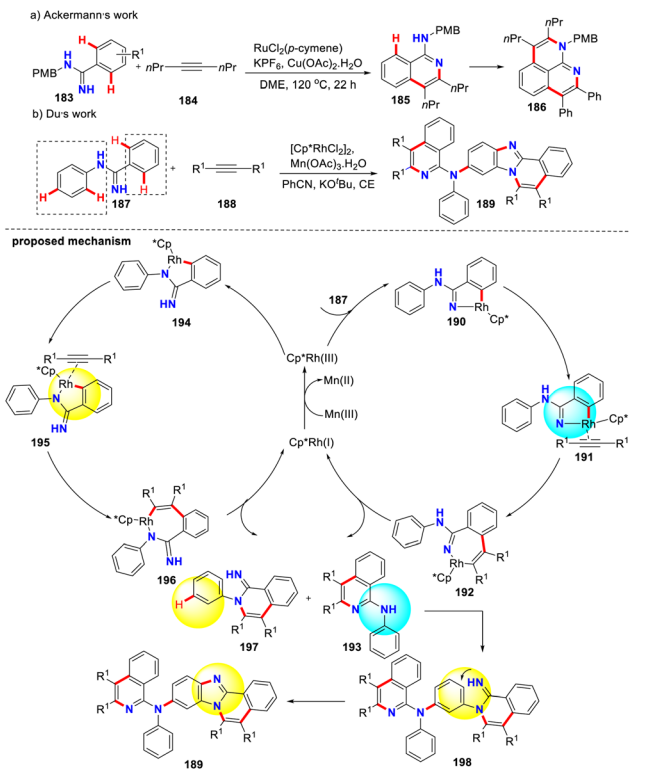
Interestingly enough, in 2019, Zhou group[61] developed a catalyst-controlled highly selective synthetic strategy to produce phosphoryl-indoles and phosphoryl-isoquinolines through a selective C–H bond activation of *N*-phenylbenzimidamide and the subsequent divergent couplings with diazophosphonate compounds (Scheme 32). Different C–H activation pathways of the substrate *N*-phenylbenzimidamide by altering the Rh(III)/Ru(II) catalyst systems prepared diverse privileged scaffolds. The H/D exchange experiment indicated that the C–H activation process preferred to occur on the *C*-phenyl ring under the Rh(III) catalytic system, while C–H activation preferred to occur on the *N*-phenyl ring under the Ru(II) catalytic system. In Ru(II) catalytic system, a Ru–C(alkyl) migratory insertion into the C=N bond could give the species



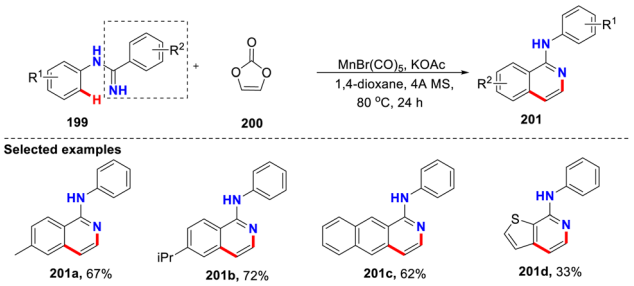
Scheme 32 Highly selective C–H bond activation of *N*-arylbenzimidamide and divergent couplings with diazophosphonate compounds.

181, which underwent further protonolysis, intramolecular nucleophilic addition, and subsequent elimination of CH_3CONH_2 to give the target product **179**. This protocol might find wider application in the discovery of lead compounds in the future, and verified the importance of the Rh in the occurrence of the C–H activation in *C*-phenyl ring.

In addition, the *para*-methoxybenzyl (PMB)-substituted benzamidine furnished the product through a twofold C–H/N–H-bond functionalization with two alkynes (Scheme 33a),[57] thereby high-lighting the ability of the 1-aminoisoquinolines themselves to serve as useful substrates for directed C–H-bond transformations. In 2020, Du group[62] reported a tandem process of multiple C–H activation and intermolecular highly *meta*-selective C–H amination between *N*-phenylbenzimidamide and alkynes (Scheme 33b). Initially, assisted by the N=C group, the *ortho* C–H bond of the *C*-phenyl ring of **187** was activated to generate a five-membered rhodacycle **190**. Subsequently, **190** underwent alkyne insertion, followed by reductive elimination, to form **193** as well as Cp*Rh(I). Reoxidation of Rh(I) to Rh(III) by $Mn(OAc)_3 \cdot 2H_2O$ completed the catalytic cycle. Separately and simultaneously, assisted by the N–C group, the *ortho* C–H bond of the *C*-phenyl ring was activated to furnish another five-membered rhodacycle intermediate **194**. After that, coordination of alkyne to rhodacycle intermediate **194** and insertion of alkyne into the Rh–C bond afforded a seven-membered rhodacycle intermediate **196**. Reductive elimination of **196** leaded to the formation of **197** and regenerates Cp*Rh(I). Then **197** and **193** underwent steric-effect-controlled intermolecular *meta* C–H amination to form



Scheme 33 Rhodium-catalyzed multiple C–H activation/highly *meta*-selective C–H amination between amidines and alkynes.



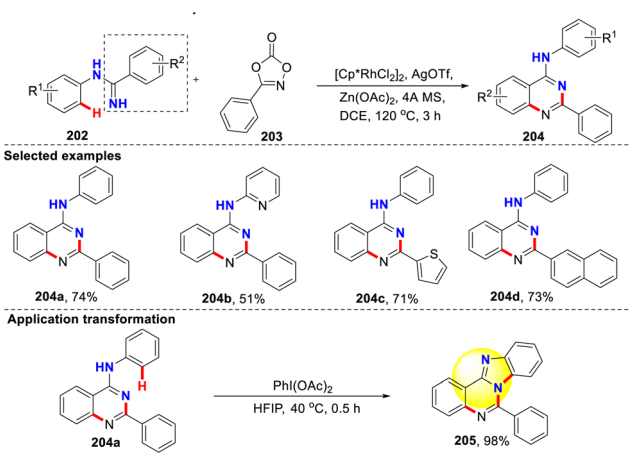
Scheme 34 Mn(II)-catalyzed [4 + 2] annulation of *N*-aryl amidines with vinylene carbonate.

intermediate **198**. In the final stage of this cascade reaction, an intramolecular C–H amination delivered the product.

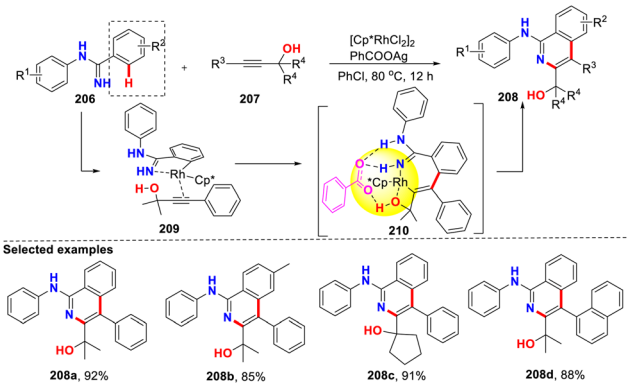
In 2021, Li group[63] developed Mn-catalyzed [4 + 2] annulation of aryl amidines with vinylene carbonate for the synthesis of 1-aminoisoquinolines (Scheme 34). The vinylene carbonate was used as a acetylene surrogate through removing CO_2 in the transition-metal-catalyzed coupling reactions. In addition, the protocol obviates the need for any oxidants and shows good functional group tolerance and high atom efficiency.

At the same year, Cui group[64] reported Rh(III)-catalyzed [4 + 2] annulation of *N*-arylbenzamidines with 1,4,2-dioxazol-5-ones for the synthesis of 4-aminoquinazolines (Scheme 35). This strategy proceeded with excellent regioselectivity, broad substrate scope and high step economy, and two C–N bonds were formed in reaction. In addition, the benzimidazo-[1,2-*c*]quinazolines **205** could also be synthesized *via* a phenyl-iodine diacetate (PIDA)-mediated intramolecular C–H cyclo-amination of **204a**.

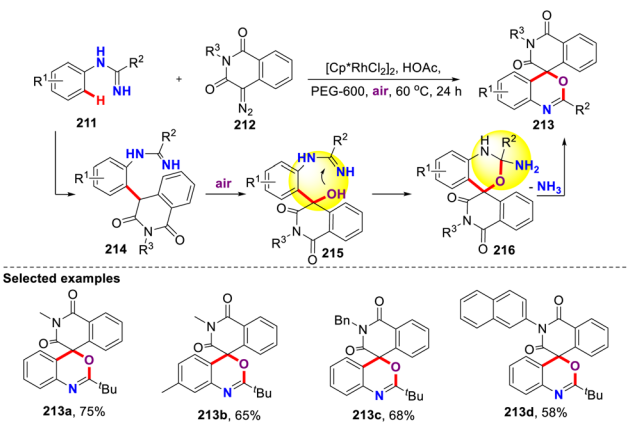
Subsequently, Cui group[65] explored Rh(III)-catalyzed C–H bond activation/annulation reactions of propargyl alcohols with *N*-arylbenzamidines to synthesize 1-aminoisoquinolines through a noncovalent interaction (Scheme 36). The hydroxyl group in **207** might provide binding affinity for Rh, and $PhCOO^-$ facilitated the formation of the intramolecular hydrogen bonding with **206** and **207**, which guided the



Scheme 35 Rh(III)-catalyzed [4 + 2] annulation of *N*-arylbenzamidines with 1,4,2-dioxazol-5-ones.



Scheme 36 Rh(III)-catalyzed [4 + 2] annulation of *N*-arylbenzamidines with propargyl alcohols.



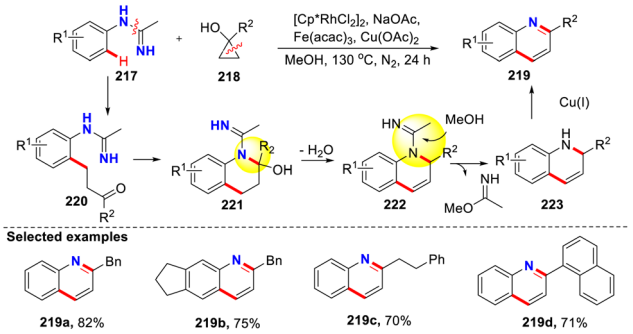
Scheme 37 Rh(III)-catalyzed [4 + 1 + 1] annulation of *N*-aryl amidines with diazo homophthalimides.

regioselective migratory insertion. Only one isomer was obtained in this transformation, and the reactions proceeded with a broad substrate scope and high atom economy. In addition, the hydroxyl could be removed to afford the olefins.

In 2022, a Rh(III)-catalyzed [4 + 1 + 1] spirocyclization of *N*-aryl amidines with diazo homophthalimides and O_2 to construct the hitherto unreported spiro[benzo[*d*][1,3]oxazine-4,4′-isoquinoline] derivatives has been developed by Fan group[66] (Scheme 37). Interestingly, the intermediate **214** reacted with oxygen in air and further transformed into **215**, which underwent intramolecular *O*-nucleophilic addition and elimination of ammonia to afford product **213**. In addition, this novel protocol featured easily obtainable substrates bearing diverse functional groups, structurally and pharmaceutically valuable products, and mild reaction conditions, is cost-free and clean, and has an abundant oxygen source and a sustainable reaction medium.

4 The [3 + 3] annulation of amidines in C–H activation

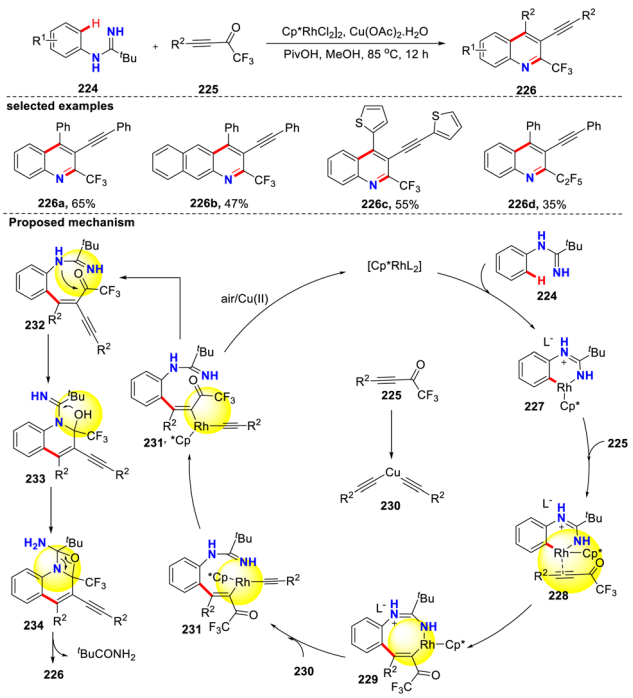
Different from imine, the C–N bond of imidamides was difficult to cleave due to the high stability. When NH of imidamides took



Scheme 38 Rh(III)-catalyzed [3 + 3] annulation of imidamides with cyclopropanol.

part in nucleophilic attack instead of imine, the other substrate needed to provide sufficiently long chain of electrophilic point, which avoided forming an intermediate with macrocyclic tension with imine.

Cyclopropanols, as the β-aryl ketone precursor, can serve as a readily available C_3 synthon for the construction of cyclic compounds.[67,68] To realize cyclization of β-aryl ketone precursor, a bifunctional nucleophilic directing group that attacked the resulting carbonyl group needs to be employed. In 2017, Li group[69] disclosed a Rh(III)-catalyzed annulative coupling between cyclopropanlos and imidamides for the synthesis of 2-substituted quinolines, where cyclopropanlos acted as a C_3 synthon (Scheme 38). With the assistance of a bifunctional imidamide directing group, the reaction occurred *via* sequential C–H/C–C cleavage and C–C/C–N bond



Scheme 39 Rh(III)-catalyzed [3 + 3] cascade annulation reactions of *N*-aryl amidines with CF_3-ynones.

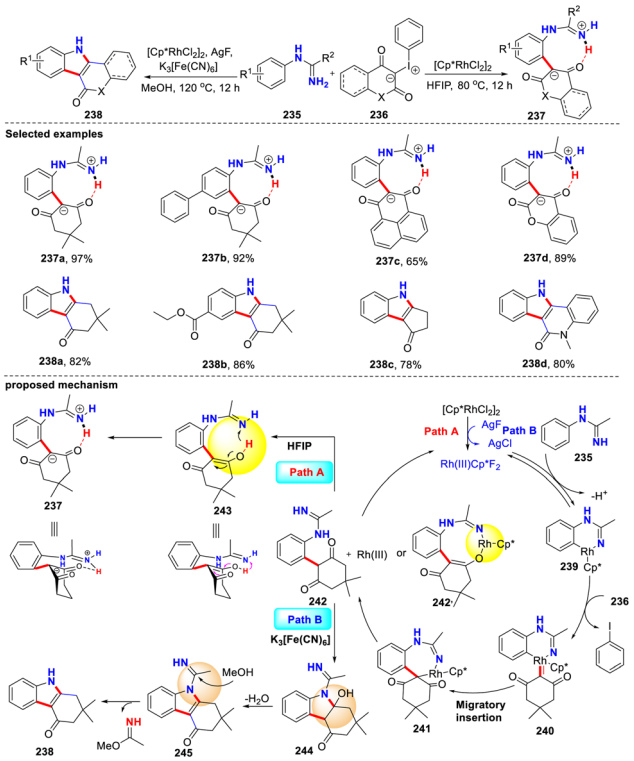
formation. According to the proposed mechanism, intramolecular nucleophilic addition of **220** generated a hemiaminal **221**, dehydration of which delivered an *N*-protected 1,4-dihydroquinoline intermediate **222**. Nucleophilic deprotection of **222** furnished the intermediate **223**, which was readily oxidized even by Cu(I) species to eventually furnish the product.

In 2024, Fan group[70] developed Rh(III)-catalyzed cascade reactions of *N*-aryl amidines with two CF_3-ynones for the synthesis of CF_3- and alkynyl-substituted quinoline derivatives (Scheme 39). In this cascade procedure, the CF_3-ynone played multiple roles by acting not only as an alkenylating reagent but also as an alkynylating reagent and a source of the CF_3 group. Initially, under the promotion of Cu(II), CF_3-ynones **225** underwent detrifluoroacetylation to form an alkynyl copper species **230**, which was then trapped by intermediate **229** to give intermediate **231**. From intermediate **231**, **231′** was formed through equilibration. Subsequently, a reductive elimination reaction took place with **231′** to furnish intermediate **232**, which underwent intramolecular *N*-nucleophilic addition to give intermediate **233**. The intermediate **233** underwent intermolecular *O*-nucleophilic addition to form intermediate **234**. Finally, an aromatization driven ring-opening reaction of the 1,3-oxazetidine moiety took place to give product **226**.

5 The intramolecular proton transfer process of amidines in C–H activation

Intramolecular proton transfer is an important process in chemical reactions and biological transformations.[71] In particular, the translocation of reactive carbanion centers can be achieved through 1,*n*-proton transfer in either a direct or an assisted manner (*via* the protonation/deprotonation mechanism).[72] However, these pathways rely on intramolecular carbon-to-carbon proton transfers, achieving the intramolecular proton transfer through transition metal-catalyzed C–H bond activation process is still a challenge due to the system incompatibility.

In 2023, Cui group[73] developed Rh(III)-catalyzed divergent C–H bond functionalization of *N*-aryl amidines with iodonium ylides. Carbazolones and zwitterionic salts were diversely constructed through intermolecular annulation and intramolecular proton transfer under the different reaction conditions (Scheme 40). Except for the coordination with metal, *N*-aryl amidines were used as the proton acceptor for the first time, affording the ammonium zwitterionic salts, which affords a remarkable and meaningful expansion in the area of multifunction directing groups. In path **A**, the intermediate **242** took enol-isomerization to give intermediate **243**, which underwent intramolecular proton transfer progress to afford a new carbon anion and ammonium **237**. In addition, the intermediate **241** might also undergo enol-isomerization to form O–Rh–N specie **242′** and followed by proton transfer process to afford **243** and the active catalyst species. In path **B**, the intramolecular nucleophilic addition of intermediate **242** afforded intermediate **244** with the help of $K_3[Fe(CN)_6]$, followed by elimination of water to yield intermediate **245**. Finally,



Scheme 40 Rh(III)-catalyzed divergent C–H functionalization of *N*-aryl amidines with iodonium ylides.

nucleophilic deprotection of intermediate **245** furnished the product **238**.

6 Conclusion

In this review, we have presented the progress of the transition-metal catalyzed C–H activation of amidines to synthesize heterocyclic compounds in the past decade. A wide range of original procedures for synthesizing various classes of *N*-heterocyclic systems have been developed on the basis of amidines and their derivatives through diverse annulation strategies. Different from other DGs, multiple activity reaction positions of amidines presented a difficult challenge. Although much progress has been achieved in this field, there are problems and demands for more applications of amidines in organic synthesis. For example, it is still difficult to achieve the C–H activation at the *meta*- or *para*-position of amidines. Meanwhile, transition-metal-catalyzed C–H activation of amidines to construct large and small ring compounds is very limited. Recently reported methods pave the way for the future of this exciting field where many more discoveries are surely waiting to be uncovered. In summary, the field of amidines chemistry is growing because of its high efficiency in the preparation of *N*-heterocycles. The potential of these amidine compounds is far from being fully realized. We hope that this review will be a spur for other researchers to join the field and we look forward to monitoring the literature as the synthetic opportunities that exist for this transformation are exploited.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Author contributions

Jie Ren and Yijia Xiong contributed equally. Jie Ren: investigation, literature curation, formal analysis, writing – original draft; Yijia Xiong: investigation, formal analysis literature curation, writing – original draft; Qian Li: literature curation; Bin Wang: investigation; Guanglu Wang: investigation, formal analysis; Bingyang Wang: investigation, formal analysis; Huimin Liu: writing – review & editing; Xuepeng Yang: supervision, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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