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Recent advances in the synthesis of bridgehead (or ring-junction) nitrogen heterocycles *via* transition metal-catalyzed C–H bond activation and functionalization

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Bridgehead nitrogen (or ring-junction nitrogen) heterocycles are one of the most privileged scaffolds in synthetic chemistry and medicinal chemistry. For decades, transition metal-catalyzed C–H activation has provided straightforward access to bridgehead nitrogen heterocycles in an atom-economical manner. Palladium, rhodium, ruthenium, iridium, cobalt, nickel, silver, and copper catalysts were used for the successful synthesis of these skeletons. Herein, we summarize recent advances that are made in the synthesis of bridgehead nitrogen heterocycles *via* diverse transition metal-catalyzed C–H activations and C–H functionalizations. This review covers the period from May 2004 to April 2020.

1. Introduction

Bridgehead nitrogen (ring-junction nitrogen) heterocycles are among the most privileged cores in natural products (Fig. 1)[1] and therapeutic pharmaceuticals[2] (Fig. 2). These scaffold architectures play important roles in chemical biology and drug discovery. For example, rutaecarpine,[3] amaryllidaceae alkaloids,[4] luotonin A and B,[5] (+)-austamide,[6] lamellarin D,[7] and camptothecin[8] have diverse biological activities. Alprazolam,[9] midazolam,[10] vardenafil,[11] sitagliptin,[12] ponatinib,[13] dolutegravir,[14] filgotinib,[15] upadacitinib,[16] baloxavir marboxil,[17] and remdesivir[18] were approved to treat a variety of serious diseases. In particular, the FDA has recently approved the emergency use of remdesivir for COVID-19.[19] Consequently, these heterocycles have attracted great attention from synthetic chemists and medical scientists.[20] In order to obtain these scaffolds efficiently, various methods involving cycloaddition reactions,[21] cyclization reactions,[22] reduction reactions,[23] multicomponent reactions,[24] cyclization of *N*-acyliminium,[25] transition-metal-catalyzed cyclizations[26] *etc.* have been developed. Among these methods, transition metal

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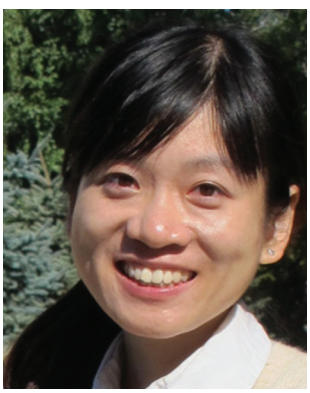
Biao Nie

Biao Nie received his MS from China Pharmaceutical University in 2010. He joined the HEC Pharm Group in 2010 where his research interests were focused on drug synthesis. He then joined Jiang's group as a PhD candidate under the supervision of Professor Huanfeng Jiang in 2016, where his primary research focus is on transition-metal-catalyzed C–H functionalization and its applications in drug synthesis.



Wanqing Wu

Wanqing Wu received her PhD from Peking University with Professor Zhen Yang and Chi-Sing Lee in 2010. And then she joined Professor Huanfeng Jiang's group as a postdoctoral researcher at South China University of Technology (SCUT). In 2014, she was promoted to Professor and her research interests include the development and applications of carbon-heteroatom triple bond transformations.

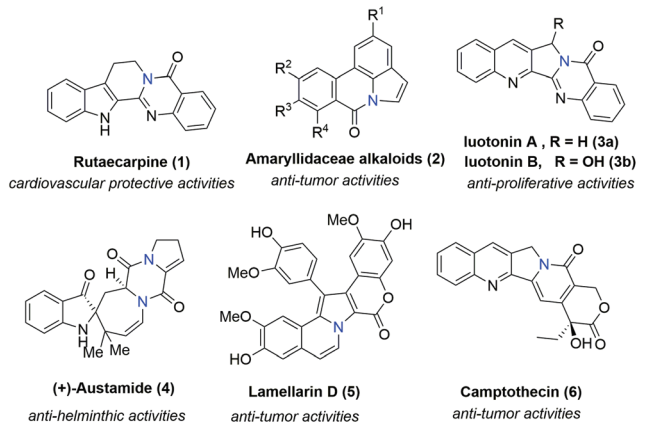


Fig. 1 Some natural products bearing bridgehead nitrogen heterocycle scaffolds.

catalyzed C–H activation provided a straightforward way to access bridgehead nitrogen heterocycles in an atom-economical manner, by a facile one-pot synthesis of complex molecules without the requirement of substrate prefunctionalization.[27] One of these examples has been shown in the synthesis of two imidazopyridine drug molecules: alpidem and zolpidem (Scheme 1).[28]

Ferraccioli[29] and Guo[30] reviewed palladium-catalyzed and copper-catalyzed C–H functionalization reactions for the construction of heterocycles respectively. In 2016, various transition metal-catalyzed heterocycle syntheses *via* C–H activation were reviewed by Wu and co-workers.[31] However, their coverage is not specific to bridgehead nitrogen heterocycles. Meanwhile, the Sharma group covered transition-metal-catalyzed synthesis of imidazopyridines.[32] Zhang *et al.* summarized copper-catalyzed C–H functionalizations for the synthesis of bridgehead nitrogen heterocycles.[33] Yet these reviews were limited to one type of heterocycle nucleus or to a particular metal catalysis. Due to the importance of bridgehead nitrogen heterocycles and the rapid development of C–H activation methodologies, a timely review which is specific to the synthesis of bridgehead nitrogen heterocycles *via* diverse transition metal-catalyzed C–H activations and functionalizations would be desirable and useful for the exploration of new reactions and beneficial for drug discovery.

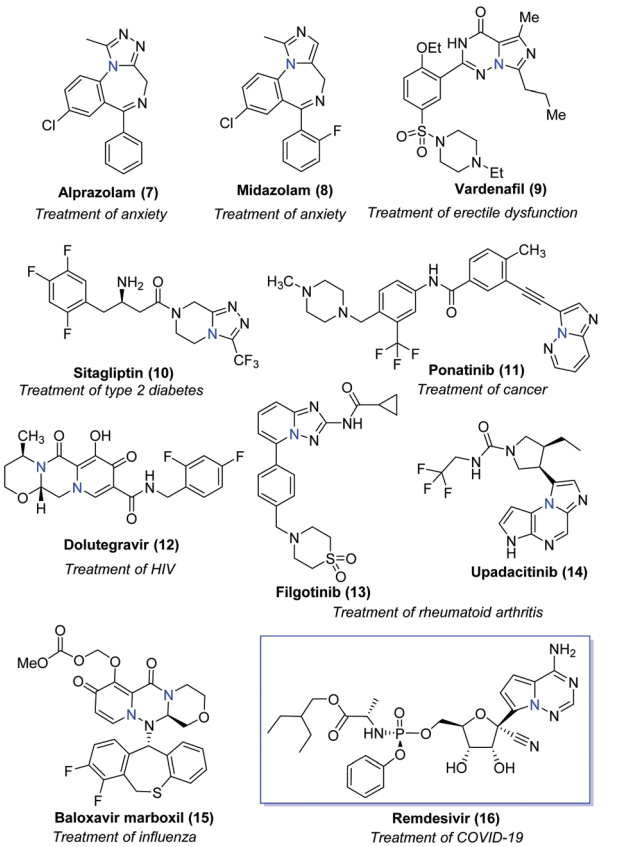


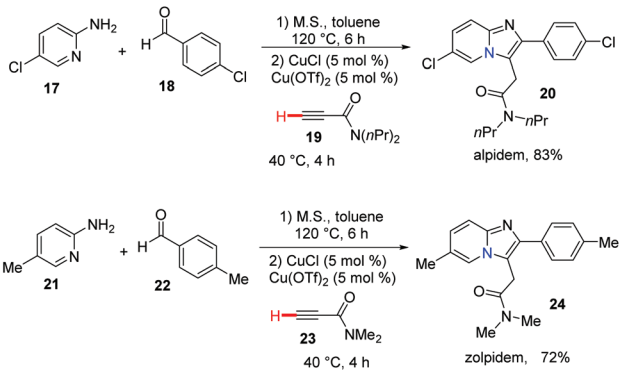
Fig. 2 Some launched pharmaceuticals containing bridgehead nitrogen heterocycles moieties.

Yingjun Zhang

Yingjun Zhang obtained his BSc degree in 2001 and his PhD in 2007 from Hunan University. He was a postdoctoral researcher at Okayama University of Science, Japan (2007–2008) before joining the HEC Pharm Group as a research chemist. He was a group leader on drug discovery (2008–2010), before being promoted to director (2010-) taking in charge of the drug discovery program.

Huanfeng Jiang

Huanfeng Jiang received his PhD from the Shanghai Institute of Organic Chemistry (SIOC) with Professor Xiyan Lu in 1993. And then he joined the Guangzhou Institute of Chemistry as a research fellow. In 2003, he moved to the South China University of Technology (SCUT) as the Leading Professor of Chemistry. He received Chinese Chemical Society-BASF Young Investigator's Award in 2002 and the National Natural Science Funds for Distinguished Young Scholar in 2006. His research interests focus on synthetic methodology, and green and sustainable chemistry.



Scheme 1 One pot synthesis of alpidem and zolpidem *via* copper-catalyzed C–H functionalization reactions.

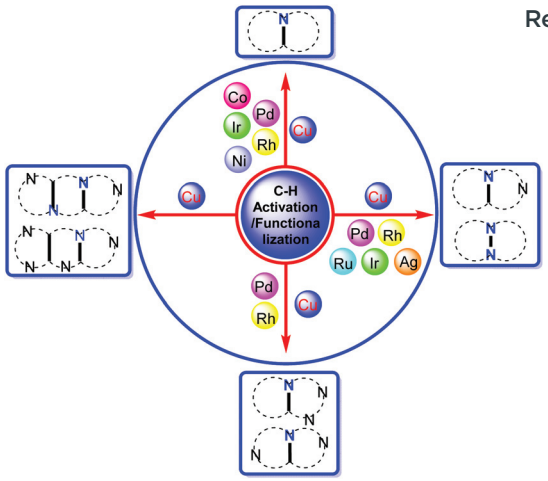


Fig. 3 A concise summary of the preparation of different kinds of bridgehead nitrogen heterocycles by various transition metal-catalyzed C–H bond activations and functionalizations.

Therefore, we present this review organized according to different kinds of metals for the C–H activation and functionalization, further subdividing according to the fused nitrogen heterocycle structure (Fig. 3). This review covers the time period from the year 2004 to 2020. The notable features of this review are as follows: (i) various transition metal catalysts including Pd, Rh, Ru, Ir, Co, Ni, Ag and Cu are involved; (ii) diverse kinds of bridgehead nitrogen heterocycles are covered; (iii) C–H bond activation including C(sp^2)–H, C(sp)–H, and C(sp^3)–H is depicted; (iv) selected examples, mechanisms and potential applications (particularly in drug discovery) of reactions are discussed.

2. Transition metal catalyzed synthesis of bridgehead nitrogen heterocycles

2.1 Palladium-catalyzed synthesis of bridgehead nitrogen heterocycles

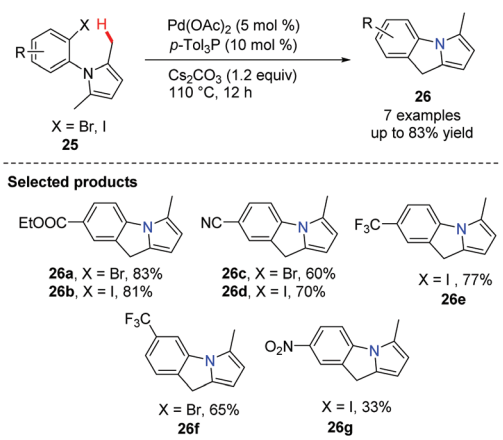
Knochel and co-workers developed a novel palladium-catalyzed intramolecular cyclization leading to condensed N-heterocycles **26** (Scheme 2).[34] These polyheterocycles are frequently found as the cores of both natural products and drug molecules; the preparation of the starting *N*-arylpyrrole **25** proved to be extremely simple. This cyclization involved a Pd-catalyzed C(sp^3)–H (benzylic type) activation step and screening indicated that the ligand *p*-Tol_3P and the base Cs_2CO_3 are superior to the other ligand/base combinations explored for this transformation.

Oestreich reported a *C*-2 alkenylation of indoles with substituted alkenes by utilizing a $Pd(OAc)_2$-pyridine ligand system in 2012 (Scheme 3).[35] The key step here is an *endo* cyclization of alkenes onto indoles temporarily tethered to the indole nitrogen atom by an amide linkage.

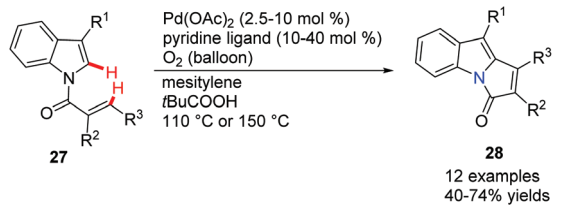
Lautens and co-workers developed a palladium-catalyzed/norbornen-mediated complex for the synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives **31** *via* the C(sp^2)–H functionalization reaction of pyrazoles **29** and aryl iodides **30** (Scheme 4).[36] These skeletons have been found in some natural and biologically active compounds, including lettowianthine and lamellarin D.

Ji Zhang

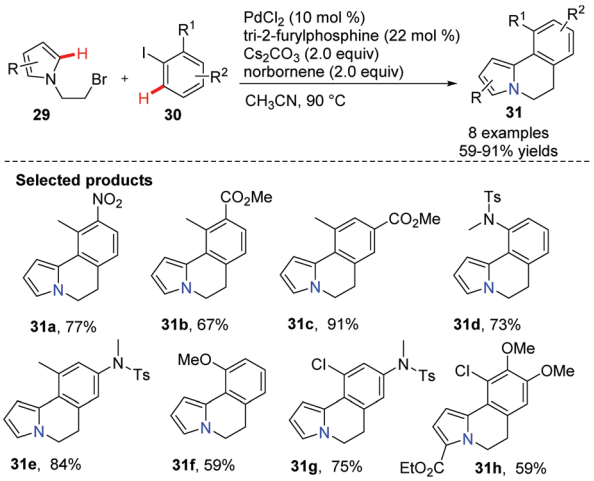
Ji Zhang received his academic training from the South China Normal University (BS, 1983), Beijing Normal University, China (MS. 1987) and obtained his Ph. D (1997) from the University of Victoria, Canada with Prof. Reginald H. Mitchell. He took positions as a research chemist at Abbott Laboratories in Chicago (1997–2000), associate research fellow of Pfizer Global Research & Development at Ann Arbor, Michigan (2000–2007), and principal scientist of Bristol-Myers Squibb at Princeton/New Brunswick, New Jersey, USA (2007–2011). Currently, he is a Chief Scientific Officer of HEC Pharm Group in China.



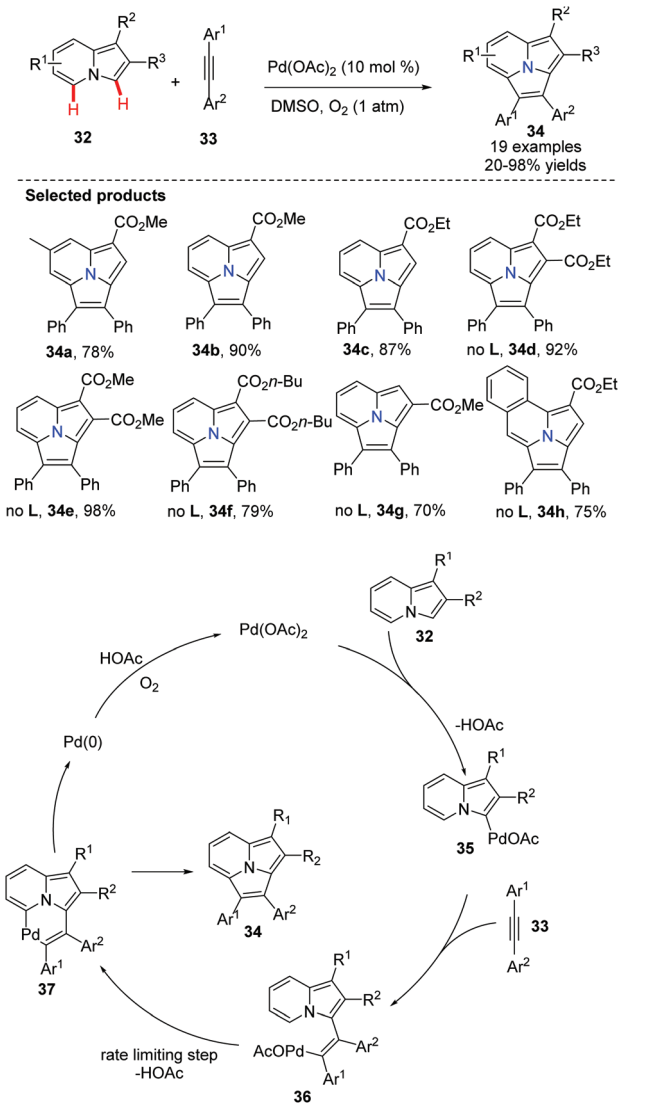
Scheme 2 Palladium-catalyzed intramolecular cyclization.



Scheme 3 Palladium-catalyzed intramolecular cyclization.



Scheme 4 Palladium-catalyzed alkylation/direct arylation sequence.



Scheme 5 Dual C–H activation and a plausible mechanism.

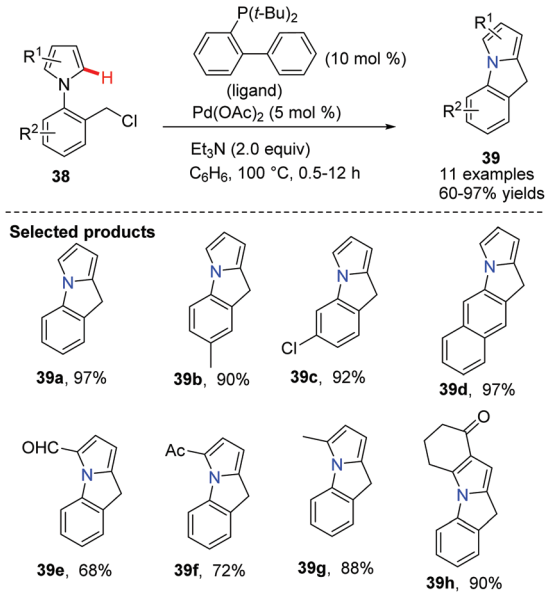
Recently, Hu and co-workers described a dehydrogenative Heck annulation reaction of indolizine **32** with diaryl acetylene **33** *via* dual C(sp^2)–H bond cleavage (Scheme 5).[37] A detailed mechanistic study confirmed that C–H bond metalation of the 7-position of the indolizine is the rate-limiting step. By optimizing and screening various additives and solvents, they found that the ligand 2,6-difluorobenzoic acid was the most efficient additive and DMSO the ideal solvent. This protocol has provided a simple and straightforward route to arylpyrrolo [2,1,5-*cd*]indolizines **34** under base-free conditions. In order to avoid regioisomers, symmetric alkynes were used.

Chang discovered a $Pd(OAc)_2$-catalyzed cyclization of *N*-(2-halobenzyl)-substituted pyrroles **38** to afford polycyclic compounds **39** (Scheme 6).[38] The reaction of substrates bearing electron-deficient groups on the pyrrole was found to undergo cyclization with faster rates compared to those bearing electron-donating groups. This method has provided an efficient route to the pyrroloindoles **39** which are difficult to obtain using the conventional Friedel–Crafts approach.

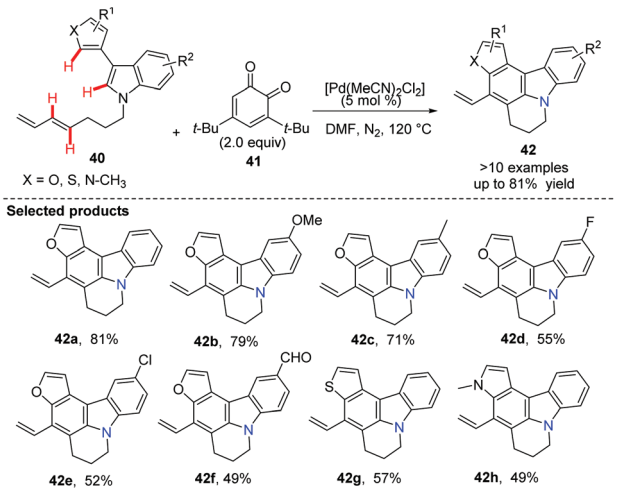
Booker-Milburn and co-workers pioneered a palladium-catalyzed C(sp^2)–H activation/cascade strategy for the synthesis of polyheterocycles **42** from readily available materials **40** (Scheme 7).[39] In order to avoid the furan moiety undergoing conjugate addition with the oxidant, a sterically bulky quinone **41** was used as an oxidizing agent. It was found that a short reaction time, typically 30 minutes, at an elevated temperature favoured this transformation. A large range of polycyclic compounds containing pyrrol, indole, furan and thiophene, such as **42a** to **42h**, were prepared in one step.

In the proposed mechanism, compound **40** undergoes C–H activation by coordination of the palladium(II) center to the diene **43**. Then, the intermediate **44** is formed by the cyclization by *syn*-carbometalation of the diene, which is followed by an attack of the second heterocyclic ring onto this electrophilic complex to give **45**. Next, dehydrogenation of **45** leads to **46**. Finally, the oxidation of the product **46** delivers **42** under mild reaction conditions (Scheme 8).

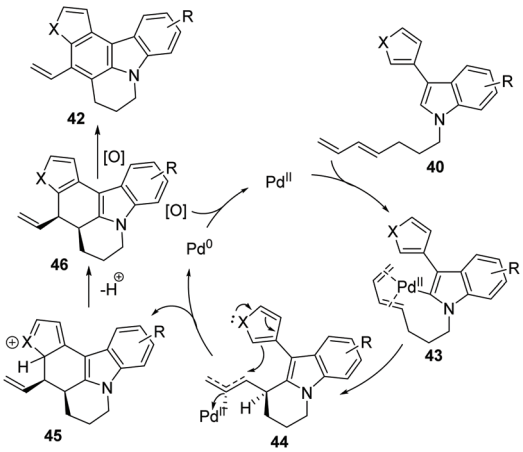
Xu, Loh and co-workers reported a feasible and efficient one-pot approach for the synthesis of pyrroloisoindolone derivatives **48** using *N*-vinyl acetamides by palladium-catalyzed intramolecular C(sp^3)–H activation (Scheme 9).[40] The strategy offered straightforward access to valuable nitrogen-containing products **48a–48k** under mild reaction conditions. A proposed



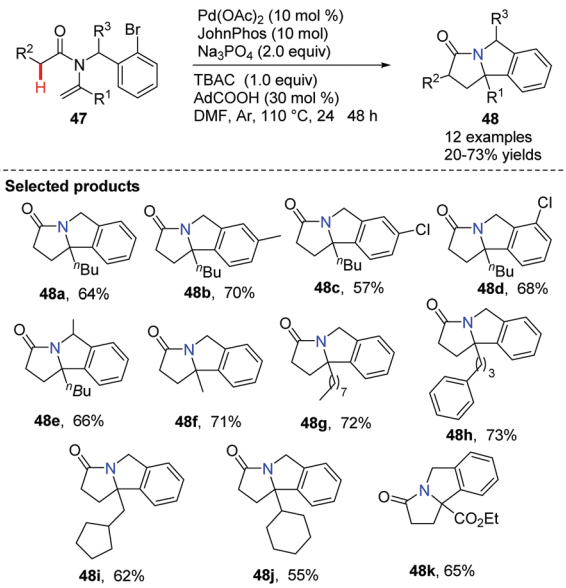
Scheme 6 Pd-Catalyzed synthesis of pyrroloindoles.



Scheme 7 Synthesis of polyheterocycles by the C–H activation cascade sequence.



Scheme 8 A plausible mechanism for the synthesis of polyheterocycles.

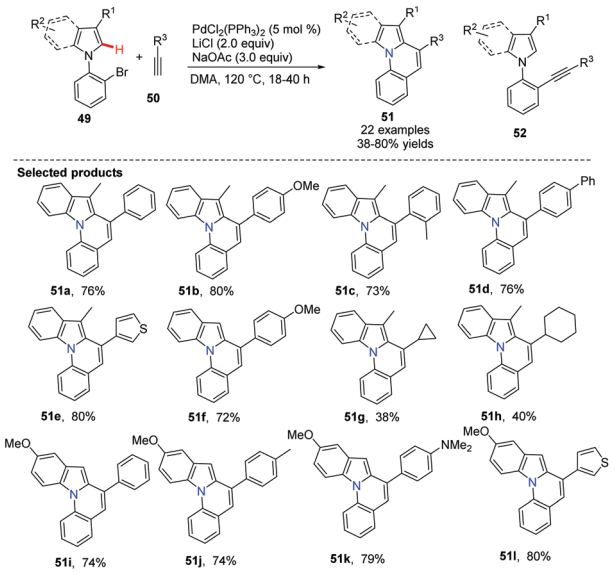


Scheme 9 Palladium-catalyzed domino coupling reaction.

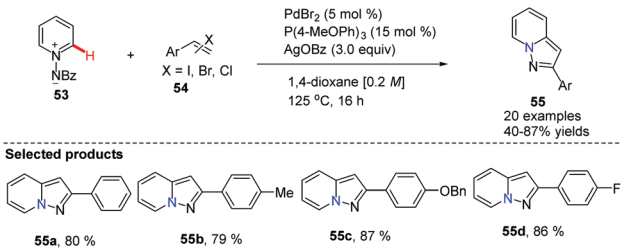
mechanism suggested that this is an intramolecular Heck cyclization involving 5-*exo* cyclization, C(sp^3)–H activation and reductive elimination during the catalytic cycles.

Verma and co-workers disclosed the palladium-catalyzed Sonogashira coupling conjoined C(sp^2)–H activation for the syntheses of pyrrolo[1,2-*a*]quinoline derivatives **51**.[41] It is important to avoid the uncyclized product **52** during the tandem transformation. After an extensive screening of Pd(II) sources [$PdCl_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2(PPh_3)_2$], additives such as LiCl and CuI, solvents (CH_3CN, DMF, DMSO, DMA) and bases (Et_3N, K_3PO_4, KO^{t}Bu, NaOAc), the best and general combination for these substrates was determined to be 5 mol% of $PdCl_2(PPh_3)_2$, 3.0 equiv. of NaOAc, 2.0 equiv. of LiCl in DMA at 120 °C for the tandem cyclization. This method was also used for the synthesis of pyrrolo[1,2-*a*]quinolines when 1-(2-bromophenyl)-pyrrole and terminal alkynes were used under the same reaction conditions (Scheme 10).

Substituted pyrazolo[1,5,*a*]pyridines are important molecules which are often employed as indole isosteres due to their relatively high metabolic stability in drug discovery. In 2011, Charette and co-workers reported the study of a domino direct alkynylation and cyclization of *N*-iminopyridinium ylides using alkenyl bromides and alkenyl iodides (Scheme 11).[42] Compared with previously reported synthetic methods, this protocol is greatly advantageous because only a two-step process is required. The selected screening of reaction conditions found silver benzoate to be the most favourable silver salt; a P(4-MeOPh)$_3$/$PdBr_2$ ratio of 3 : 1 provided the best results. Solvent choice was examined showing that 1,4-dioxane



Scheme 10 Palladium-catalyzed tandem coupling reaction and cyclization.



Scheme 11 Domino direct alkynylation and cyclization of *N*-iminopyridinium ylides with alkenyl bromides or iodides.

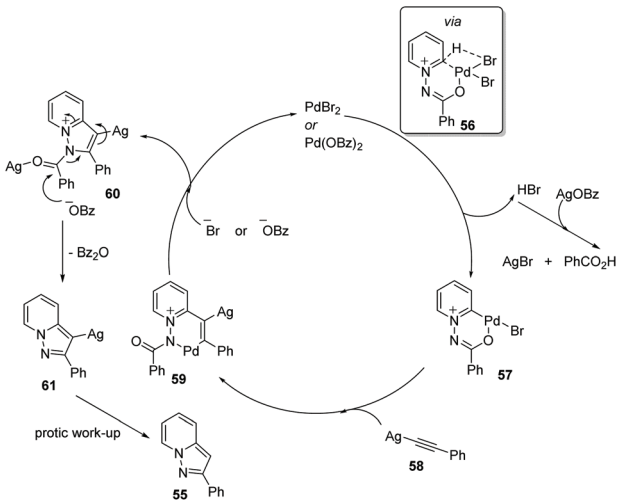
is ideal and running the reaction at 125 °C for 16 h provided the best general outcome for the substrates involved.

Charette and co-workers conducted mechanistic studies and confirmed the formation of alkynes from alkenyl iodides, by a competition reaction. It was found that the reaction proceeded quickly once the alkyne was generated, and thus alkynes were identified as optional starting materials for this transformation (Scheme 12 and 13).

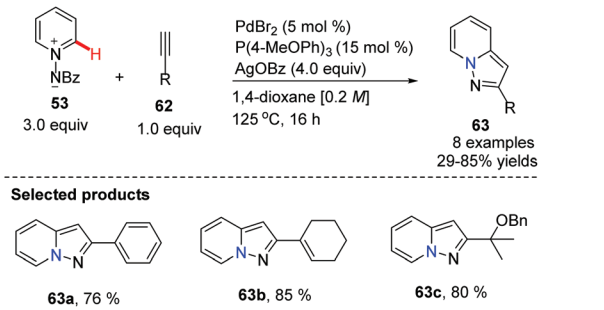
Direct C(sp^2)–H azidation, followed by N–N bond formation to give novel bridgehead nitrogen heterocycles was rarely observed until 2013 when Jiao and co-workers first showcased a novel Pd-catalyzed azidation of arylpyridines *via* C(sp^2)–H activation using azides as an external nitrogen source (Scheme 14).[43] This study is significant because it provides a concise, alternative approach to bioactive pyrido[1,2-*b*]indazoles from readily available arylpyridines.

SanMartin, Dominguez and co-workers developed a new strategy for the rapid construction of a series of pyrazolo[1,5-*f*] phenanthridines **67** from simple starting materials, such as acetophenones and arylhydrazines **66**.[44] The cyclization by intramolecular biaryl bond formation is the key step, accomplished by direct C–H activation utilizing $Pd(OAc)_2$ as the catalyst (Scheme 15).

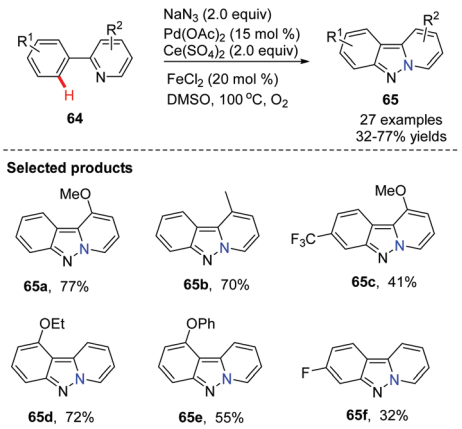
Chen, Wu and co-workers developed a novel approach for the synthesis of indazolo[3,2-*b*]quinazolinone derivatives **70** *via* palladium-catalyzed C–H activation/intramolecular amin-



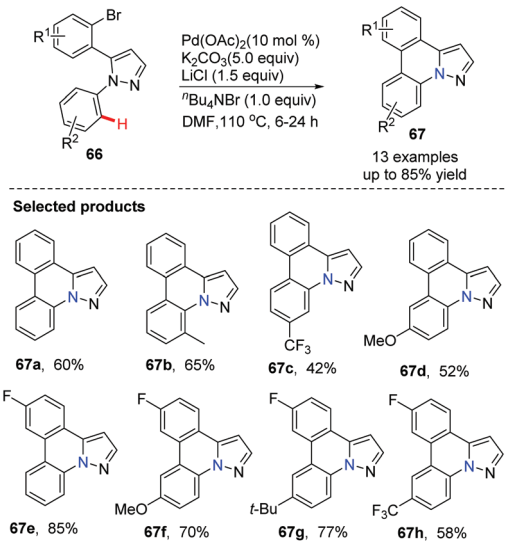
Scheme 12 Proposed catalytic cycle involving the C–H activation.



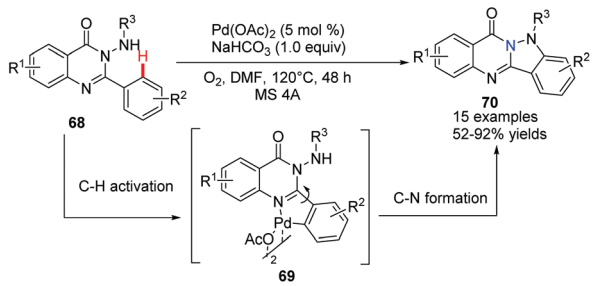
Scheme 13 Domino direct alkynylation and cyclization of *N*-iminopyridinium ylides with alkynes.



Scheme 14 Palladium-catalyzed nitrogenation reaction.



Scheme 15 Synthesis of pyrazolo[1,5-*f*]phenanthridines by direct arylation.



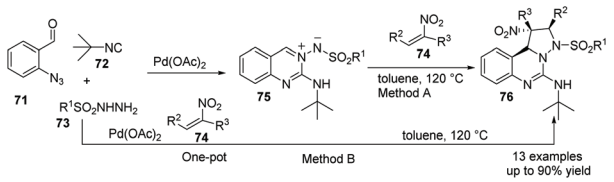
Scheme 16 Synthesis of indazolo[3,2-*b*]quinazolinone derivatives *via* Pd-catalyzed C–H activation/intramolecular amination.

ation of 2-aryl-3-(arylamino)quinazolinones **68** in moderate to excellent yields (Scheme 16).[45] Furthermore, the potential utility of the products was demonstrated as a new class of blue fluorophores for fluorescent materials. Preliminary mechanistic studies suggested that a palladacycle dimer could be the key intermediate, which underwent a cascade cyclometalation and C–H amination sequence.

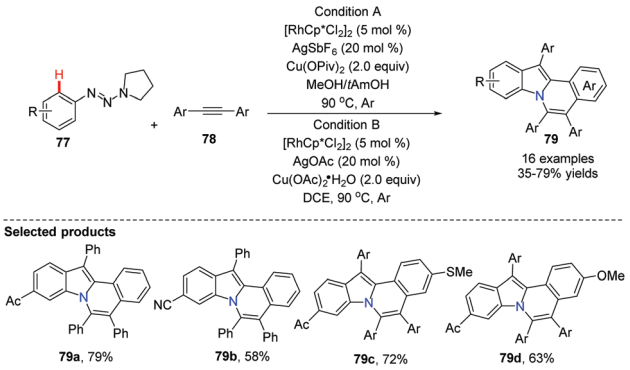
In 2019, Sawant *et al.* reported that under Pd-catalyzed conditions, azomethine imine **75** reacted with nitroolefins **74**, giving bridgehead nitrogen containing heterocycles **76**.[46] A one-pot, four component approach (Method B) also gave this potential pharmaceutically useful polyheterocyclic skeleton from readily available 2-azidobenzaldehyde **71**, isocyanide **72**, aryl sulfonyl hydrazide **73** and nitroolefins **74** (Scheme 17).

2.3. Rhodium-catalyzed synthesis of bridgehead nitrogen heterocycles

Utilizing Rh as a catalyst, silver and copper salts as co-catalysts, Wu, Zhang and Huang developed a one-step synthesis of indolo[2,1-*a*]isoquinolines **79** *via* a double C–H annulation



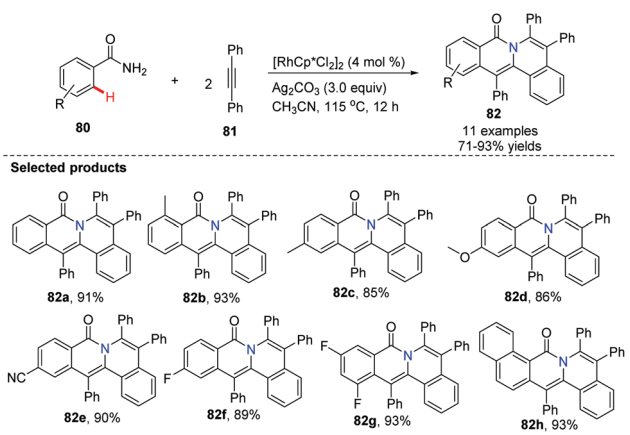
Scheme 17 Pd-Catalyzed cyclocondensation of azomethine imine.



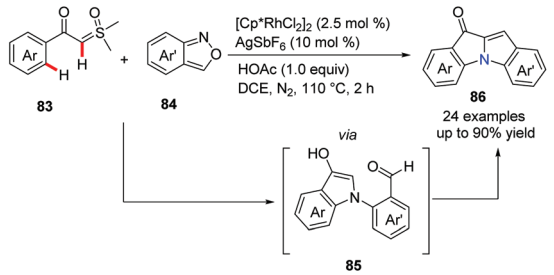
Scheme 18 Synthesis of indolo[2,1-*a*]isoquinolines *via* a triazene-involved C–H annulation cascade.

cascade (Scheme 18). Interestingly, they employed triazene **77** as an internally cleavable directing group.[47] The kinetic isotope effects suggested that the alkyne insertion step is rate limiting for the second C–N annulation.

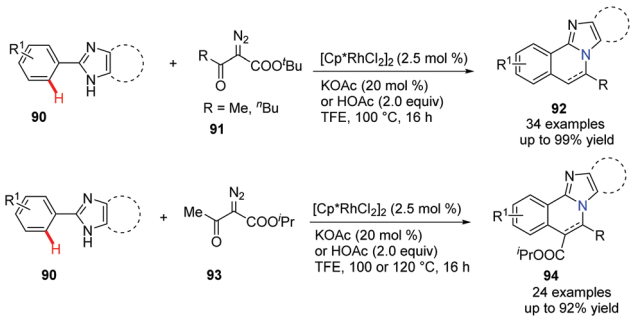
Li and co-workers pioneered the study of Rh-catalyzed double oxidative coupling of primary benzamides and 2.0 equiv. of symmetrical alkynes,[48] providing the bridgehead nitrogen heterocycle **82** in good to excellent yields (71–93%) *via* double C–H activation and oxidative coupling (Scheme 19). Since isoquinolones were prepared from secondary benzamides and alkynes under the almost identical conditions, this method was found to be a valuable improvement for building



Scheme 19 Rh(III)-Catalyzed double oxidative coupling between primary benzamides and alkynes.



Scheme 20 Rh-Catalyzed coupling reaction of sulfoxonium ylides and anthranils.



Scheme 22 Rh(III)-Catalyzed annulation of 2-arylimidazoles with diazoketoesters to access imidazoisoquinolines.

novel bridgehead nitrogen heterocycles from quinazolones or dihydroquinazolinones with alkynes.

Recently, a novel approach to bridgehead nitrogen-fused indolones has been developed by Cheng's group (Scheme 20).[49] A rhodium-catalyzed reaction of aroyl sulfoxonium ylides **83** and anthranils **84** proceeded well to build three bonds in one pot, giving desired products **86** in moderate to good yields. A tentative mechanistic study suggested that the catalytic cycle involves Rh promoted C–H activation and *ortho*-amination of α-aroyl sulfoxonium ylides. Finally, the second indole ring was constructed *via* intermediate **85** by the Aldol condensation.

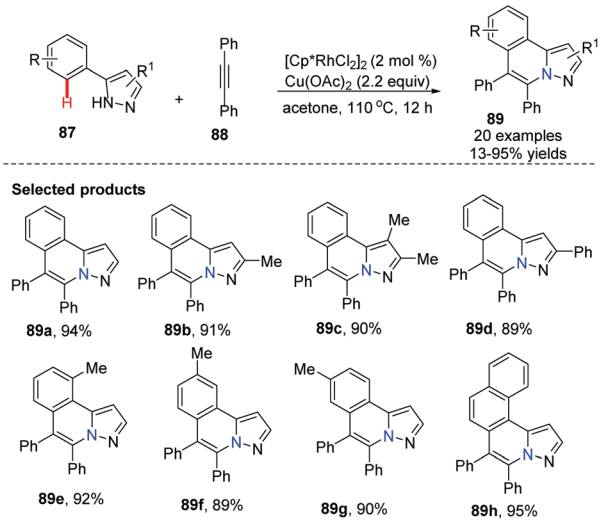
Li and co-workers developed a Rh-catalyzed oxidative coupling of 5-aryl-1*H*-pyrazoles **87** with diphenyl-acetylenes **88**.[50] In this transformation, pyrazoles acted as an ideal directing group to facilitate C–H bond activation to access novel heterocycles with good to excellent yields, although only symmetrical alkynes were studied (Scheme 21).

Imidazo[2,1-*a*]isoquinolines are bridgehead nitrogen fused heterocycles found in many drugs and bioactive compounds. In 2018, Song *et al.* reported an efficient and practical approach *via* Rh(III)-catalyzed [4 + 2] annulation of 2-arylimidazoles **90** and α-diazoketoesters **91** (Scheme 22).[51] Obviously, under acidic reaction conditions, the decarboxylation products **92** were obtained in good to excellent yields when *t*-butyl ester was used.

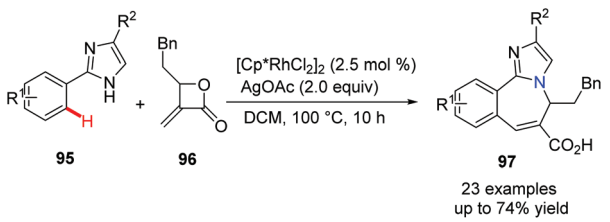
It is well known that benzoazepine derivatives are valuable compounds with significant biological and pharmaceutical activities. Meanwhile, imidazole is an often-found essential scaffold in the drug discovery program. In 2019, Zhang, Fan and their co-workers developed a novel and efficient method for combining both benzoazepine and imidazole pharmacophores together.[52] The Rh(III)-catalyzed C(sp^2)–H activation and functionalization of 2-phenylimidazole and methyleneoxetanone *via* [4 + 3] annulation gives the desired coupling products, fused heterocycles **97**, in moderate to good yields (Scheme 23). This is a reliable and atom-economical approach from simple and inexpensive starting materials and is expected to find wide application.

Sulfoxonium ylides have been introduced recently as convenient carbene precursors which are much safer compared with the analogous diazo compounds. In 2018, Ellman *et al.* developed a Rh(III)-catalyzed coupling reaction between *C*-alkenyl azoles and sulfoxonium ylides and *in situ* cyclodehydration gave substituted bridgehead nitrogen-fused [5,6]bicyclic heterocycles **100** with complete regioselectivity (Scheme 24).[53] A proposed mechanism suggests that the C–H functionalizations of *C*-alkenyl azoles and sulfoxonium ylides were involved.

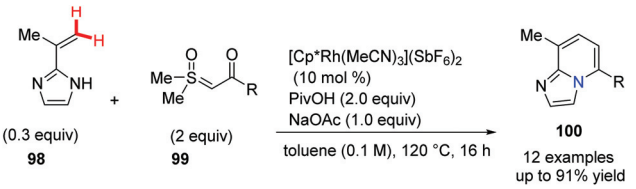
Diazepine and quinoxaline are the most important privileged scaffolds in drug discovery. Recently, Sun *et al.* developed a powerful and versatile approach to these bridgehead



Scheme 21 Rh(III)-Catalyzed C–C/C–N coupling between aryl-pyrazoles with alkynes.



Scheme 23 Rh(III)-Catalyzed C–H functionalization and annulation to prepare benzoazepine using methyleneoxetanone.

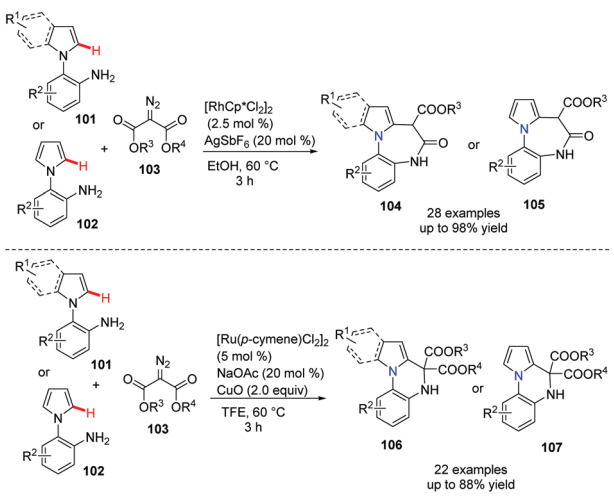


Scheme 24 Rh(III)-Catalyzed C–H functionalization of *C*-alkenyl azoles with sulfoxonium ylides.

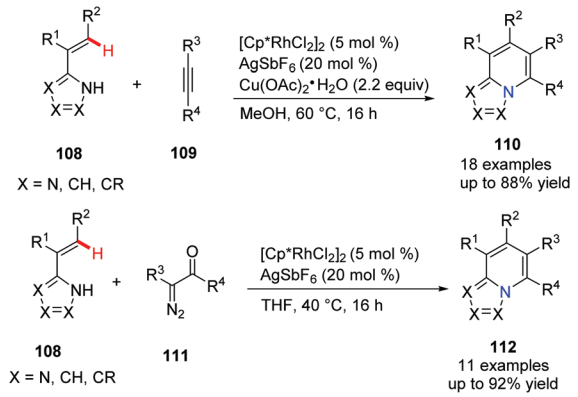
nitrogen fused heterocycles.[54] Notably, under the Rh(III) catalyst, the annulation of indolo anilines and diazo compounds proceeded well *via* the free amine assisted C–H activation, followed by amidation leading to the diazepino[1,7-*a*]indole **104** or **105** in good to excellent yields. On the other hand, when Ru(II) was used as the catalyst, the coupling reaction involves the formation of a Ru–carbene complex, followed by $-NH_2$ group insertion and cascade cyclization *via* a metallo-ene type reaction, a further β-hydride elimination, giving the indolo[1,2-*a*]quinoxaline **106** or **107** as the major product in good to excellent yields (Scheme 25).

In 2017, Ellman's group disclosed a novel approach to synthesize privileged [5,6]-bicyclic heterocycles **110** with bridgehead nitrogen by Rh(III)-catalyzed C–H activation of *C*-alkenyl azoles (Scheme 26).[55] Since one of the reactants can be alkenyl imidazoles, pyrazoles, or triazoles, it could provide the heterocycle products with nitrogen incorporated at different sites. On the other hand, the coupling partners, such as alkyne and diazoketone, also give azolopyridines with various substitution patterns which make the new method very attractive for medicinal chemistry.

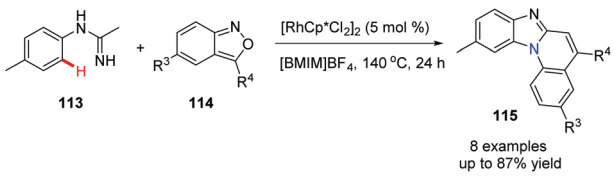
In 2020, Li, Wu and co-workers reported a novel and practical approach to benzimidazo[1,2-*a*]quinolones **115**.[56] The cascade reaction from imidamides and anthranils involves a Rh(III)-catalyzed C–H activation, followed by a intermolecular amination and cyclization process (Scheme 27).



Scheme 25 Rh(III) or Ru(II)-controlled divergent annulation to diazepine and quinoxaline derivatives.



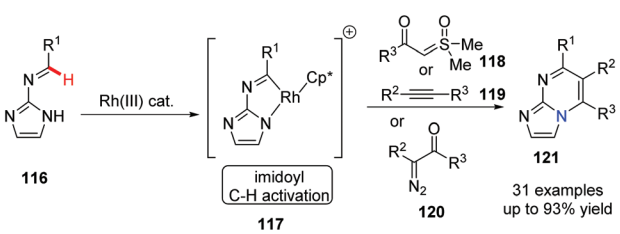
Scheme 26 Rh(III)-Catalyzed C–H activation of *C*-alkenyl azoles to access bicyclic bridgehead nitrogen heterocycles.



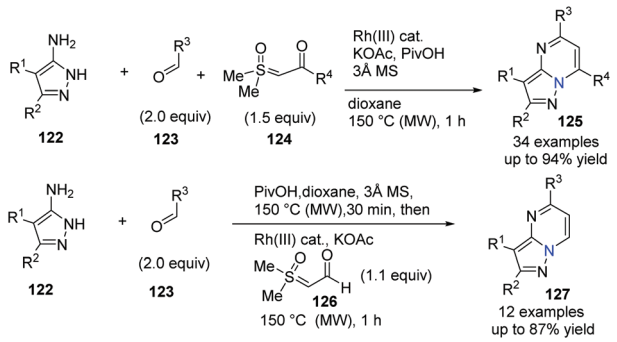
Scheme 27 Rh(III)-Catalyzed C–H activation to access benzimidazoquinolines.

Bicyclic [5,6]-bridgehead nitrogen fused heterocycles are privileged pharmacophores as FDA-approved drug and clinical candidates. In 2018, Ellman and his group first reported Rh(III)-catalyzed imidoyl C–H activation for the preparation of substituted azolopyrimidines **121** (Scheme 28).[57] The annulations of *N*-azolo imines with sulfoxonium ylides, diazoketones and alkynes gave the desired bridgehead nitrogen fused heterocycles in good to excellent yields. This novel approach could have a valuable application in drug discovery.

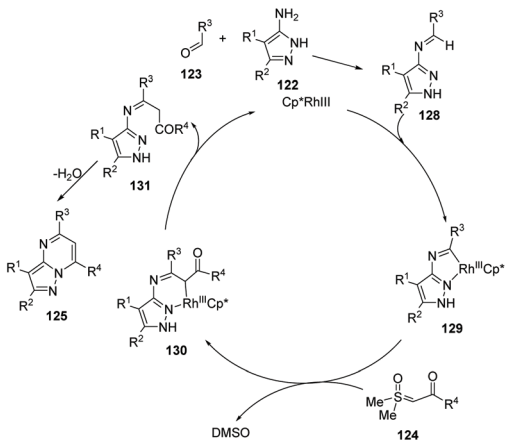
Three-component coupling reactions from aldehydes, aminopyrazoles and newly readily available sulfoxonium ylides enable access to complex molecules under straightforward conditions with a short reaction time. Ellman's group further developed a successful Rh(III)-catalyzed protocol to the general synthesis of many pyrazolo[1,5-*a*]pmidines **125** in good yields (Scheme 29).[58] Notably, good functional group compatibility is an great advantage for this versatile and efficient transform-



Scheme 28 Synthesis of pyrazolopyrimidines *via* Rh(III)-catalyzed imidoyl C–H activation.



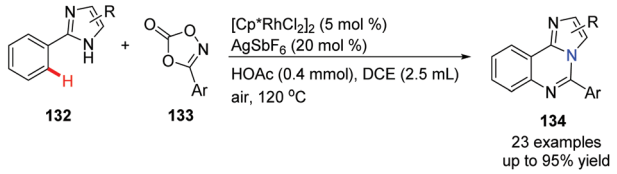
Scheme 29 Three-component coupling of aminopyrazoles, aldehyde and sulfoxonium ylides to access pyrazolopyrimidines.



Scheme 30 Proposed mechanism for annulation.

ation, and it was suggested that Rh(III)-catalyzed imidoyl C–H activation was involved in annulation (Scheme 30). On the other hand, in a one-pot, stepwise reaction, formyl ylide **126** was first utilized smoothly.

Imidazo[1,2-*c*]quinazolines are widely present in drug molecules. Several methods that utilized substituted anilines as the starting materials have been developed to build these scaffolds. Different from these known methods, Cheng reported a Rh(III), and Ag(I)-co-catalyzed annulation *via ortho*-C–H activation of 2-arylimidazoles (Scheme 31).[59] A series of fused heterocycles **134** were prepared in good to excellent yields from simple and readily available 2-arylimidazoles **132**



Scheme 31 Rh(III)Ag(I)-cocatalyzed annulation *via* C–H activation of arylimidazoles.

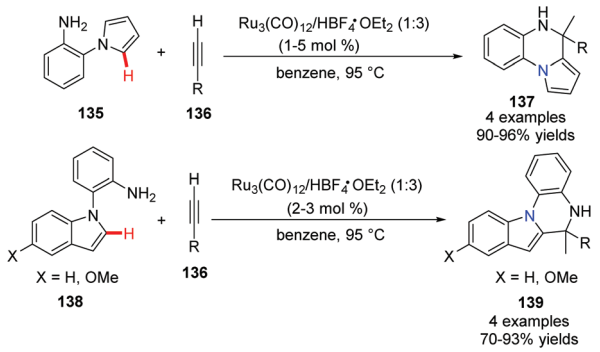
and 1,4,2-dioxazol-5-ones **133** which provided rhodium carbene species by the extrusion of CO_2.

2.4. Ruthenium-catalyzed synthesis of bridgehead nitrogen heterocycles

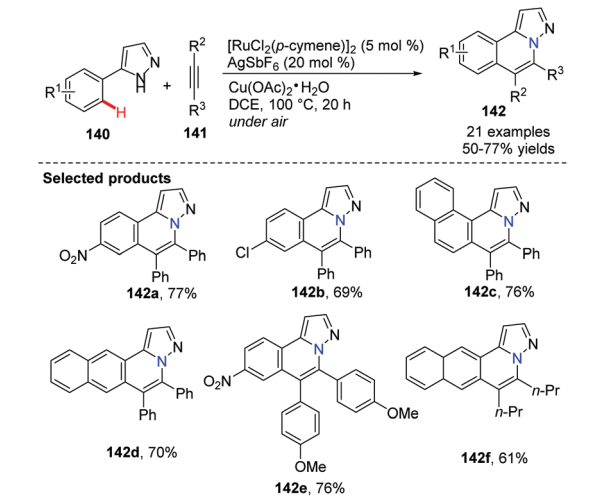
Yi and co-workers reported a cationic ruthenium–hydride complex for C–H activation of benzocyclic amines to access tricyclic compounds **137**.[60] Substituted quinolines and quinoxalines could be formed *via* the N–H and C(sp^2)–H functionalization reaction of benzocyclic amines and terminal alkynes (Scheme 32).

In 2012, Ackermann and co-workers reported using 5 mol% of cationic ruthenium(II), 20 mol% $AgSbF_6$ as a promoter, and $Cu(OAc)_2{\cdot}H_2O$/air as the oxidant to promote an oxidative alkyne annulation process with substituted 1*H*-pyrazoles (Scheme 33).[61] This method generated the bridgehead heterocycles **142** from readily available starting materials with high functional group tolerance.

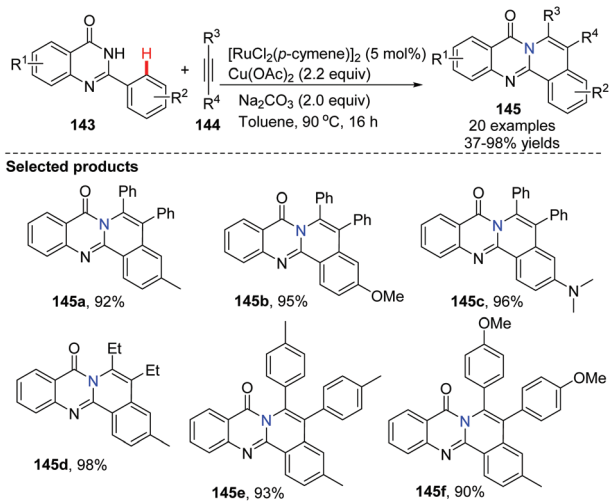
In 2014, Peng and co-workers applied the ruthenium-catalyzed oxidative cross-coupling/annulation of quinazolones with symmetric alkynes to the synthesis of 8*H*-isoquinolino[1,2-*b*]



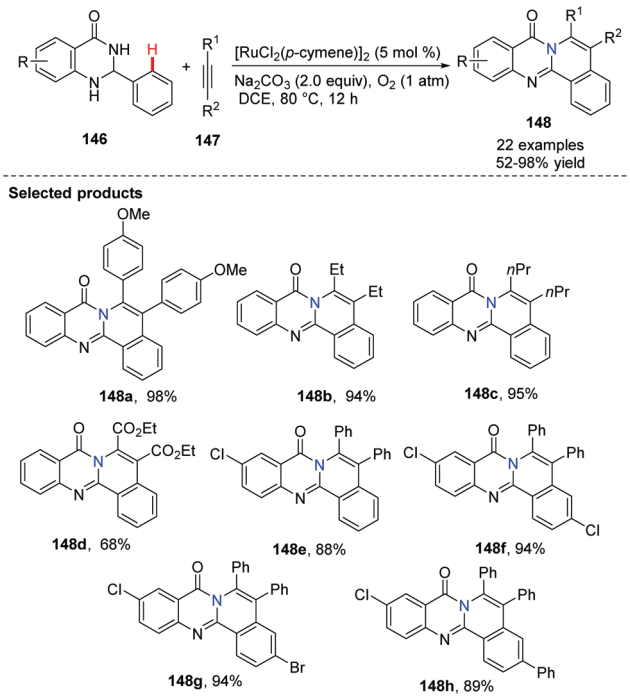
Scheme 32 Coupling reaction of benzocyclic amines and alkynes to form tricyclic heterocycles.



Scheme 33 Oxidative alkyne annulations with pyrazoles.



Scheme 34 Ru-Catalyzed cross-coupling/annulations of quinazolones with alkynes.



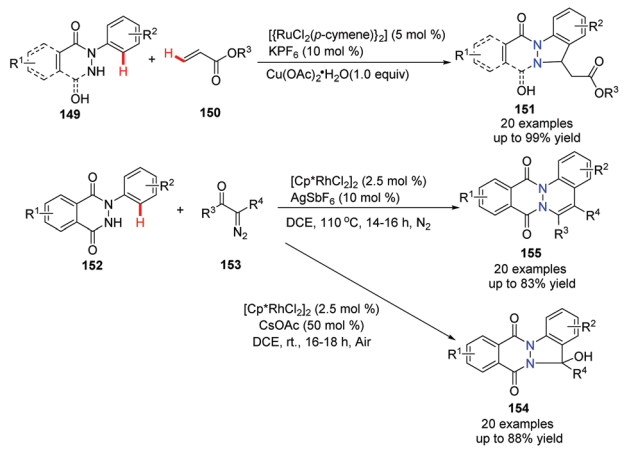
Scheme 35 Amide-directed cross-coupling/annulation.

quinazolin-8-one derivatives **145** (Scheme 34).[62] After screening of reaction conditions we found that using 2.2 equiv. of $Cu(OAc)_2$ as the oxidant, and 2.0 equiv. of Na_2CO_3 as the base in toluene at 90 °C for 16 h provided the best results for these fused polycyclic heteroarenes with good to excellent yields, although moderate regioselectivities were obtained when unsymmetrical alkynes were used as reactants.

Slightly different from Peng's approach, Nagaiah demonstrated Ru-catalyzed aerobic oxidative dehydrogenation followed by cross-coupling/annulation of dihydroquinazolinones **146**, instead of the use of quinazolinones.[63] The method avoided the use of $Cu(OAc)_2$ as the oxidant and purification of intermediates. This synthetic method provided a facile route to access a class of highly functionalized, N-fused polycyclic compounds **148**. When unsymmetrically, disubstituted alkynes were used, two regioisomeric products were obtained (Scheme 35).

The use of *N*-arylphthalazine-1,4-dione **148** to construct bridgehead nitrogen fused and functionalized phthalazines has received some investigation recently. It was reported that a Ru-promoted oxidative alkenylation of *N*-aryl pyridazinediones and *N*-aryl phthalazinediones with acrylates resulted in indazole derivatives **151** in good to excellent yields (Scheme 36).[64] In addition, it was found that Rh(III)-catalyzed annulations of *N*-arylphthalazine-1,4-dione with α-diazo carbonyl compounds gave either the [4 + 1] or [4 + 2] annulation product, depending on the additive in the reaction conditions.

Similarly, under different reaction conditions, using either Ru(II) or Ir(III) catalyst for C–H activation and annulation with 1,3-diketone-2-diazo compounds, *N*-arylphthalazine-1,4-diones were converted to phthalazinocinnolinediones **158** in good to excellent yields, and phenylquinazolinones were transformed to isoquinolinoquinazolinones under mild conditions respectively (Scheme 37).[65]

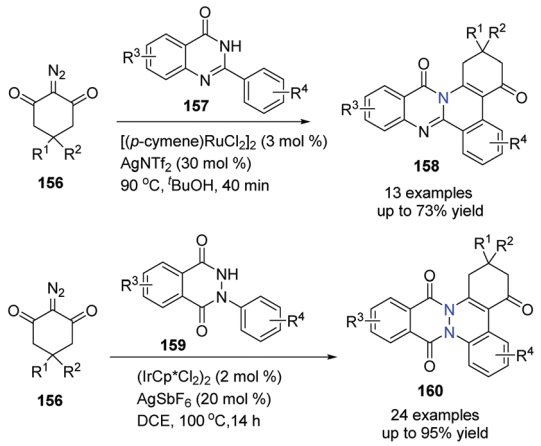


Scheme 36 Ru(II) or Rh(III)-catalyzed annulation of *N*-arylphthalazinedione with acrylates or diazo carbonyl compounds.

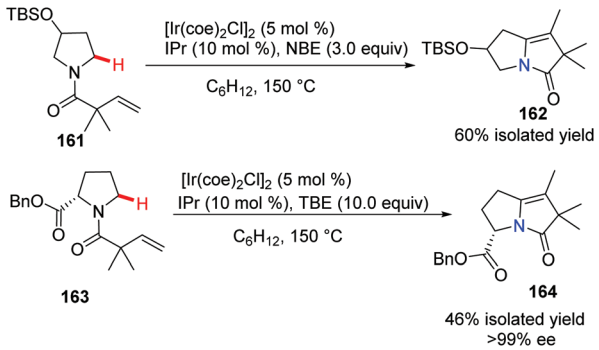
2.5. Iridium-catalyzed synthesis of bridgehead nitrogen heterocycles

The Sames group successfully demonstrated a novel intramolecular oxidative cross-coupling of $C(sp^3)$–H bonds and alkenes under neutral and iridium-catalyzed conditions (Scheme 38).[66] It is noteworthy that when optically pure proline derivative **163** serves as the starting material, it gave bridgehead nitrogen heterocycle **164** with excellent chiral purity (>99% ee).

The indole skeleton exists in various biologically active natural products and medicines, therefore much effort has



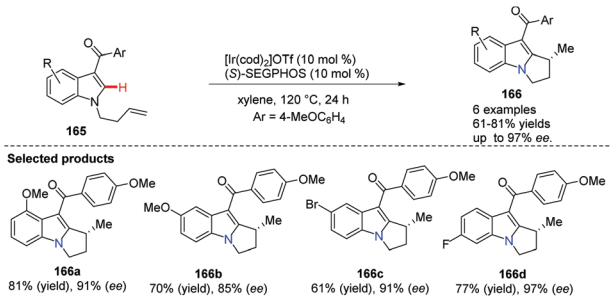
Scheme 37 Ru(II)/Ir(III)-catalyzed C–H bond activation/annulation of cyclic amides to prepare bridgehead nitrogen heterocycles.



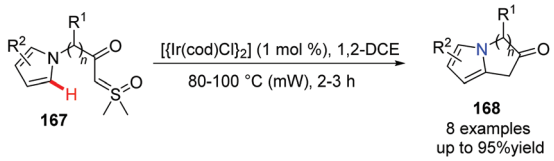
Scheme 38 Iridium-catalyzed oxidative cyclization.

been expended to develop novel and catalytic approaches *via* C(sp^2)–H bond activation. Ellman and Bergman pioneered the studies of the Rh-catalyzed enantioselective reaction using *N*-allylindoles to access N-fused bridgehead tricycles with chiral phosphoramidites as ligands.[67] Recently, Shibata and co-workers developed an intramolecular and highly enantioselective C–H activation of *N*-alkenylindoles that utilized iridium.[68] A *para*-anisoyl group at the 3-position of the indoles operated as an efficient directing group (see **166a** to **166d**), and the combination of cationic iridium(I) and chiral diphosphine ligands achieved excellent desired product **166** with up to 97% ee (Scheme 39).

Sulfoxonium ylides have recently received increased attention; they serve as novel carbene surrogates catalyzed by transition metals for the rapid construction of bridgehead nitrogen heterocycles. In 2019, Aïssa and his group found that when catalyzed by an iridium catalyst, without the assistance of a directing group, chemo-specific cyclization of α-carbonyl sulfoxonium ylides **167** for the functionalization of the pyrrolic C–H bond occurred, giving bicyclic 5–5 and 5–6 systems **168** in good to excellent yields (Scheme 40) respectively.[69]



Scheme 39 Intramolecularalkylations of *N*-alkenylindoles at the C-3 position using the directing group approach.



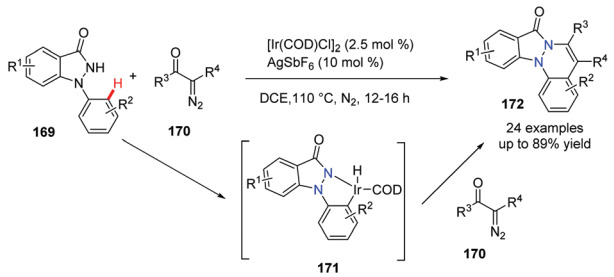
Scheme 40 Ir-Catalyzed functionalization of the pyrrolic-C–H bond to prepare bridgehead nitrogen heterocycles.

The use of α-diazo carbonyl compounds for Rh-, Ru- or Pd-catalyzed carbene insertion/cyclization has been investigated by many academic labs. Although the Ir-catalyzed carbenoid functionalization has been reported for the synthesis of heterocycles, its use to access bridgehead nitrogen fused polycycles is limited. In 2018, Sakhuja *et al.* reported an Ir-promoted annulation of 1-arylindazolones with α-diazo carbonyl compounds, providing indazolone-fused cinnolines **172** in good to excellent yields (Scheme 41).[70] Obviously, the Ir(I) species facilitates the N–H oxidative addition of 1-arylindazolone and affords the five-membered Ir(III) intermediate **171** which reacts with α-diazo carbonyl compounds, to generate the final desired product.

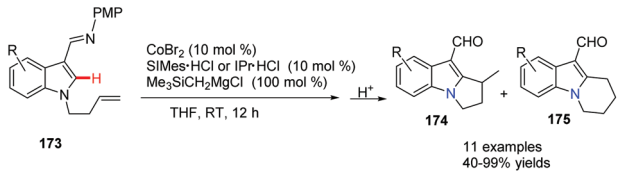
2.6. Cobalt-catalyzed synthesis of bridgehead nitrogen heterocycles

Yoshikai and co-workers reported a cobalt-N-heterocyclic carbene (NHC)-catalyzed intramolecular hydroarylation reaction on an indole to give dihydro-pyrrolo-indole and tetrahydropyridoindole derivatives (Scheme 42).[71] Notably, by careful choice of the NHC ligands, the selective formation of 5-*exo* **174** and 6-*endo* product **175** was controlled well. This method provided an efficient route to access a class of highly functionalized tricyclic compounds with good yields and regioselectivity.

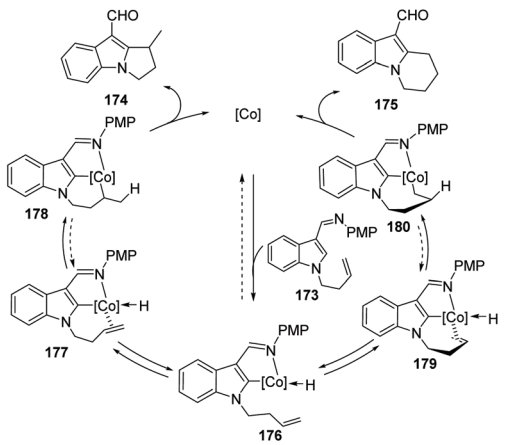
The authors proposed that the reaction was initiated by chelation-assisted oxidative addition of the C–H bond to a cobalt species to give key intermediate **176.** Subsequent insertion of the olefin into the Co–H bond leads to either six-membered **178** or seven-membered **180** intermediates, which undergo reductive elimination to give the title compound **174** or **175.** The olefin insertion step is probably the regioselectivity determining step of the reaction (Scheme 43).



Scheme 41 Ir-Catalyzed annulation to access indazolone-fused cinnolines.



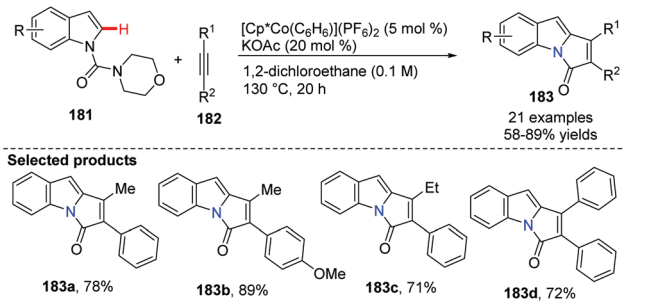
Scheme 42 Intramolecular hydroarylation leading to dihydropyrrolo-indole and tetrahydropyridoindole.



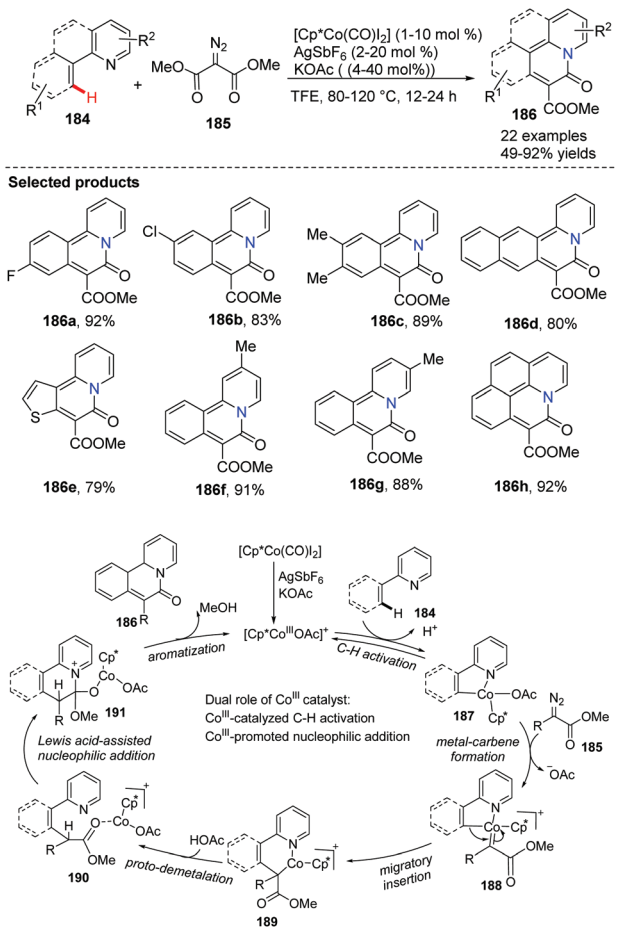
Scheme 43 Proposed reaction mechanism.

Kanai and co-workers recently innovated the utility of a cationic, high-valent cobalt(III) complex for the C(sp^2)–H bond functionalization of *N*-carbamoyl indoles **181**.[72] The *C*-2 indole alkenylation/annulation sequence proceeded smoothly in the presence of a Cp*Co(III) complex, giving the corresponding pyrrolo-indolone compounds **183** in 58–89% yields (Scheme 44).

Glorius and co-workers accomplished a cobalt(III)-catalyzed directed C(sp^2)–H functionalization of various 2-arylpyridines **184** with carbene precursors **185** in 2015.[73] The dual role of cobalt(III) catalyst as a transition metal and a Lewis acid might be vital to the C–H activation step and sequential cyclization (Scheme 45). This method provided novel bridgehead nitrogen heterocycles **186** efficiently with broad structural diversity, as



Scheme 44 Directed C–H alkenylation/annulation.

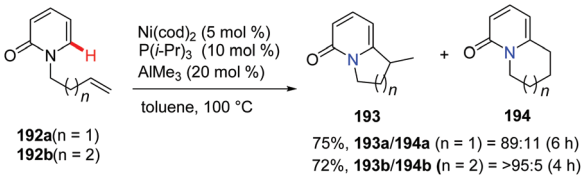


Scheme 45 Directed C–H bond functionalization of 2-arylpyridines with carbene precursors and a putative mechanism.

the *ortho*-pyridine substrates are crucial directing groups for the arene C–H bond activation.

2.7. Nickel-catalyzed synthesis of bridgehead nitrogen heterocycles

Hiyama and co-workers reported intramolecular cyclization of alkenyl pyridone derivatives **192** using $Ni(cod)_2/AlMe_3$ (as a Lewis acid) catalysis in 2009.[74] The intramolecular addition proceeded mainly in an *exo-trig* fashion to afford predomi-



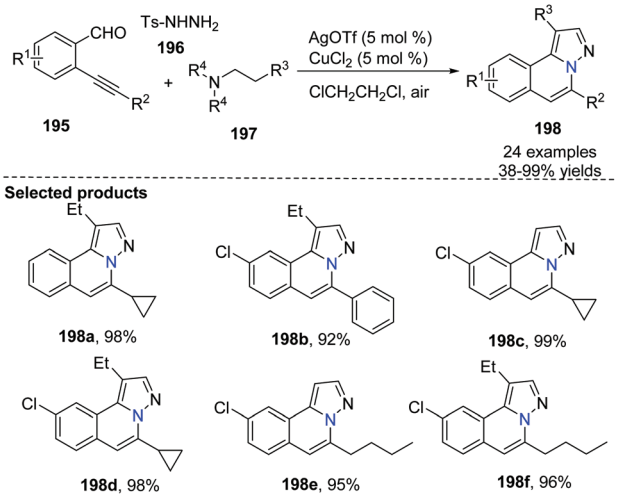
Scheme 46 Intramolecular alkenylation leading to bicyclic pyridone derivatives.

nantly bicyclic substituted pyridone **193** along with the minor isomer **194** in combined high yields and good regioselectivity (Scheme 46).

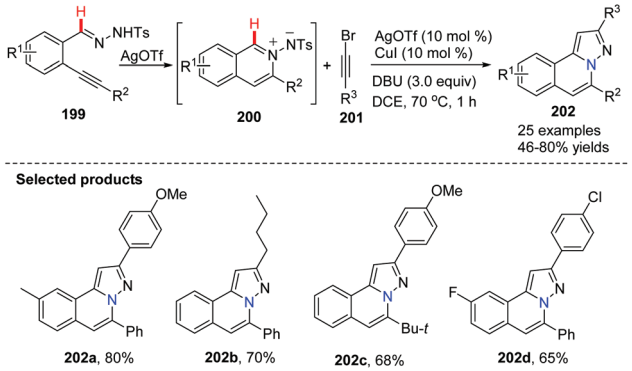
2.8. Silver-catalyzed synthesis of bridgehead nitrogen heterocycles

Wu and co-worker described a silver and copper co-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and a tertiary amine, which provides a novel and efficient route for the generation of *H*-pyrazolo[5,1-*a*]isoquinolines **198** (Scheme 47).[75] The reaction process involved the following steps: (i) Silver-catalyzed cyclization of 2-alkynylbenzaldehyde and sulfonohydrazide. (ii) Copper-catalyzed oxidation of an aliphatic C–H bond of tertiary amines, and subsequent intermolecular cyclization/aromatization. The reaction occurs under mild conditions and provides excellent results employing simple operations.

An example applied to *N*-iminoisoquinolinium ylides, which generated *in situ* ylides as directing groups for further C–H activation transformations, was developed by Chen, Peng and co-workers in 2012.[76] Without using a palladium(II) catalyst, they described a catalytic pathway in which silver triflate (10 mol%) and copper iodide (10 mol%) co-promoted tandem alkynyl active cyclization of *N*-iminoisoquinolinium ylides and bromoalkynes to form *H*-pyrazolo[5,1-*a*]isoquinolines **202** in good



Scheme 47 Synthesis of *H*-pyrazolo[5,1-*a*]isoquinolines catalyzed by Ag(I)/Cu(II).



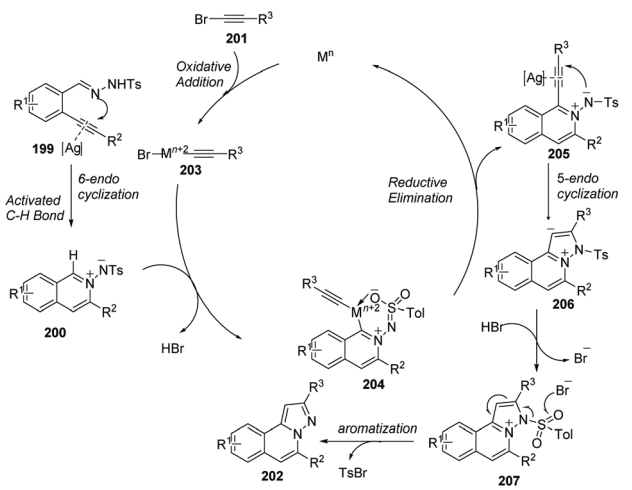
Scheme 48 AgOTf/CuI co-catalyzed tandem alkynylative cyclization reaction to form *H*-pyrazolo[5,1-*a*]isoquinolines.

yields under mild reaction conditions (Scheme 48). The C–H bond activation mechanism is given in Scheme 49, suggesting that *N*-iminoisoquinolinium ylides are ideal building blocks for the synthesis of novel bridgehead nitrogen heterocycles.

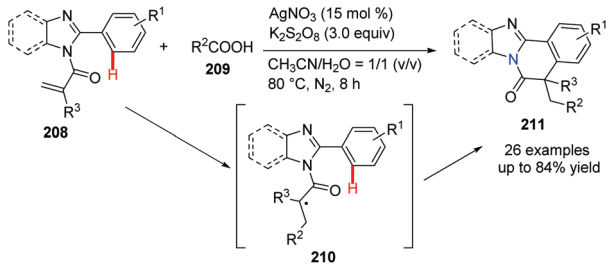
It should be noted that construction of benzimidazo-isoquinoline fused polycycles *via* radical type cyclization is not highly efficient. Recently, Wei, Yu and their co-workers reported a silver-catalyzed decarboxylative radical cascade cyclization.[77] In the presence of $K_2S_2O_8$/$AgNO_3$, the reaction of *N*-methacryloyl-2-phenylbenzoimidazole **208** with carboxylic acids **209** gave desired heterocycle **211** under mild reaction conditions (Scheme 50). Based on the mechanistic study, it is believed that radical intermediate **210** was generated after releasing CO_2 from the corresponding carboxylic acid, followed by the addition of the reactive radical to the aromatic C=C bond.

2.9. Copper-catalyzed synthesis of bridgehead nitrogen heterocycles

Metal-catalyzed modern C–C cross coupling reactions and C–N bond forming reactions, such as the modern Ullmann reaction



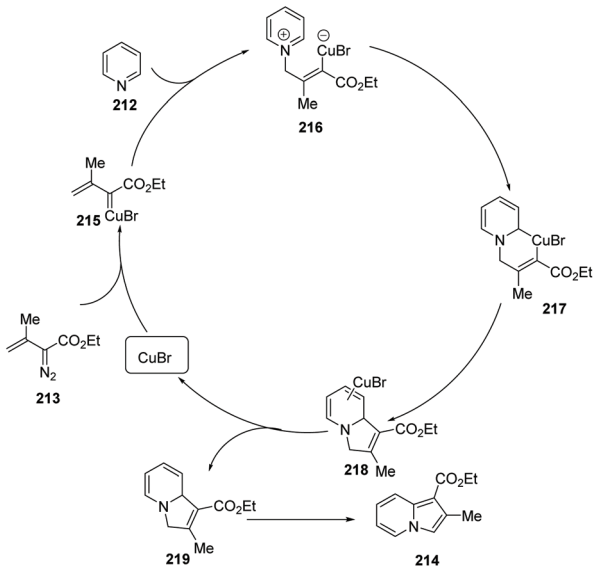
Scheme 49 Plausible mechanism involved the formation of *N*-iminoisoquinolinium ylides and C–H activation.



Scheme 50 Silver salt promoted decarboxylative radical cyclization to access bridgehead nitrogen heterocycles.

and palladium or copper-catalyzed C–H functionalization, have provided a powerful tool for the synthesis of nitrogen-containing heterocycles in a novel and simple way. In contrast to palladium, rhodium, nickel and other transition metals, copper and copper salts are inexpensive and exhibit relatively low toxicity. Over the past decade, modern organocopper chemistry has developed from stoichiometry to the current catalytic processes. It was found that nitrogen-containing ligands can increase the catalytic activity, solubility and stability of the copper–amine complex which serves to promote catalytic reaction, shifting these complexes from heterogeneous to homogeneous catalysis. Modern organocopper chemistry has become a toolbox for chemists in all areas (pharmaceutical, materials science, dyes, *etc*...).

Tomás and co-workers exploited a copper(I)-catalyzed regioselective cyclization *via* addition of vinyldiazoacetates **213** to electron-deficient pyridines **212**,[78] leading to indolizine derivatives **214** with several reaction features (Scheme 51), including mild reaction conditions and a simple set up with inexpensive and readily available materials. A proposed mechanism is illustrated in Scheme 52. Initially, copper(I) alkenyl carbene **215** reacts with pyridine *via* Michael 1,4-addition, forming activated pyridine intermediate dipole **216**, which subsequently undergoes cyclization to generate the copper(III) metallacycle **217**. Metallacycle **217** suffers from reductive elimination forming a new C–C double bond, producing the Cu(I) complex **218** Finally, with the release of CuBr the desired product **219** is

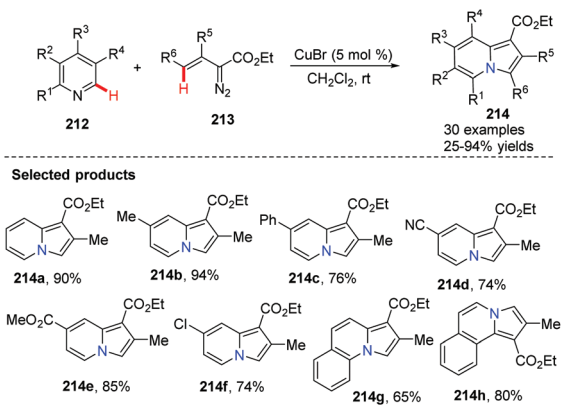


Scheme 52 Proposed mechanism for the Cu(I) catalyzed synthesis of indolizine derivatives.

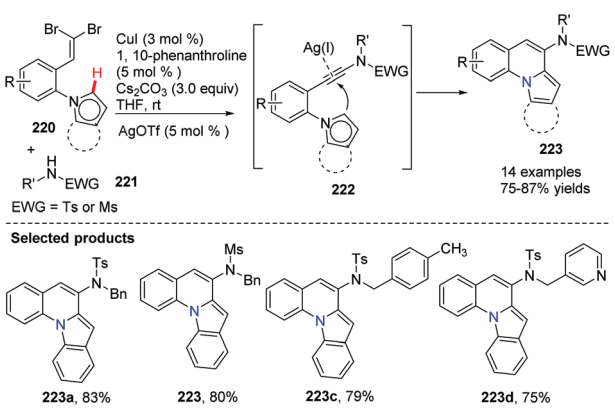
delivered to end the catalytic cycle. Notably, when simple benzo-fused pyridines, such as quinoline and isoquinoline, were used as the starting materials, they reacted with vinyldiazoacetate **213**, affording pyrrolo[1.2-*a*]quinolone **214g** and pyrrolo[2,1-*a*]isoquinoline **214h** in good yields.

Utilizing Cu(I) and Ag(I) as catalysts, a highly efficient route for the synthesis of novel pyrrolo or indolo[1,2-*a*]quinolones **223** was developed from *gem*-dibromovinyls **220** and sulphonamides **221** (Scheme 53).[79] It is worth mentioning that, for the cyclization process, the C_{sp^2}–H bond of *ortho* five-membered heterocycles does not require prefunctionalization. This method is simple, convenient and more efficient as it can be accomplished in a one-pot fashion in a short reaction time with diminished catalyst loading.

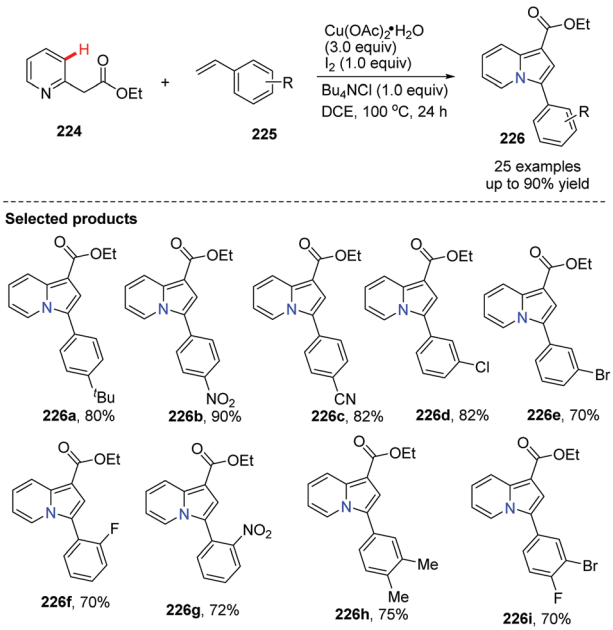
The group of Jia reported an indolizine synthesis by oxidative cross-coupling and cyclization of 2-(pyridin-2-yl)acetate **224** and alkenes **225** *via* a $Cu(OAc)_2/I_2$ mediated reaction



Scheme 51 Synthesis of indolizine derivatives.



Scheme 53 Synthesis of pyrrolo-/indolo[1,2-*a*]quinolines.

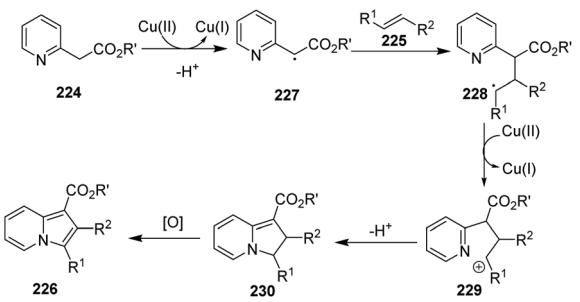


Scheme 54 Synthesis of indolizine *via* oxidative cross-coupling/cyclization.

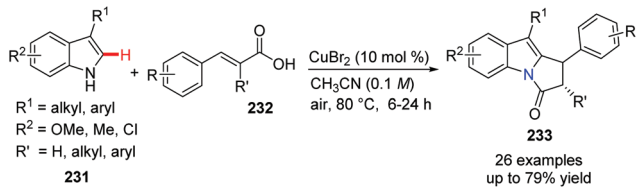
(Scheme 54).[80] The control experiment using TEMPO as a radical scavenger suggested that a radical pathway is likely and a plausible mechanism is depicted in Scheme 55. A series of 1,3-di- and 1,2,3-trisubstituted indolizines **226** were easily prepared in modest to excellent yields.

Some bioactive natural products and pharmaceuticals contain the pyrrolo[1,2-*a*]indole core. To build this privileged structural motif, Zhou, and Deng *et al.* developed an environmentally benign approach to access these valuable molecules from readily available indole/tryptamine **231** and β-arylacrylic acids **232** (Scheme 56).[81] This oxidative coupling reaction, a formal Michael addition and dehydration occurring in the presence of catalytic $CuBr_2$ in CH_3CN under air, turned out to be mild and scalable. This method is likely to be a powerful and versatile method for the synthesis of a large number of indole alkaloids.

Imidazopyridine is an important pharmacophore, and it is found in many biologically active compounds. Although a variety of synthetic approaches have been developed, most of



Scheme 55 Plausible mechanism to form substituted indolizine.

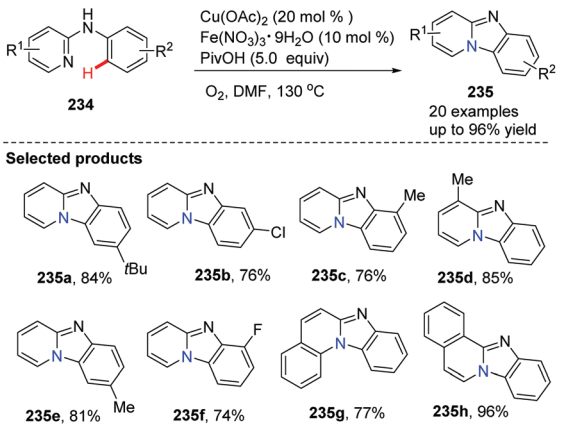


Scheme 56 Cu(II)-Catalyzed oxidative coupling between indole/tryptamine and arylacrylic acids.

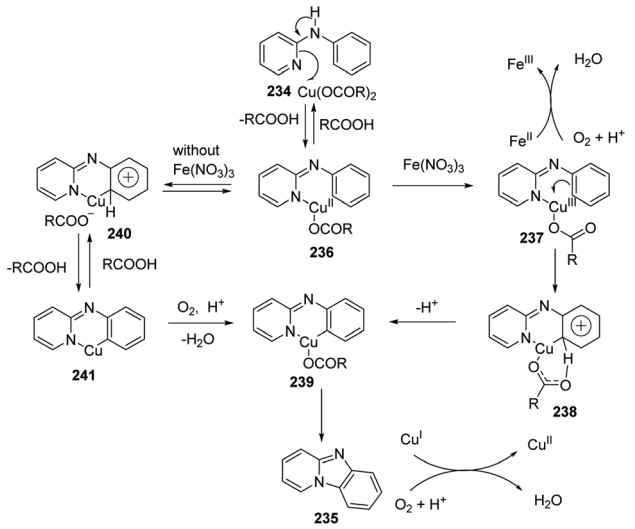
them are limited in scope and require multi-steps, have low yields, or have difficult isolations and purifications. Therefore, investigation of straightforward and green methods for the synthesis of imidazopyridines from simple and readily available starting materials is greatly desired. By using 20 mol% of $Cu(OAc)_2$ and 10 mol% of $Fe(NO_3)_3$ as co-catalysts, without pre-functionalization of the starting material, a novel and efficient synthesis of pyrido[1,2-*a*]benzimidazoles **235** through direct C–H activation of *N*-aryl-2-aminopyridines **234** was elegantly demonstrated initially by Zhu and co-workers (Scheme 57)[82] who showed that a direct intramolecular C(sp^2)–H amination is practical and effective. This method should have great potential in drug research and development because the raw material *N*-aryl-2-aminopyridines **234** can be easily prepared from halopyridines and phenylamine.

The proposed mechanism is depicted in Scheme 58: beginning with pyridyl nitrogen attack and the formation of a Cu(II) adduct **236** which then undergoes oxidization to afford more electrophilic Cu(III) intermediate **237**. Afterwards, six-membered ring transition state **238** is generated and the elimination of the aromatic ring protons gives a reactive Cu(III) intermediate **239**. Reductive elimination rapidly delivers the product **235**.

In 2011, Zhu, Zhang and co-workers further exploited and developed a copper-catalyzed intramolecular dehydrogenative amino-oxygenation.[83] From readily available *N*-allyl-2-aminopyridines and using molecular oxygen as the oxidant, they quickly and effectively prepared imidazol[1,2-*a*]pyridines **243**.



Scheme 57 Efficient synthesis of pyrido[1,2-*a*]benz-imidazoles *via* direct intramolecular C(sp^2)–H amination.

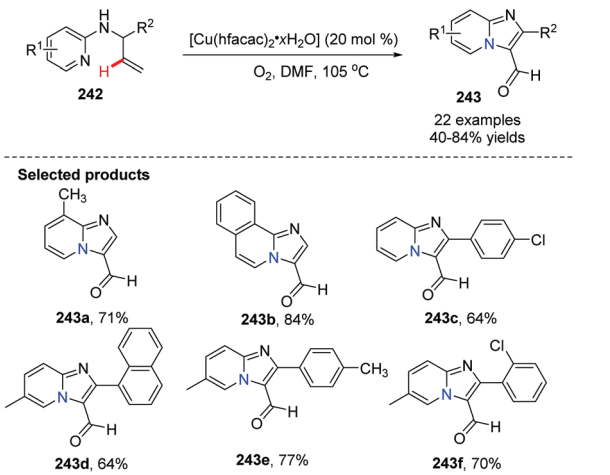


Scheme 58 Proposed mechanism catalyzed by Cu(II)/Fe(III) salt.

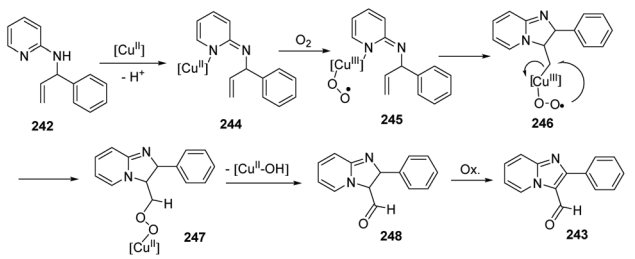
Notably, aldehyde functional groups survive without further oxidation to the corresponding acids (Scheme 59).

A plausible mechanism is displayed in Scheme 60. The process is initiated by coordination of **242** with the copper(II) catalyst to form **244**. Single-electron transfer then occurs from Cu to O_2 to generate the peroxy–copper(III) intermediate **245**, which undergoes insertion into the carbon–carbon double bond to form an alkyl copper(III) **246**. Isomerization of the resulting exocyclic peroxy–copper(III) intermediate yields the copper(II) **247** with concurrent formation of a carbon–oxygen bond. Elimination of Cu(II)–OH releases aldehyde **248**, which undergoes spontaneous aromatization to produce desired **243**.

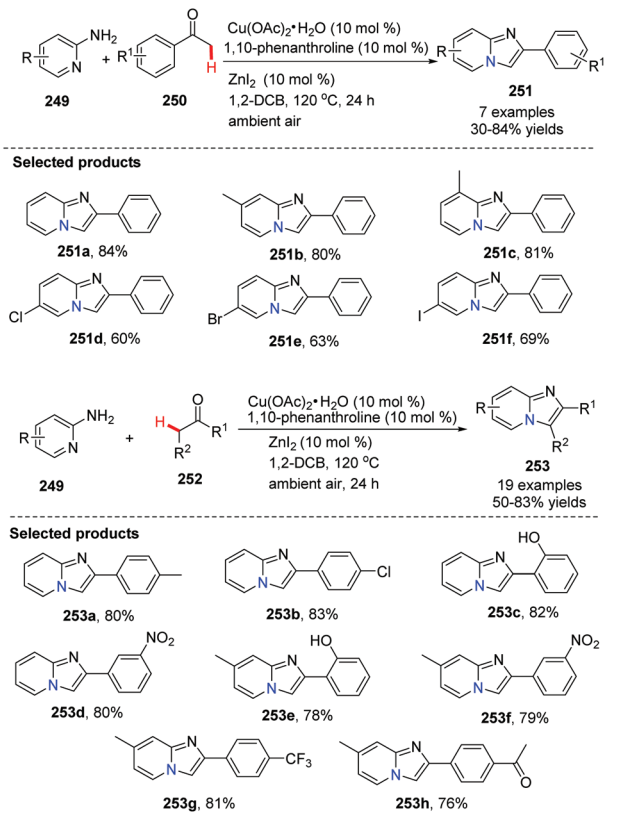
Different from an intramolecular cyclization approach developed by Zhu's group, Hajra and co-workers reported a copper-catalyzed intermolecular cyclization reaction, as an alternative approach for the synthesis of imidazo[1,2-*a*]pyridines from readily available 2-aminopyridines and acetophenone in 2013 (Scheme 61).[84] The reaction was performed using 1,10-phenanthroline as the ligand and ZnI_2 as the additive in 1,2-dichlorobenzene, by heating in the presence of air. Using this method, zolimidine, a marketed antiulcer drug was prepared. A probable mechanism is shown in Scheme 62. Initially, imine **254** is formed by ZnI_2 as a catalyst. The imine transforms to enamine **255** after tautomerization, reacting with $Cu(OAc)_2$ to form the adduct **256**, which is then readily converted into intermediate **257**. Deprotonation of **257** will give **258**, which is then oxidized to the reactive [Cu(III)] intermediate **259**. Finally, product **251** is afforded through reductive elimination along with the formation of Cu(I) species which is oxidized by the aerobic oxygen to close the catalytic cycle.



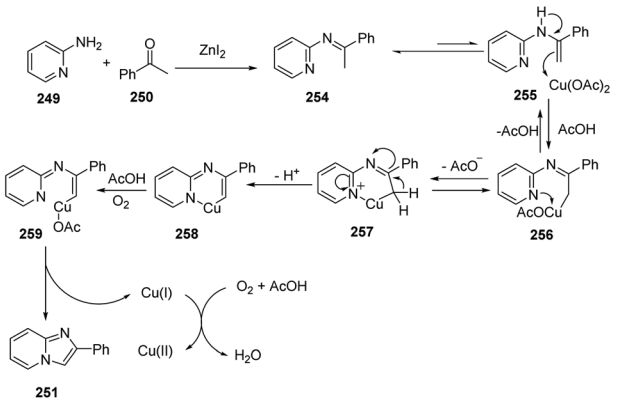
Scheme 59 Synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehyde *via* Cu(II) catalyzed dehydrogenative aminooxygenation.



Scheme 60 Plausible mechanism involved the Cu(II) catalyzed C–H activation.



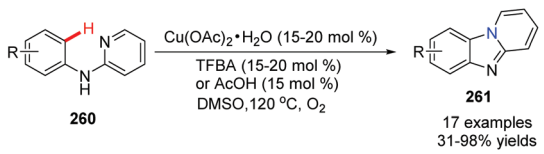
Scheme 61 Synthesis of imidazo[1,2-*a*]pyridines.



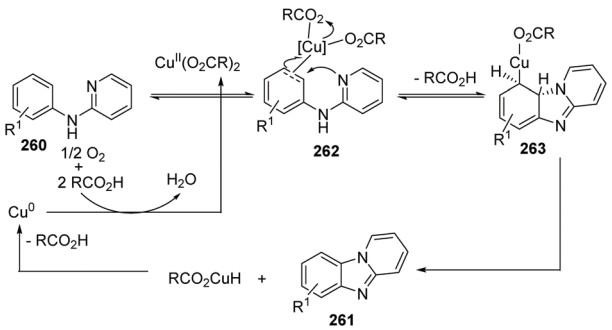
Scheme 62 Probable mechanism for the synthesis of imidazo[1,2-*a*] pyridines.

Maes and co-workers reported an approach for the synthesis of pyrido[1,2-*a*]benzimidazoles **261** from *N*-phenylpyridin-2-amine **260** using $Cu(OAc)_2$ as the catalyst in 2010 (Scheme 63).[85] Reactions were performed under an atmosphere of O_2, a solvent of DMSO, using a catalytic amount of 3,4,5-trifluorobenzoic acid (TFBA) as the promoter. During the catalytic cycle, reductive elimination of RCO_2H from $RCO_2Cu(II)H$ yields Cu(0) (Scheme 64).

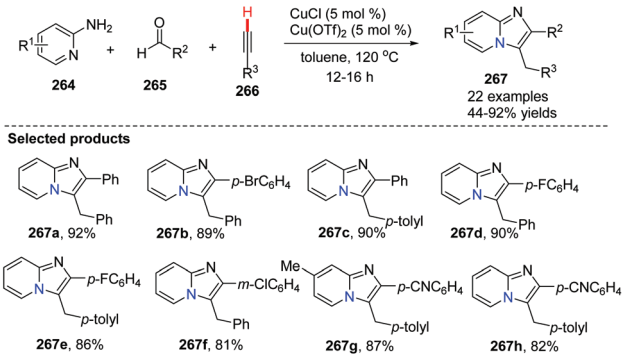
In 2010, Gevorgyan and co-workers developed a highly efficient method for the synthesis of imidazo[1,2-*a*]pyridine, imidazoquinoline and imidazoisoquinoline derivatives **267** by the copper-catalyzed three-component coupling reaction of aryl-, heteroaryl-, and alkylaldehydes with 2-aminopyridines **264** and terminal alkynes (Scheme 65).[28] This reaction has been applied in a highly efficient one-pot synthesis of alpidem and zolpidem. Recently, for drug-like molecules, the use of C–H



Scheme 63 Synthesis of pyrido[1,2-*a*]benzimidazoles.



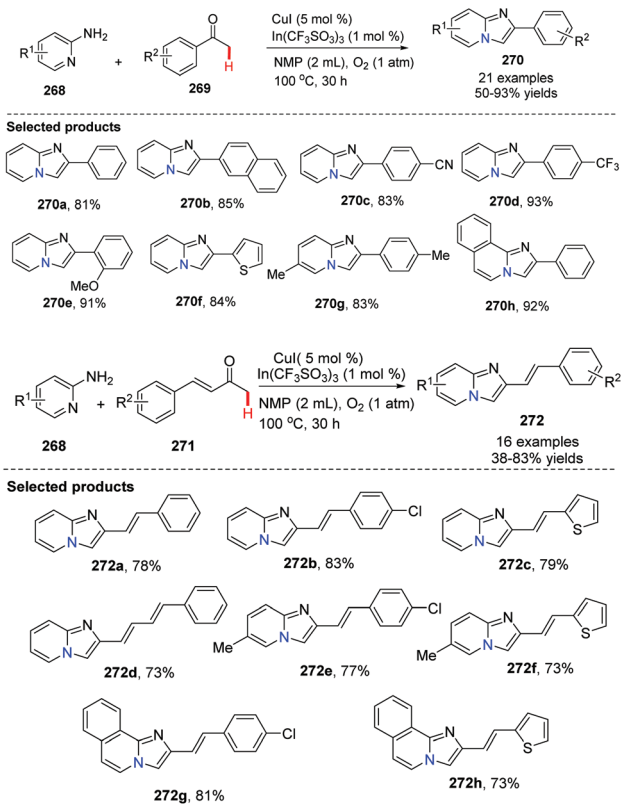
Scheme 64 Proposed mechanism for the intramolecular C–H amination.



Scheme 65 Copper-catalyzed one-pot synthesis of Alpidem and Zolpidem.

functionalization is becoming more and more important for diversification and for generating new drugs, and it should be a key transformation kept in the medicinal chemists' toolbox.

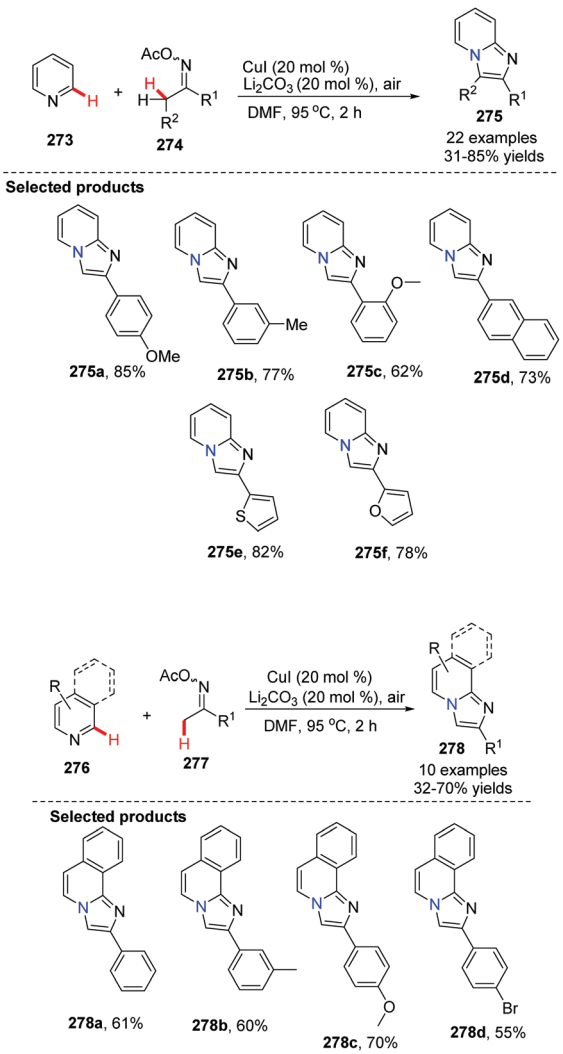
In addition to the Hajra catalytic system [Cu(II)/ZnI_2/1,10-phen] for tandem imine formation-oxidative cyclization, Zhang, Su and co-workers applied a CuI-catalyzed aerobic oxidative α-amination cyclization of 2-aminopyridine and acetophenone (or unsaturated ketones) to provide [1,2-*a*]pyridines in 2013 (Scheme 66).[86] By carefully screening reaction conditions, they found that adding 1 mol% of $In(CF_3SO_3)_3$ as an



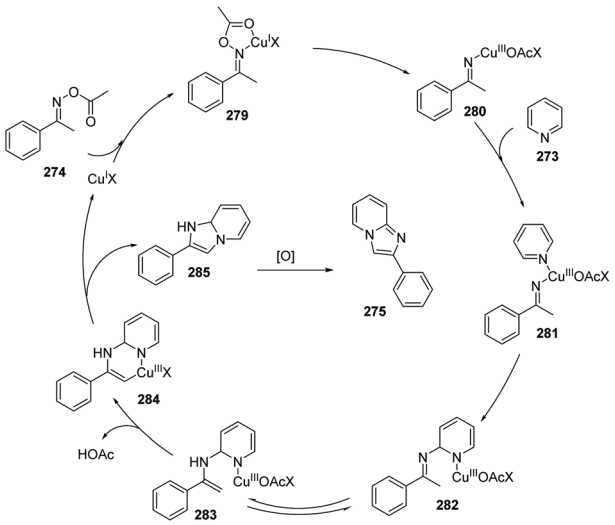
Scheme 66 Synthesis of substituted imidazoheterocycles catalyzed by CuI.

additive was necessary. Without In(III) salt or $CuBr_2$ as an additive, the reaction was not productive when NMP was used as a solvent.

Unlike the oxidative cyclization of arylketones with 2-aminopyridines to access imidazopyridine which is heavily being investigated and developed by two research groups, an alternative disconnection method to build the imidazopyridine core uses the pyridine and an acylated oxime. In 2013, Jiang *et al.* reported the novel conversion of pyridine to imidazo[1,2-*a*]pyridines *via* copper-catalyzed aerobic dehydrogenative cyclization with ketone oxime esters (Scheme 67).[87] Other N-containing heteropolycycles, such as isoquinoline, also worked well in this transformation. The possible mechanism is proposed, which includes the formation of a Cu(III)-imino species **280** which is proposed to undergo reductive elimination of a six-membered Cu(III) intermediate **284**. Copper-catalyzed pyridine C(sp^2)–H bond and oxime ester C(sp^3)–H bond activation provides the by-products H_2O and CH_3COOH (Scheme 68).



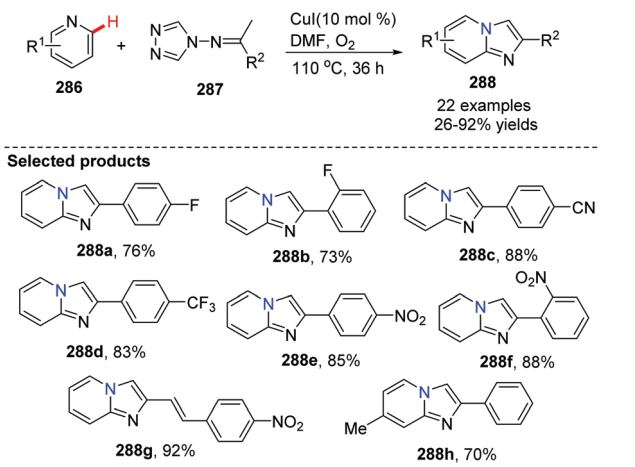
Scheme 67 Conversion of pyridine to imidazo[1,2-*a*]pyridines.



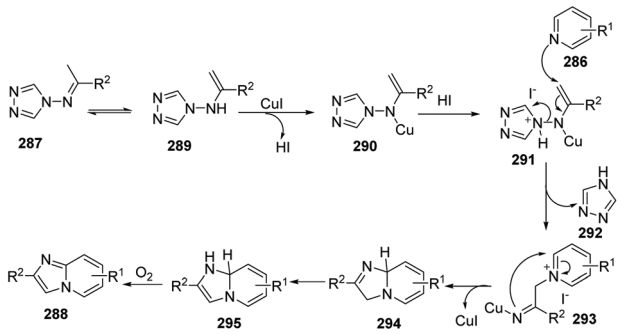
Scheme 68 Plausible catalytic cycle mediated by CuI.

Similar to Jiang's method, and concurrent with his findings, in 2013, Fu and co-workers developed another novel and efficient copper-catalyzed aerobic oxidative C(sp^2)–H functionalization of substituted pyridines with *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amines, generating imidazo[1,2-*a*]pyridine derivatives **288** (Scheme 69).[88] First, the isomerization of *N*-(alkylidene)-4*H*-1,2,4-triazol-4-amine gives **289**, then coordination of the copper catalyst (CuI) provides complex **290** with the liberation of HI, afterwards treatment of **290** with HI leads to **291**. Nucleophilic attack of substituted pyridine on the alkenyl moiety in **291** affords **293** with the elimination of 4*H*-1,2,4-triazole, and intramolecular cycloaddition, isomerization, and the final oxidation lead to the target product **288** with regeneration of the catalyst CuI (Scheme 70).

In 2011, the group of Xi described CuI-catalyzed tandem coupling of 1,4-dihalo-1,3-dienes **297** with readily available azoles **296** *via* N–H bond and C–H bond activation for the syn-



Scheme 69 Copper-catalyzed aerobic oxidative synthesis of imidazo[1,2-*a*]pyridines.

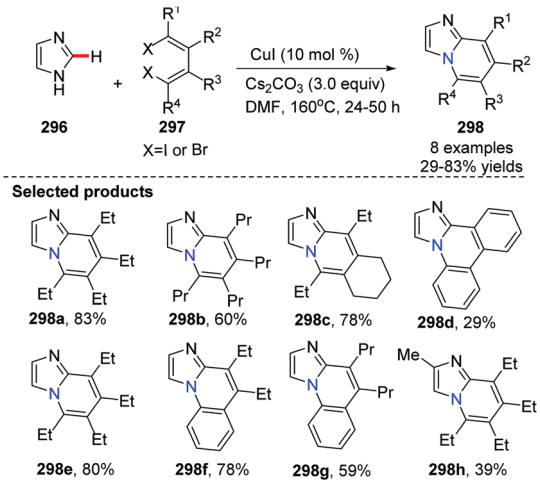


Scheme 70 Possible mechanism for the Cu(I)-catalyzed synthesis of imidazo[1,2-*a*]pyridines.

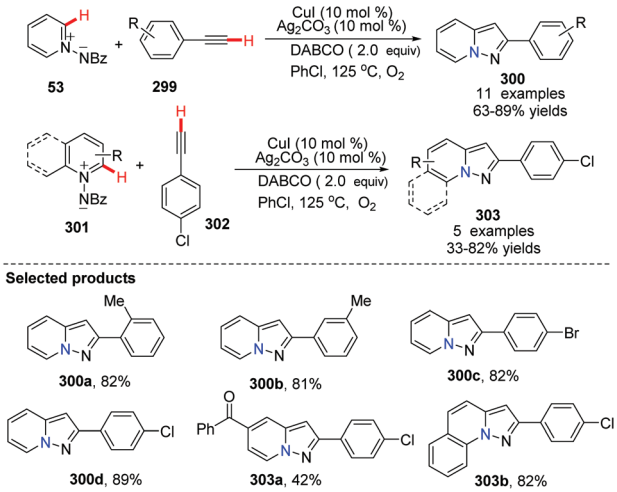
thesis of nitrogen-bridgehead fused heterocycles **298** (Scheme 71).[89] They detailed the reaction stepwise pathway *via* a designed experiment and found that the N–H bond was activated preferentially for the first *N*-alkenylation, followed by a subsequent C(sp^2)–H bond alkenylation on imizole. This method provided an efficient route to the synthesis of azolopyridine derivatives.

In 2013, Jiao and co-workers independently updated a CuI (10 mol%) and Ag_2CO_3(10 mol%) co-catalyzed direct dehydrogenative annulation of *N*-iminopyridinium ylides with terminal alkynes using oxygen as the oxidant, leading to pyrazolo[1,5-*a*] pyridine derivatives (Scheme 72).[90]

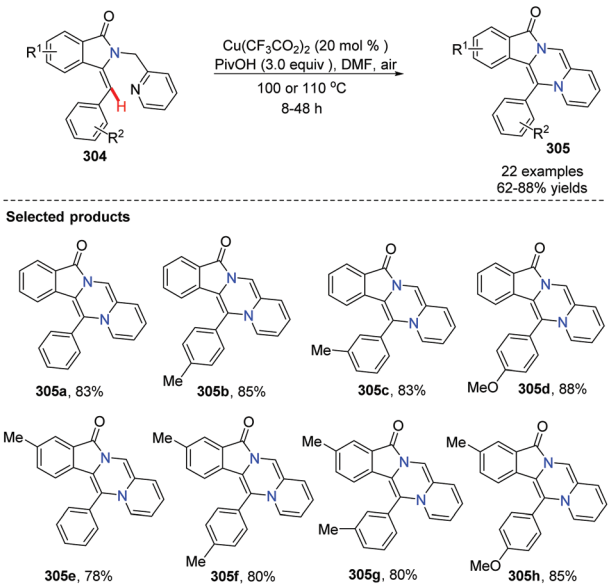
Fu and co-workers developed an efficient copper-catalyzed aerobic oxidative, intramolecular alkene C–H amination leading to N-heterocycles **305** utilizing cheap and readily available $Cu(O_2CCF_3)_2$ as the catalyst in 2011.[91] This method provided a new and useful strategy for constructing complex N-heterocycles (Scheme 73). The authors suggested the possible mechanism involving copper salt catalyzed C(sp^2)–H activation (Scheme 74).



Scheme 71 Tandem synthesis of substituted azolopyridines catalyzed by CuI.



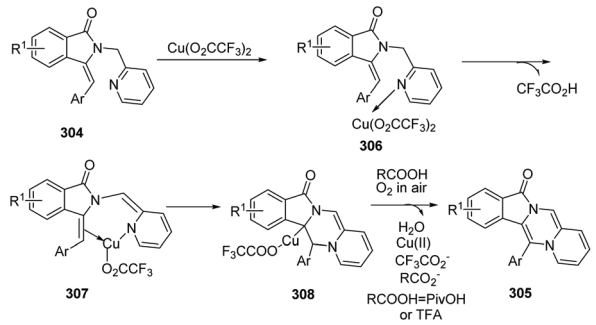
Scheme 72 Copper(I)/Ag_2CO_3-catalyzed oxidative annulation of *N*-iminopyridinium ylides.



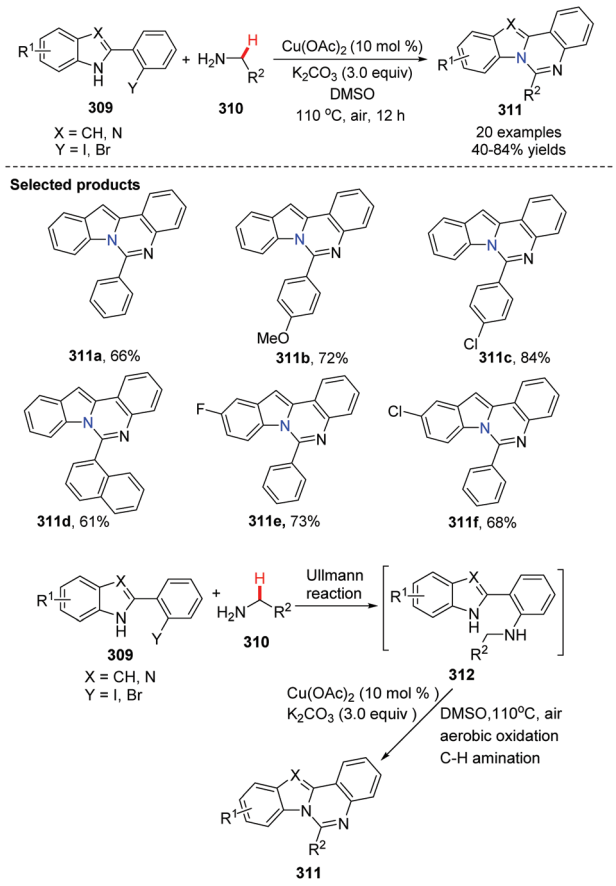
Scheme 73 Synthesis of N-heterocycles *via* C(sp^2)–H amination.

In 2012, Zhang and his group reported copper-catalyzed sequential Ullmann *N*-arylation and aerobic oxidative C–H amination for the efficient synthesis of indolo[1,2-*c*]quinazoline derivatives 311 (Scheme 75).[92] Notably, the reaction involved C(sp^3)–H bond activation, and this bond is considered to be the most chemically inert. They found that selecting R^2 group is particularly critical. From a structural point of view, R^2 group was aromatic or heteroaromatic. This method would be useful for the synthesis of innovative drug candidates by rapidly providing new molecular entities.

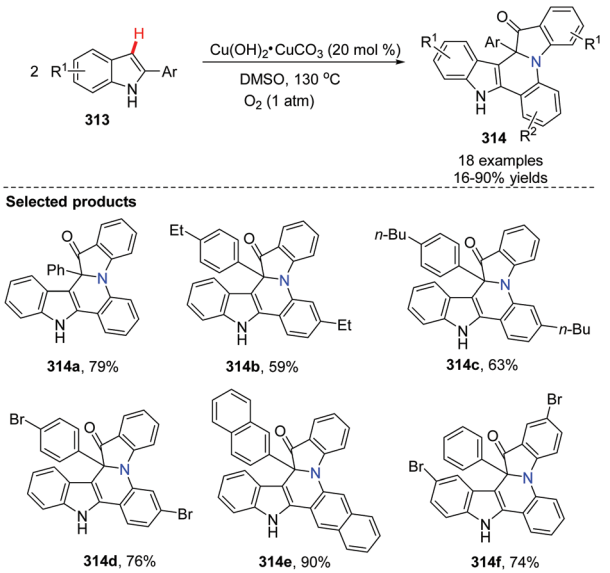
Zhang, Zou and co-workers developed a method for the synthesis of a series of fused nitrogen-containing heterocycles containing indole and quinoline skeletons by a copper-catalyzed reaction from 2-arylated indoles (Scheme 76).[93] The reac-



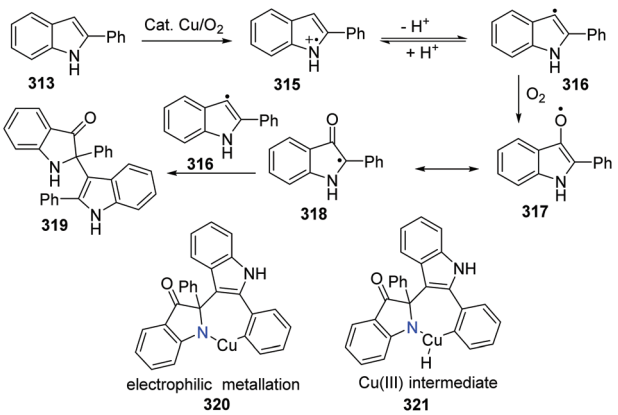
Scheme 74 Possible mechanism for copper-catalyzed C(sp^2)–H amination leading to N-heterocycles.



Scheme 75 Convenient route to indolo[1,2-*c*]quinazoline derivatives.



Scheme 76 Oxidative cyclization of 2-arylindoles.



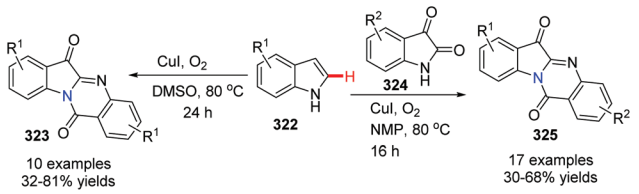
Scheme 77 Plausible reaction mechanism of oxidative cyclization of 2-arylindoles.

tion involved aerobic oxidative C–H bond functionalization and aromatic C–H amination. It is worth mentioning that the reaction built fused cycles containing a quaternary carbon atom, a short and efficient synthesis accomplished *via* a new strategy. ^{18}O-Labelled experiments revealed that molecular O_2 is not only the oxidant, but also the reactant.

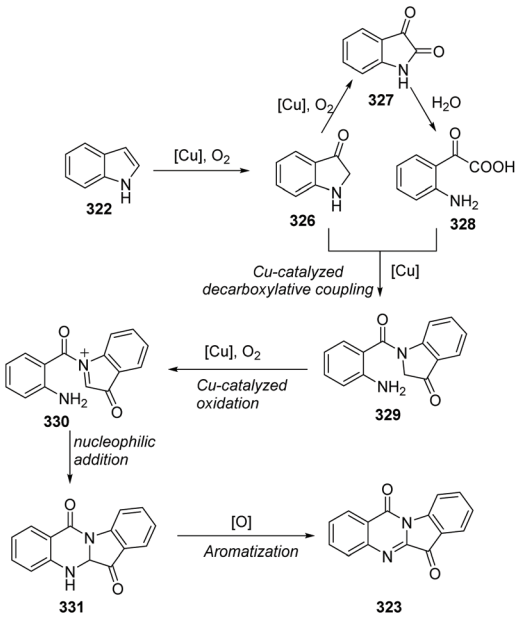
A plausible reaction mechanism was proposed as shown in Scheme 77. Firstly, the indole radical cation **315** is formed in the presence of a copper catalyst and oxygen *via* the electron transfer process. The subsequent deprotonating equilibrium gives the indolyl radical **316**, which is oxidized by the oxygen/copper system to afford intermediate **317**. The combination of intermediates **318** and **316** delivers the oxidized dimer of 2-phenylindole **319**. The subsequent cyclization might occur *via* the oxidative addition and reductive elimination process of a Cu(I)/Cu(III) cycle, where the oxygen drives the process forward. The electrophilic metalation and reductive elimination pathway is another possible route.

In 2013, Lu, Wang and co-workers reported two concise methods for the preparation of tryptanthrins from indoles (Scheme 78).[94] In the presence of CuI and oxygen, heating indoline itself in DMSO at 80 °C yielded tryptanthrin derivatives **323**. On the other hand, the reaction of indoline with isatin **324** in NMP at 80 °C afforded tryptanthrin derivatives **325**.

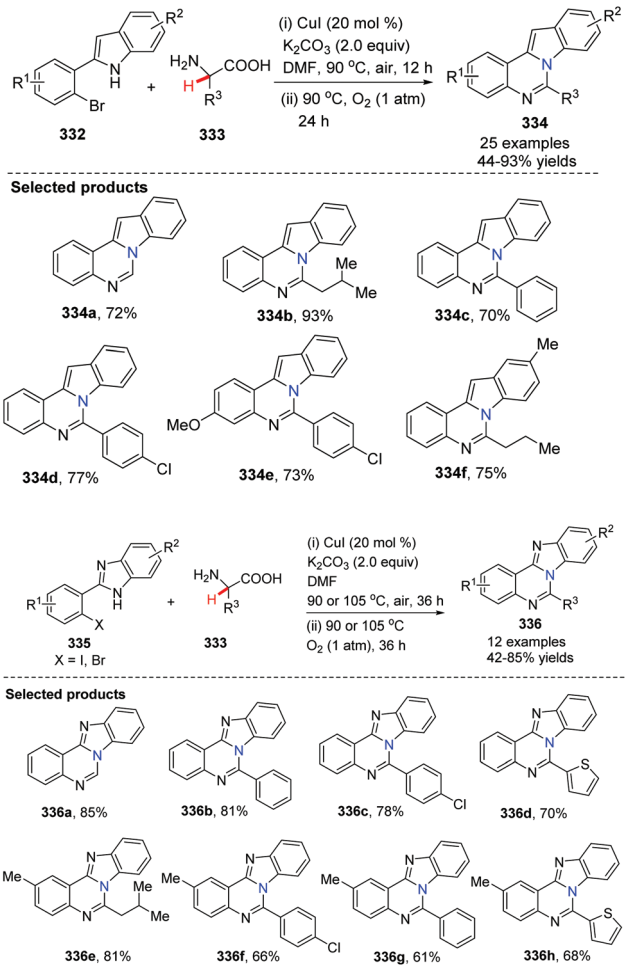
They postulated a possible mechanism as shown in Scheme 79. Initially, **322** is aerobically oxidized to indolin-3-



Scheme 78 CuI-Catalyzed synthesis of tryptanthrin derivatives.



Scheme 79 Proposed mechanism for the synthesis of tryptanthrin derivatives.

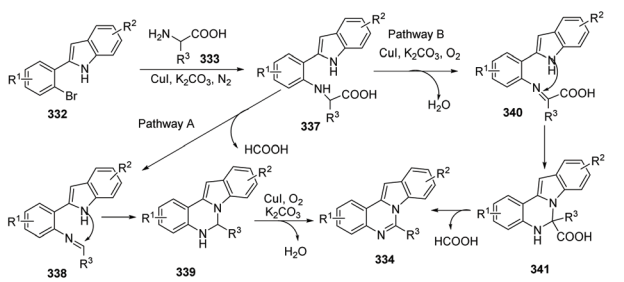


Scheme 80 Copper-catalyzed synthesis of *H*-indolo[1,2-*c*]quinazoline derivatives.

one **326**, which could further oxidize to isatin **327**. Then, **327** undergoes hydrolysis to form α-oxoacetic acid **328**. Copper-catalyzed decarboxylative coupling between **326** and **328** furnishes **329**. Compound **329** is sequentially oxidized to imminium **330** *via* copper-catalyzed oxidation. Then, intramolecular nucleophilic addition of the amino group to *N*-acylimminium provides the fused ring intermediate **331**. Finally, **323** is obtained *via* dehydrogenative aromatization of **331**.

Fu and co-workers developed a CuI-catalyzed reaction of 2-(2-bromophenyl)-1*H*-indole **332** with α-amino acids leading to indolo-quinazoline derivatives **334** (Scheme 80).[95] The reactions undergo copper-catalyzed *N*-arylation, aerobic oxidative dehydrogenation, intramolecular cyclization and dissociation of formic acid. The process uses cheap and readily available α-amino acids as the nitrogen source. When 2-(2-halophenyl)-1*H*-benzo[*d*]imidazole **335** is employed as the starting material, it provides benzo[4,5]imidazo[1,2-*c*]quinazoline derivatives **336**. This method shows simplicity and practical advantages and should find wide application for the construction of other N-fused heterocycles.

A possible mechanism for the copper-catalyzed reaction of substituted 2-(2-bromophenyl)-1*H*-indoles with α-amino acids leading to benzo[4,5]imidazo[1,2-*c*]quinazolines is suggested in Scheme 81. Firstly, Cu-catalyzed *N*-arylation of α-amino acid **333** with substituted 2-(2-bromophenyl)-1*H*-indole **332** affords **337**. And then intermediate **337** undergoes one of two domino pathways. In pathway A, oxidative elimination of formic acid from **337** gives **338**. Intramolecular cyclization of **338** provides **339**, and copper-catalyzed aerobic oxidative dehydrogenation of **339** affords the target product **334**. In pathway B, copper-

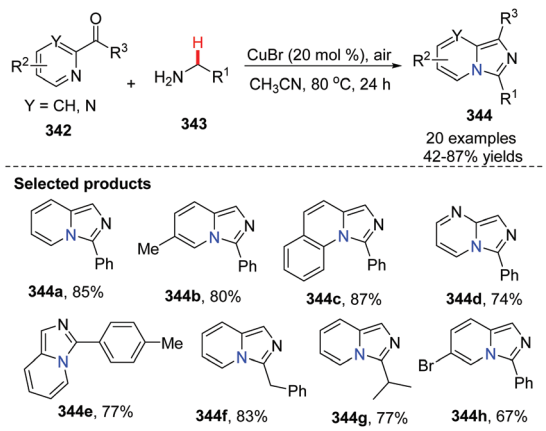


Scheme 81 Possible mechanism for the synthesis of *H*-indolo[1,2-*c*] quinazoline derivatives.

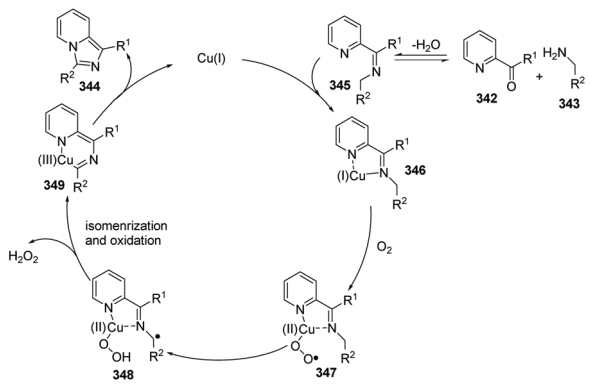
catalyzed aerobic oxidative dehydrogenation of **337** provides **340**, intramolecular cyclization of **340** leads to **341**, and loss of formic acid from **341** to aromatize the system gives **334**.

In 2014, Ye, Zeng and co-workers developed the first Cu(I)-catalyzed direct C(sp^3)–H amination of N-heteroaryl aldehydes or ketones with alkylamines leading to rapid and concise access to imidazo[1,5-*a*]pyridines (Scheme 82).[96] A possible mechanism involving a catalytic cycle is shown in Scheme 83. Firstly, the Cu(I) ion coordinates with the pyridine N-atom and imine N-atom in **346**. Since the reaction is under an oxygen atmosphere, compound **347** is generated. Subsequently, the corresponding Cu(II)-superoxo radical **347** would abstract the intramolecular hydrogen atom from the coordinated imine to produce Cu(II) intermediate **348**, through a six-membered transition state. The proposed Cu(III) species **349** is then attained *via* isomerization/oxidation processes. Finally, the reductive elimination of the Cu(III) intermediate leads to the formation of imidazo[1,5-*a*]pyridine **344** with regeneration of the Cu(I) catalyst to close the catalytic cycle.

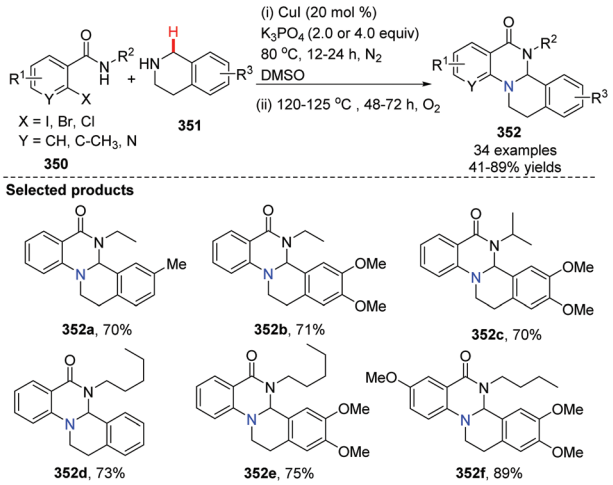
In 2014, Fu and co-workers developed a novel copper-catalyzed, one-pot method for the preparation of tetrahydroisoquinolino[2,1-*a*]-quinazolinone derivatives (Scheme 84).[97] This approach utilized a sequential copper-catalyzed *N*-arylation and intramolecular aerobic oxidative cyclization. The first step or *N*-arylation was conducted under an inert atmosphere (N_2) and following C(sp^3)–H activation, oxidative cyclization occurred under an oxygen atmosphere.



Scheme 82 Synthesis of imidazo[1,5-*a*]pyridines *via* Cu(I)-catalyzed transannulation.



Scheme 83 Proposed catalytic cycle mediated by Cu(I).

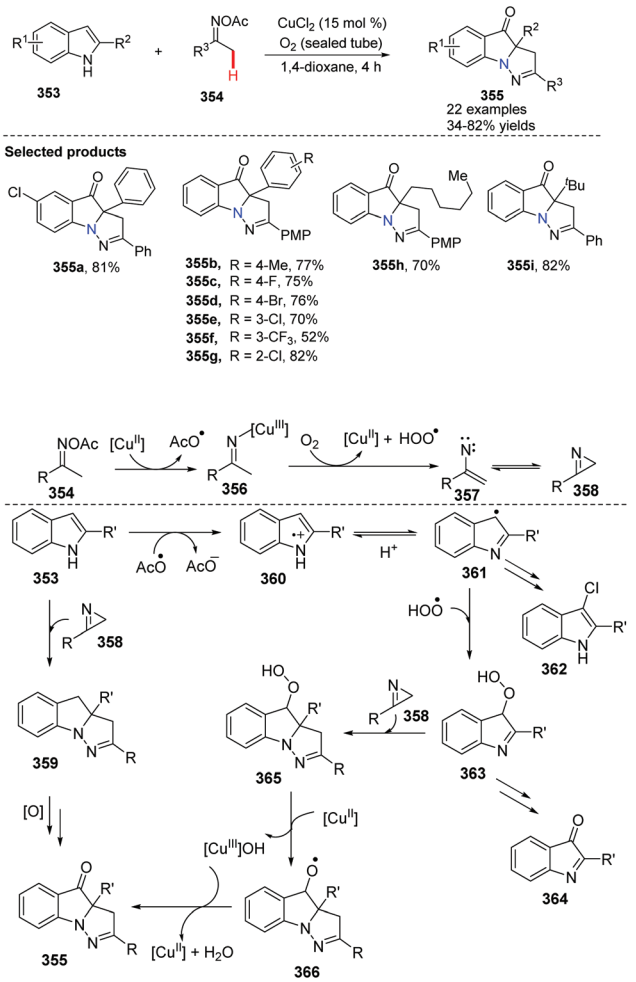


Scheme 84 Synthesis of tetrahydroisoquinolino[2,1-*a*]quinazolinone derivatives.

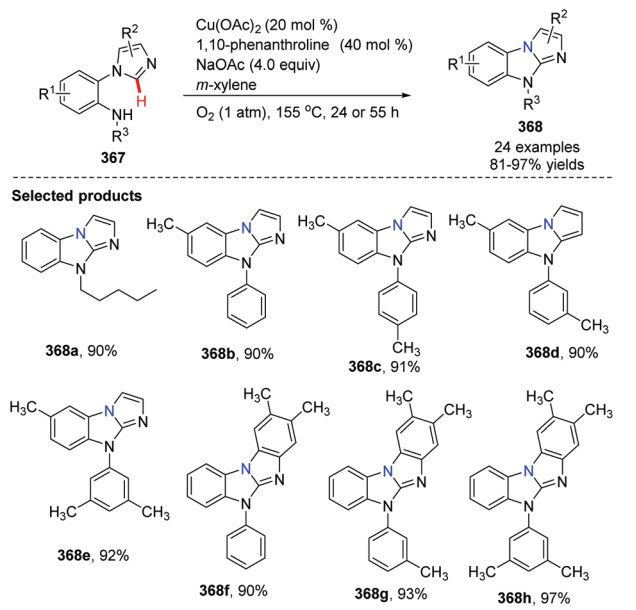
Recently, Huang, Deng and co-workers initialized the study of cyclization of indole with oxime acetates by copper-catalyzed coupling (Scheme 85).[98] A series of pyrazolo[1,5-*a*]indole derivatives **355** have been prepared efficiently. This novel approach elegantly *tri*-functionalized N1, C2 and C3 of indoles in a one-pot fashion using internal/external co-oxidation with oxygen and 15 mol% $CuCl_2$ to promote the process. Mechanistic studies indicated that the reaction proceeds through a radical intermediate.

In 2012, Fu and co-workers developed an efficient copper-catalyzed aerobic oxidative intramolecular C(sp^2)–H amination leading to imidazobenzimidazole derivatives (Scheme 86).[99] Imidazo C(sp^2)–H functionalization led to effective and convenient amination closing of the imidazole ring system. A proposed mechanism is shown in Scheme 87. Initial coordination of substrate **367** with the complex $L_nCu(OAc)_2$ and oxidative insertion in the presence of NaOAc provide the key intermediate **369**. Reductive elimination affords the target product **368**, releasing the Cu(II)L_n catalyst under oxygen. The authors found that yields clearly increased when phenanthroline was applied as the ligand.

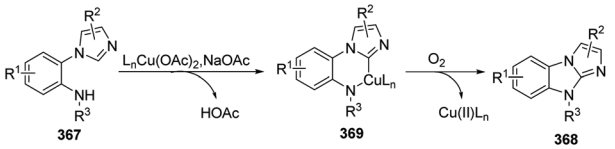
Qiao *et al.* conveniently prepared imidazo/benzimidazo–quinazolinones **371** *via* an intramolecular C–H amination of readily available starting materials in the presence of CuCl as the catalyst (Scheme 88).[100] Interestingly, Cu(II) salts such as $Cu(OAc)_2$ are not suitable catalysts. A possible mechanism is shown in Scheme 89. Similar to the previously proposed mechanism, coordination of substrate **370** with CuCl forms **372**. Then in the presence of NaOAc, intramolecular coordination allows oxidative insertion providing copper complex **374**. Further oxidative addition leads to the Cu(III) complex



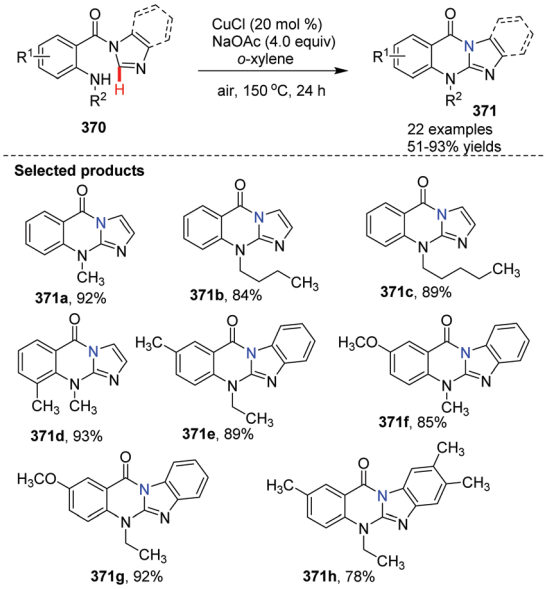
Scheme 85 Cu(II)-Catalyzed aerobic oxygenation and cyclization of indoles with oxime acetates.



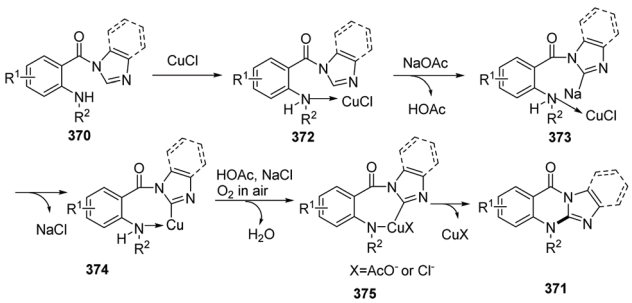
Scheme 86 Synthesis of imidazobenzimidazole derivatives.



Scheme 87 Possible mechanism for copper-catalyzed C–H amination.



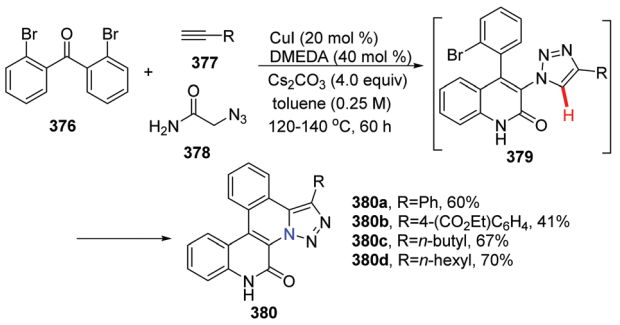
Scheme 88 Synthesis of 5-substituted imidazo/benzimidazoquinazolinones.



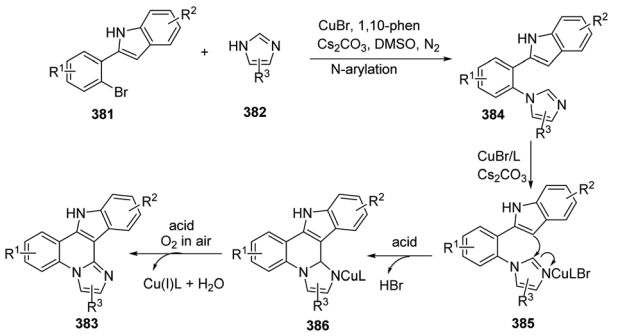
Scheme 89 Possible mechanism of copper-catalyzed synthesis of substituted imidazo/benzimidazoquinazolinones.

375. Finally, reductive elimination gives the target product **371**, releasing CuCl to close the catalytic cycle.

Recently, Qian and co-workers described a Cu-catalyzed three-component cascade reaction, *via* copper-mediated click chemistry, C–H functionalization, the Goldberg amidation, the Camps cyclization and C–H arylation, providing an efficient procedure for the synthesis of nitrogen polyheterocycles (Scheme 90).[101] These compounds, especially dibenzotriazolo-naphthyridinones, are likely to be valuable for drug discovery



Scheme 90 One-pot construction of dibenzotriazolonaphthyridinones.



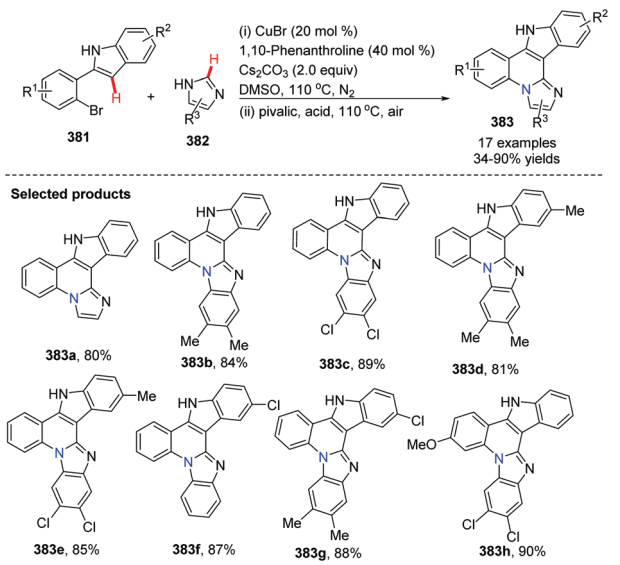
Scheme 92 Possible mechanism for the copper-catalyzed synthesis of indoloimidazoquinoline derivatives.

programs when the triple electrophile bis(2-bromophenyl) methanone was used in the one-pot condition.

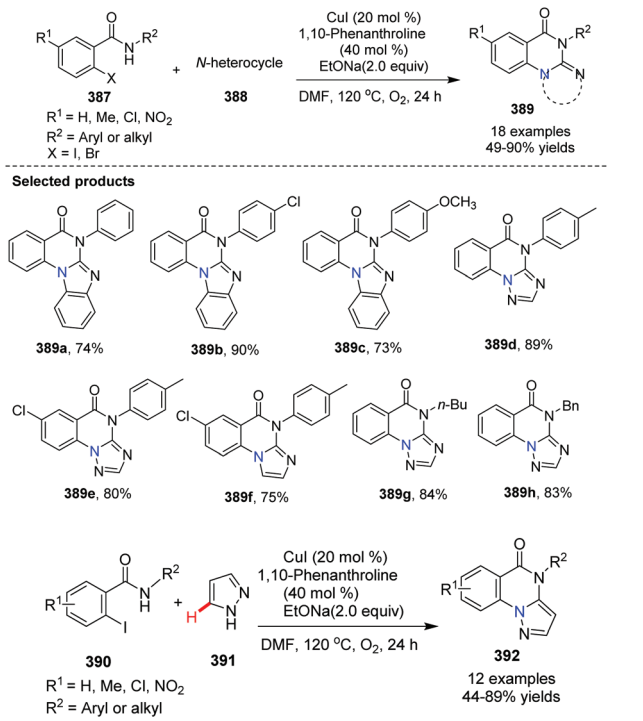
By using the readily available substituted 2-(2-bromophenyl)-1*H*-indoles, imidazole and benzoimidazoles as the starting materials and inexpensive CuBr as the catalyst, in the presence of oxygen, a novel and efficient copper-catalyzed one-pot synthesis of indoloimidazoquinoline derivatives has been developed by Fu and co-workers (Scheme 91).[102] This reaction involves *N*-arylation and an aerobic oxidative C(sp^2)–H/C(sp^2)–H coupling. The method provided more novel target compounds and new molecular entities for drug discovery. A proposed mechanism for the reaction is shown in Scheme 92. In the presence of CuBr and a ligand, *N*-arylation provides the product **384**. The coordination of CuBr with **384** gives complex **385**, and the addition of the 3-C–H in the indole group to 2′-C of the imidazole provides **386**. Finally, oxidation and elimination give the target product **383**, freeing the Cu(I) catalyst to close the catalytic cycle.

In 2013, Bao and co-workers reported the synthesis of benzimidazol[1,2-*a*]quinazolin5(6*H*)-one from 2-iodo-benzamides and N-heterocycles *via* Cu(I)-catalyzed C–N oxidative coupling/C(sp^2)–H activation/C–N formation (Scheme 93).[103] When pyrazole was used as an *N*-aryl substrate, the product of the reaction is pyrazolo[1,5-*a*]-quinazolinone **392**.

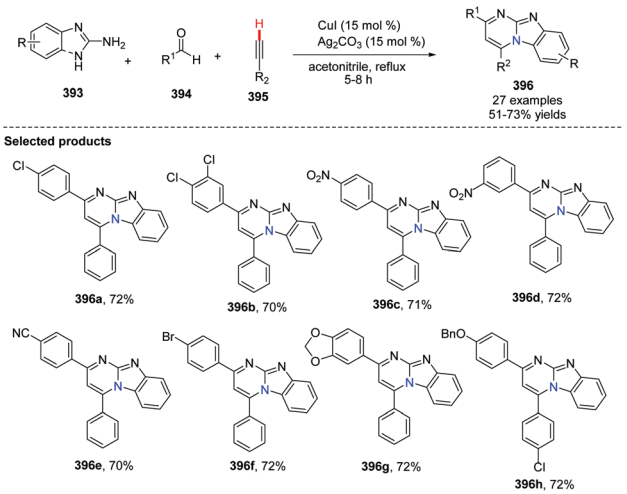
In 2014, Kumar and co-workers reported an approach for the synthesis of imidazo[1,2-*a*]pyrimidine derivatives from 2-aminobenzimidazole, benzaldehyde and alkynes (Scheme 94),[104a] using the copper salt-catalyzed multicomponent cascade coupling reaction. The reaction involves two C–N bond forming steps and one C–H bond formation. Intramolecular N–H bond and C(sp)–H bond activation is necessary to promote the reaction. In 2019, it was found by Zhang, Chai and co-workers that without adding Ag_2CO_3, in the presence of a catalytic amount of CuI and K_2CO_3, a decar-



Scheme 91 Synthesis of indoloimidazoquinoline derivatives.



Scheme 93 Synthesis of azoquinazolinones and pyrazolo[1,5-*a*] quinazolinones.

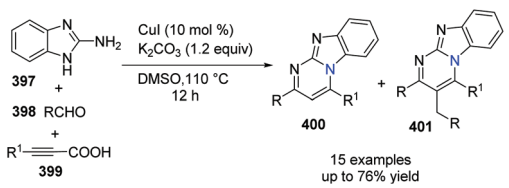


Scheme 94 Synthesis of fused imidazo[1,2-*a*]pyrimidines.

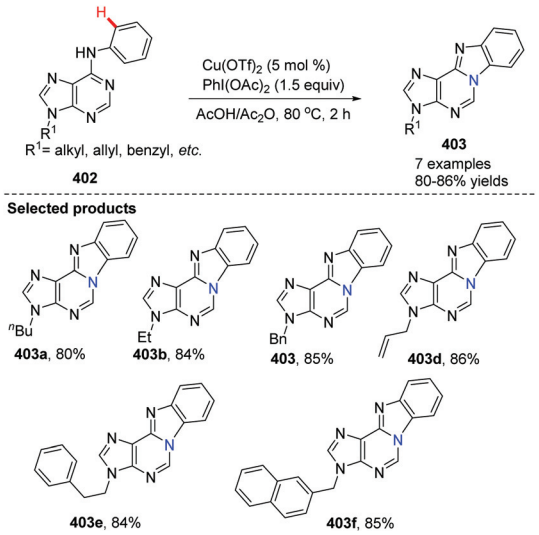
boxylic multicomponent reaction of heterocyclic azoles, aldehydes and alkynecarboxylic acid in DMSO gives the corresponding bridgehead nitrogen scaffold (Scheme 95).[104b] It is worth mentioning that the composition of the product depends on the ratio of starting materials.When 2.0 equiv. of aldehyde were used, it gave **401** as the major product.

Purine nucleosides analogues have been developed as drugs in the treatment of virus infections.[105] Thus, the modification of purine nucleosides has increasingly attracted the interest of medicinal chemists in recent years. It is worth emphasizing that C–H bond amination reactions on purine rings remain challenging due to their inherent reduced activity in metal-catalyzed transformations as a result of nitrogen coordination which is believed to deactivate the catalyst. Additionally, the poor stability of the nucleosidic bond, which can be easily broken under harsh conditions, has limited further development of these structures.

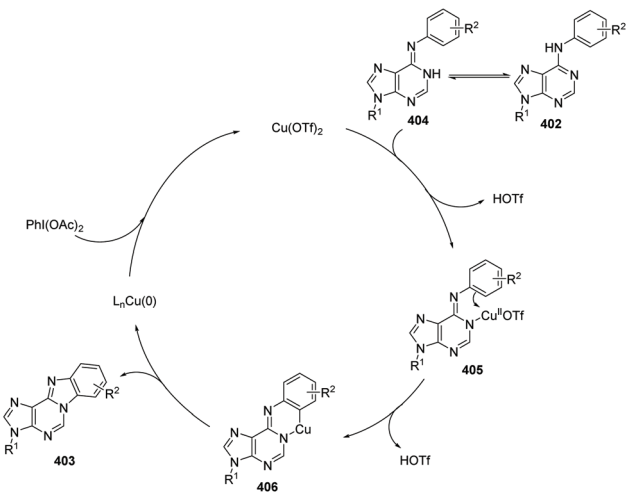
In 2012, Guo, Fossy and co-workers reported the first synthesis of novel purine-fused polycyclics *via* Cu(II) salt catalyzed C(sp^2)–H activation under mild conditions from 6-anilinopurine as the starting material (Scheme 96).[106] A possible pathway is shown in Scheme 97. Initially, coordination of $Cu(OTf)_2$ with substrate **402**, followed by an electrophilic substitution process, yields a Cu(II) intermediate. Finally, reductive elimination delivers the target product **403** and Cu(0), which can be re-oxidized to $Cu(OTf)_2$, to end the catalytic cycle.



Scheme 95 CuI-Catalyzed decarboxylic multicomponent reaction to prepare pyrimidobenzimidazoles.

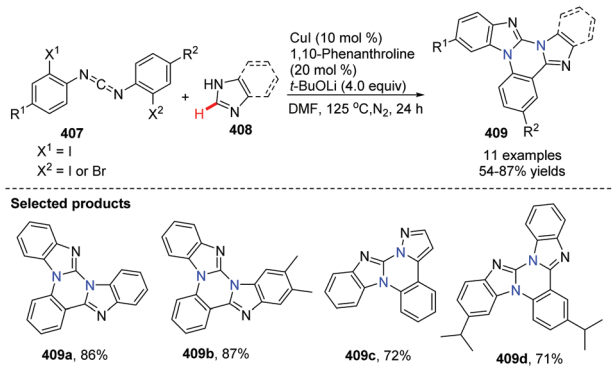


Scheme 96 Copper-catalyzed synthesis of purine-fused polycyclics.

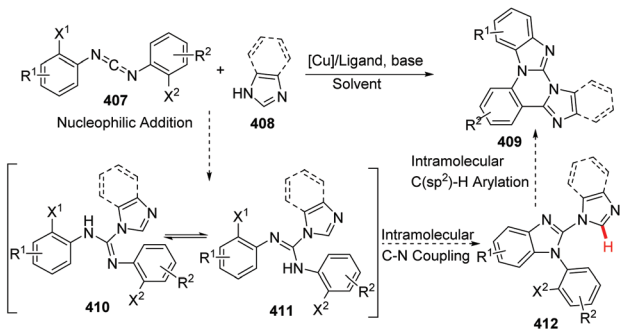


Scheme 97 Plausible catalytic cycle for the synthesis of purine-fused polycyclics.

With the optimized conditions, they found that $Cu(OTf)_2$ exhibited better catalytic activity than Cu(I), and thus $Cu(OTf)_2$ was selected as the copper source of choice. $PhI(OAc)_2$ as the oxidant was better than any other oxidants screened. Since the only by-product of the reaction is water, it is not difficult to understand why $AcOH/Ac_2O$ was chosen as the solvent, which proved to significantly improve the yield under mild conditions. They also investigated the electronic and steric effects. Results showed that substrates containing electron-withdrawing groups gave higher yields than those with electron-donating groups; substrates with substituents at the *ortho* position of the aniline ring gave lower yield than those with *para* substituents. Phenyl as a substituent is more favourable for the reaction than naphthyl as a substituent.



Scheme 98 Approach to polycyclic benzimidazole derivatives.



Scheme 99 Proposed mechanism involved the C–H activation in the catalytic pathway.

Lv and co-workers developed a Cu-catalyzed synthesis of fused polycycles from bis-(2-haloaryl)carbodiimides and benzimidazole (or indole) (Scheme 98).[107] Benzimidazo[1,2-*a*] indoles were prepared from the reaction with carbodiimides. The proposed mechanism involved the C–H activation was depicted (Scheme 99).

3. Conclusions and outlook

Transition metal-catalyzed C–H activation is a powerful strategy for the synthesis of bridgehead nitrogen heterocycles. Diverse metal catalysis including palladium, rhodium, ruthenium, iridium, cobalt, nickel, silver, and copper have been used as efficient catalysts for the activation of different C(sp^2)–H, C(sp)–H, and C(sp^3)–H bonds. Among them, Pd, Rh, and Cu are three main players. In particular, Cu catalysts have demonstrated a broad spectrum of catalytic activities. As a non-precious metal, copper is inexpensive and less toxic. In view of the green chemistry principles, copper-catalyzed reactions have bright prospects. Although significant progress has been achieved in this field, further exploration is still required in many directions: (i) the development of additional C–H functionalization protocols for the synthesis of new drug scaffolds is needed. For example, only a few methods that have been reported for transition metal-catalyzed nucleoside synthesis *via* C–H activation. (ii) New catalysts and catalytic systems are required for the transformation of bridgehead nitrogen heterocycles, so that the number of examples using other catalysts such as Ru, Co, Ir, Ni, Ag *etc*. would be increased. (iii) In contrast to C(sp^2)–H and C(sp)–H bonds, it is still challenging to activate C(sp^3)–H bonds.[108] Hence more C(sp^3)–H bond activation reactions are necessary. (iv) Due to many drugs containing bridgehead nitrogen heterocycles scaffolds, scalable reactions are strongly favored by chemists. We hope that this review would be helpful for synthetic chemists to select appropriate methods for the preparation of target molecules and promote the development of new C–H activation reactions for the synthesis of bridgehead nitrogen heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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