

C–H amination in the synthesis of *N*-heterocycles

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Abstract: *N*-heterocycles are important motifs in natural products and pharmaceuticals. Recently, the transition metal-catalyzed C–H amination has become a subject in the synthesis of *N*-heterocycles because of use of the readily available starting materials, high efficiency, economy, and practicability of the methods. This review summarizes recent advances in the copper, iron, palladium, rhodium, ruthenium, and nickel-catalyzed synthesis of *N*-heterocycles via C–H amination strategy.

Keywords: *N*-heterocycles, C–H activation, amination, transition metal-catalyzed, synthetic methods

Introduction

N-heterocyclic compounds are of unique structural units and widely exist in the bioactive molecular and natural products.¹ Because *N*-heterocyclic compounds tend to exhibit improved solubility and promote salt formation, which are helpful to improve oral absorption and bioavailability,² they are privileged structures in drug development. Recently, transition metal-catalyzed C–H activation has attracted much attention because of its great application in organic synthesis.^{3–11} Over the past decade, the transition metal-catalyzed C–H amination has achieved remarkable progress, and the highly atom economical strategy has been applied to the synthesis of *N*-heterocyclic compounds.^{12–15} This review is intended to provide an overview of copper, iron-, palladium-, rhodium-, ruthenium-, and nickel-catalyzed C–H amination in the synthesis of *N*-heterocyclic compounds.

Copper-catalyzed synthesis of *N*-heterocycles

At first, we discuss the C–H amination of arenes leading to *N*-heterocyclic compounds. In 2008, Brasche and Buchwald¹⁶ reported the copper-catalyzed C–H amination to lead to benzimidazoles (**2**) by using amidines (**1**) as the substrates (Figure 1). The intramolecular cyclization used 15 mol% Cu(OAc)₂ as the catalyst, molecular oxygen as the oxidant in dimethyl sulfoxide in the presence of 5 equiv AcOH at 100°C, and the reactions provided the benzimidazole derivatives in good yields with good tolerance of functional groups including both electron-donating and electron-withdrawing substituents. Exact mechanism for the reaction is unclear, and the authors proposed three possible pathways (Figure 2). Treatment of **1** with Cu(OAc)₂ provides **I**, intramolecular arylation of **I** leads to **II**, and deprotonation of **II** gives **2** (pathway a); intramolecular addition of **I** affords a metallacycle **III**, and **2** is subsequently obtained

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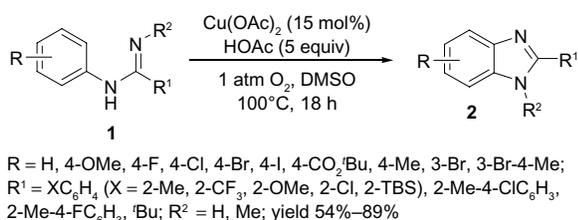


Figure 1 Copper-catalyzed synthesis of benzimidazoles.

through rearomatization and reductive elimination of the metal (pathway b). Desorption of HOAc in **II** gives a copper nitrene **IV**, and a concerted insertion of the nitrogen into an aryl C–H bond provides **2** (pathway c).

Sheng et al¹⁷ used substituted 3-iodochromones (**3**) and amidines (**4**) as the substrates, and the reactions underwent sequential intermolecular Ullmann-type N-arylation of amidines and intramolecular aerobic oxidation in air to afford chromento[2,3-*d*]imidazol-9(1*H*)-ones (**5**) in moderate to good yields (Figure 3).

In 2011, Cho et al¹⁸ reported the copper-catalyzed preparation of carbazoles (**7**) from *N*-substituted amidobiphenyls (**6**) by using hypervalent iodine(III) as the oxidant (Figure 4A). The reactions were performed quickly under mild conditions, and a free radical mechanism was proposed. In 2014, Takamatsu et al¹⁹ used MnO₂ as the oxidant, the reactions were carried out at 200°C in the presence of AcOH under microwave irradiation, and the similar C–H amination was achieved with picolinamide as the directing group (Figure 4B).

Zhou et al²⁰ developed the intramolecular copper-catalyzed approach to *N*-aryl acridones (**11**) via C–H amination (Figure 5). The protocol used aryl-(2-arylaminoaryl) methanones (**10**) as the starting materials and air as the oxidant, and the reactions were performed well under neutral conditions. The reaction undergoes intramolecular aerobic oxidative cyclization of **10** leading to intermediate **I**, and subsequent reductive elimination of **I** provides the target products (**11**).

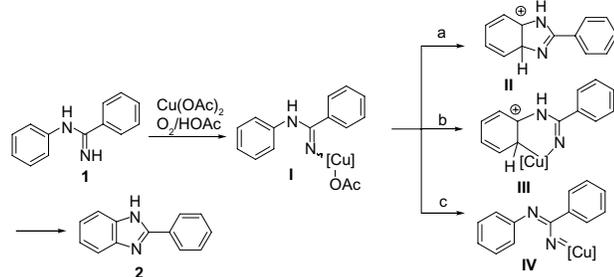


Figure 2 Proposed mechanism for the copper-catalyzed synthesis of benzimidazoles.

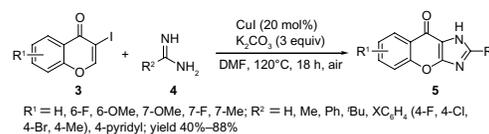


Figure 3 Copper-catalyzed synthesis of chromento[2,3-*d*]imidazol-9(1*H*)-ones.

In 2013, Li et al²¹ synthesized indazoles (**13**) via copper-catalyzed aerobic oxidative C–H amination of *N*-tosylhydrazones (**12**) (Figure 6). The method showed a good functional group tolerance. Similarly, pyrazoles (**15**) were also prepared through the intramolecular C–H amination strategy.

Berrino et al²² established synthesis of 4-aryl-2-quinolones (**17**) from 3,3-diarylacrylamides (**16**) through intramolecular copper-catalyzed C–H amination (Figure 7A). The protocol used 10 mol% CuI as the catalyst, 20 mol% PPh₃ as the ligand, 2 equiv of KO^tBu as the base, and the reactions were performed in *o*-xylene under air atmosphere. Gui et al²³ developed a similar procedure for the synthesis of phenanthridin-6(5*H*)-one derivatives (**19**) by using 2-phenylbenzamides (**18**) as the substrates (Figure 7B).

The synthesis of isoquinolin-1(2*H*)-ones via copper-mediated amination has been developed by Chary et al²⁴ (Figure 8). Reaction of 2-iodobenzamides (**20**) with alkynes in PEG 400 afforded *N*-substituted isoquinolin-1(2*H*)-ones (**21**) in moderate to good yields. The reaction undergoes sequential Sonogashira-type coupling and intramolecular cycloaddition process.

In 2012, Wang et al²⁵ developed the copper-catalyzed aerobic oxidative intramolecular C–H amination, and the corresponding imidazobenzimidazole derivatives (**23**) were obtained in excellent yields (Figure 9A). The protocol used substituted 2-(1*H*-imidazol-1-yl)-*N*-alkylbenzenamines (**22**) as the starting materials, 20 mol% Cu(OAc)₂ as the catalyst, 1,10-phenanthroline (1,10-phen) as the ligand, and molecular oxygen as the oxidant. A possible mechanism is proposed in

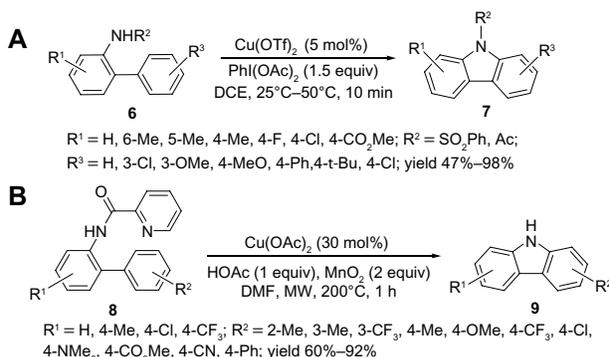


Figure 4 (A, B) Copper-catalyzed synthesis of carbazoles.

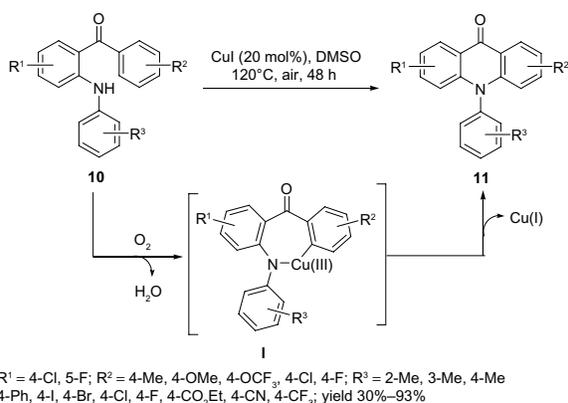


Figure 5 Copper-catalyzed synthesis of acridones.

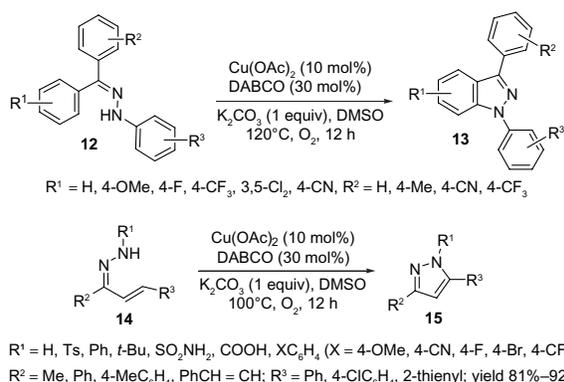


Figure 6 Copper-catalyzed synthesis of indazoles.

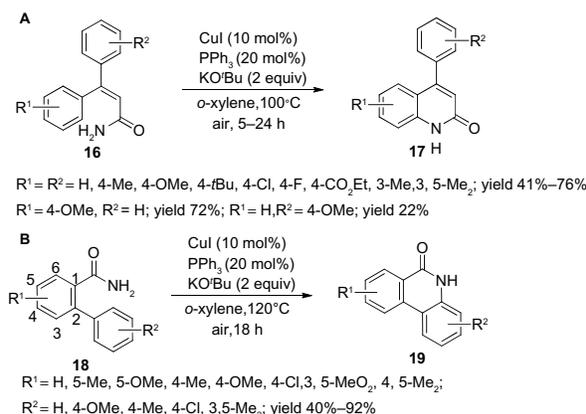
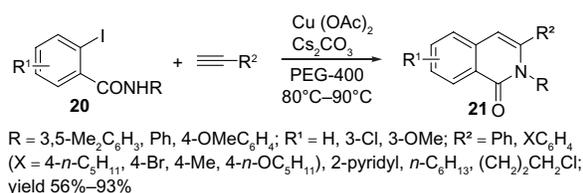
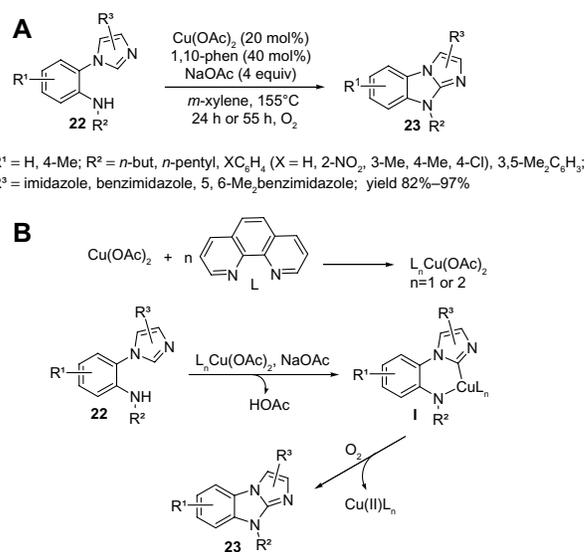
Figure 7 (A, B) Copper-catalyzed synthesis of 4-ary-2-quinolones and phenanthridin-6(5*H*)-ones.Figure 8 Copper-catalyzed synthesis of isoquinolin-1(2*H*)-ones.

Figure 9 (A, B) Copper-catalyzed synthesis of imidazobenzimidazoles.

Figure 9B. The treatment of $\text{Cu}(\text{OAc})_2$ with 1,10-phenanthroline forms complex $\text{LnCu}(\text{OAc})_2$, reaction of **22** with $\text{LnCu}(\text{OAc})_2$ provides **I**, and aerobic oxidative of **I** affords the target products (**23**) regenerating the $\text{Cu}(\text{II})$ catalyst.

In the same year, Xu and Fu²⁶ reported a sequential copper-catalyzed Ullmann-type *N*-arylation and aerobic oxidative intramolecular C–H amination by using substituted 2-halo-*N*-alkylbenzamides, 2-chloro-*N*-propylpyridine-3-carboxamide (**24**), imidazole, and benzimidazole derivatives (**25**) as the starting materials (Figure 10). The reactions applied inexpensive CuI/L -proline as the catalyst system and molecular oxygen as the oxidant. The imidazo/benzimidazoquinazolinones (**26**) were obtained in good to excellent yields. The procedure involved sequential copper-catalyzed Ullmann-type *N*-arylation and aerobic oxidative intramolecular C–H amination. Later, Chen et al²⁷ described a similar approach to azoquinazolinones.

In fact, the C–H amination of alkenes to *N*-heterocyclic compounds has been investigated. In 2011, Wang et al²⁸

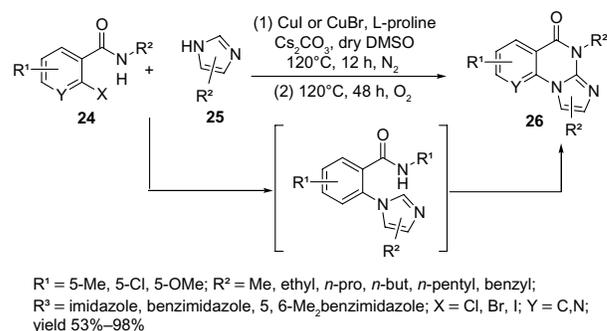


Figure 10 Copper-catalyzed synthesis of imidazoquinazolinones.

described copper-catalyzed synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes (**28**) and 1,2-disubstituted imidazole-4-carbaldehydes (**30**) from readily available *N*-allyl-2-aminopyridines (**27**) and substituted *N*-allylamidines (**29**) (Figure 11). The reactions were carried out well by using 20 mol% Cu(II) hexafluoroacetylacetonate (hfacac) catalyst in DMF or DMA at 105°C under oxygen. As shown in Figure 12, the catalytic cycle is initiated by coordination of **27** with Cu(II) to form Cu(II)-N adduct (**I**); oxidation of the Cu(II)-N adduct generates a Cu(III) intermediate (**II**). Subsequently, intramolecular cyclization of **II** provides **III**, desorption of Cu(II)OH in **III** gives **V**, and oxidative aromatization of **V** affords the desired product (**28**).

In 2007, Zeng and Chemler²⁹ developed the asymmetric synthesis of six-membered *N,S*-heterocycles (**32**) via copper-catalyzed intramolecular carboamination of alkenes (**33**) by using chiral bisoxazoline as the ligand and MnO₂ as the oxidant (Figure 13). In 2009, the same group reported the intramolecular copper-catalyzed carboamination of *N*-aryl-2-allylanilines (**33**), in which Cu(OTf)₂ was used as the catalyst, 2,2'-bipyridyl as the ligand, and MnO₂ as the oxidant (Figure 14).³⁰ A possible mechanism for the procedure was proposed as follows: coordination of Cu(II) with nitrogen in *N*-aryl-2-allylaniline (**33**) gives **I**, intramolecular addition of N-CuL to the alkenyl C=C bond in **I** provides **II**, desorption of CuL in **II** leads to **III**, and cyclization of **III** affords the target product (**34**). When a chiral oxazoline ligand was used in the reactions, 10*a*,11-dihydro-10*H*-indolo[1,2-*a*]indoles (**36**) with high enantioselectivity were prepared (Figure 15).³¹

In 2011, Lu et al³² established the efficient copper-catalyzed aerobic oxidative intramolecular alkene C–H amination leading to *N*-heterocycles (**38**) (Figure 16). The protocol used substituted 3-methyleneisoindolin-1-ones (**37**) as the starting materials, Cu(O₂CCF₃)₂ as the catalyst, and air

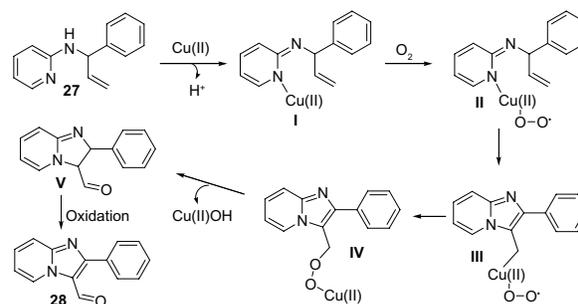


Figure 12 Proposed mechanism for the copper-catalyzed synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes.

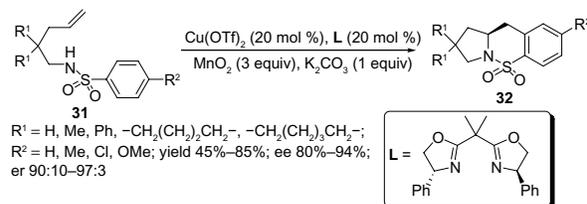


Figure 13 Copper-catalyzed synthesis of six-membered *N,S*-heterocycles.

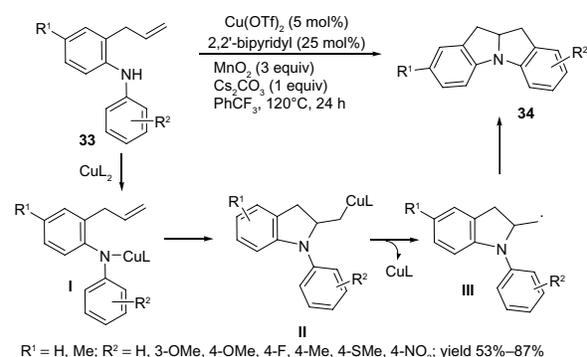


Figure 14 Copper-catalyzed synthesis of 10*a*,11-dihydro-10*H*-indolo[1,2-*a*]indoles.

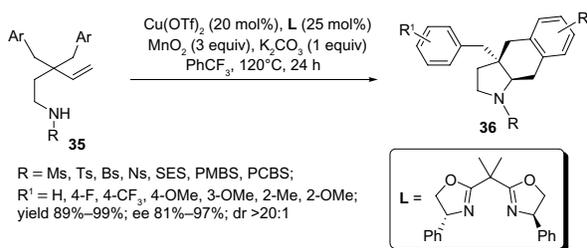


Figure 15 Copper-catalyzed enantioselective synthesis of hexahydro-1*H*-benz[*f*]indoles.

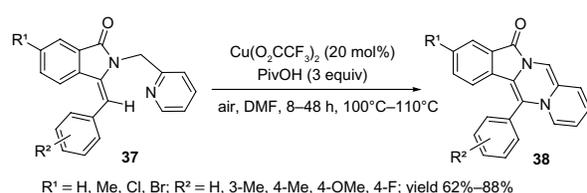
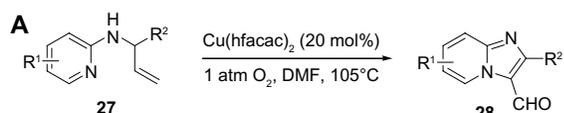
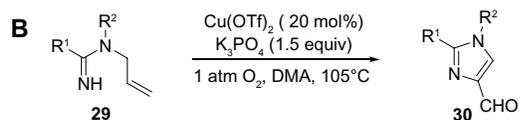


Figure 16 Copper-catalyzed synthesis of fused *N*-heterocycles.



R² = H, *i*-Pr, *c*-Hex, XC₆H₄ (X = H, 2-Cl, 3-OMe, 4-Cl, 4-Br, 4-Me, 4-OMe, 4-F, 4-CN, 4-CO₂Me)
3-pyridyl, 2-thienyl, 2-naphthyl; yield 40%–77%



R¹ = XC₆H₄ (X = H, 4-Me, 4-OMe, 4-Br), *c*-Hex; R² = Ph, 4-MeC₆H₄, Bn, Me; yield 27%–65%

Figure 11 (A, B) Copper-catalyzed synthesis of imidazo[1,2-*a*]pyridine-3-carbaldehydes and 1,2-disubstituted imidazole-4-carbaldehydes.

as the oxidant, and the corresponding *N*-heterocycles were obtained in good to excellent yields.

The copper-catalyzed C–H bond amination of alkynes is also applied in the synthesis of *N*-heterocyclic compounds. In 2013, Li and Neuville developed the copper-catalyzed synthesis of 1,2,4-trisubstituted imidazoles (**40**) from amidines (**39**) and terminal alkynes (Figure 17).³³ The protocol used 20 mol% $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ as the catalyst, 2 equiv of sodium carbonate and 2 equiv of pyridine as the additives, and molecular oxygen as the oxidant. A possible mechanism for the reaction is shown in Figure 18. Treatment of Cu(II) with **39** and terminal alkyne provides **I**, oxidation of **I** gives **II**, and reductive elimination of **II** leads to **III**. Cycloaddition of **III** affords **IV**, desorption of copper in **IV** in the presence of HX yields **40** freeing Cu(I)X, and oxidation of Cu(I)X regenerates Cu(II) catalyst.

The copper-catalyzed $\text{C}(\text{sp}^3)$ -H bond amination is effective for the synthesis of heterocyclic compounds. In 2013, Huang et al³⁴ described the Cu(I)-catalyzed intramolecular aerobic oxidative C–H amination of 2-aminoacetophenones (**41**) in the presence of 2,2'-bipyridine as the ligand, and various *N*-alkyl- or aryl-substituted isatins (**42**) were prepared in good to excellent yields (Figure 19). In the reactions, oxidation of **41** forms the corresponding acetaldehyde (**I**), intramolecular nucleophilic attack of imine to aldehyde in **I** leads to **II**, and further oxidation of **II** provides the desired product (**42**).

Chen et al³⁵ described the amination of aliphatic C–H bonds in *N*-alkylamidines (**43**), in which $\text{Cu}(\text{OAc})_2$ was used as the catalyst, $\text{PhI}(\text{OAc})_2$ as the oxidant (Figure 20). The intramolecular C–H amination was performed in the presence of K_3PO_4 at room temperature. As shown in Figure 21, treatment of **43** with copper catalyst in the presence of $\text{PhI}(\text{OAc})_2$ provides **I**, and desorption of copper in **I** forms free radical **II**. Transfer of a hydrogen free radical in **II** gives **III**, oxidation of **III** affords **IV**, and cyclization of **IV** affords the target product (**44**).

Wang et al³⁶ reported the efficient method for construction of four-membered β -lactams (**46**) based on copper-catalyzed

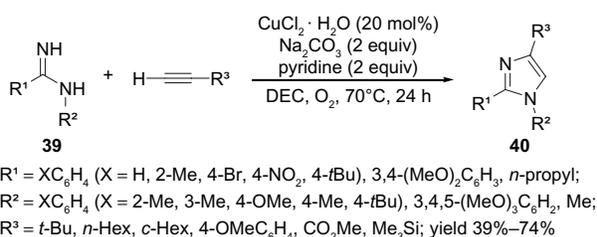


Figure 17 Copper-catalyzed synthesis of imidazoles.

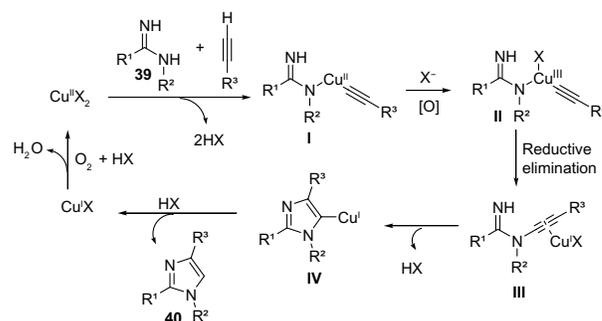


Figure 18 Proposed mechanism for the copper-catalyzed synthesis of imidazoles.

$\text{C}(\text{sp}^3)$ -H amination with 8-aminoquinolinyl as the directing group (Figure 22A). A plausible mechanism is proposed in Figure 22B. Oxidation of Cu(II) by Ag_2CO_3 affords Cu(III), treatment of Cu(III) with **45** leads to **I**, and insertion of Cu(III) to $\text{C}(\text{sp}^3)$ -H gives **II**. Reaction of **II** with HOAc affords **III**, and reductive elimination of **III** provides the target product (**46**). At the same time, Wu et al³⁷ independently reported a similar research in the presence of 20 mol% CuCl as the catalyst and duroquinone as the oxidant under air, and the corresponding products (**48**) were obtained in 69%–92% yields (Figure 23).

Iron-catalyzed synthesis of *N*-heterocycles

Iron is more abundant and inexpensive than other transition metals in nature, and it is used in C–H amination for the synthesis of *N*-heterocycles. Iron-catalyzed C–H amination of arenes to *N*-heterocycles has been investigated by some groups. In 2013, Zhang and Bao³⁸ developed the iron-catalyzed aerobic oxidative synthesis of substituted 1*H*-indazoles (**50**) and 1*H*-pyrazoles (**52**) from arylhydrazones (Figure 24). The protocol used molecular oxygen as the oxidant, the inexpensive FeBr_3 as the catalyst, and water was a sole by-product. A possible mechanism is

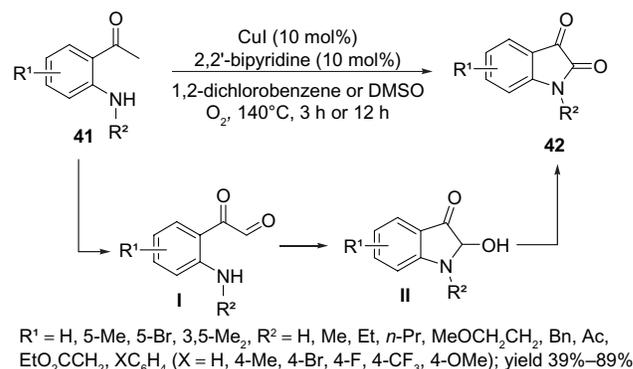


Figure 19 Copper-catalyzed synthesis of isatins.



Figure 20 Copper-catalyzed synthesis of dihydroimidazoles.

shown in Figure 25. The reaction is proposed to proceed via a Fe-catalyzed one-electron transfer process of (**49**) to get a radical cationic ion **I**, which undergoes intramolecular C–N bond formation to lead to **II**. Subsequently, deprotonation of **II** provides **III**, and **III** loses one electron and hydrogen to yield the desired product (**50**).

In 2009, Fan et al³⁹ developed synthesis of 2-pyrrolines (**55**) from readily available substrates (**53** and **54**) under mild conditions (Figure 26). Under FeCl_3 catalysis, the reaction of aziridines with arylalkynes provided the corresponding functionalized 2-pyrrolines in moderate to good yields. The proposed reaction mechanism is shown in Figure 27. Aziridine is activated by FeCl_3 to form a zwitterionic intermediate (**I**), and then reaction of **I** with phenylacetylene provides an aryl-substituted alkenyl cation (**II**). Intramolecular nucleophilic addition gives the desired product (**55**) regenerating the iron catalyst.

In 2014, Sun et al⁴⁰ described the synthesis of 4,5-dihydropyrroles (**58**) through iron-catalyzed [4C + 1N] cyclization of 4-acetylenic ketones (**56**) and primary amines (**57**) (Figure 28). The protocol used FeCl_3 as the catalyst and 1,5-pentanediol as solvent, and various substituted 4,5-dihydropyrroles were obtained in moderate to good yields. The reaction was performed through enamine formation and subsequent cyclization.

In 2014, Liu et al⁴¹ developed inter- and intramolecular amination using primary arylamines as a nitrogen source for nitrene/imide insertion and transfer reactions (Figure 29). The reaction was performed using $[\text{Fe}(\text{F}_{20}\text{TPP})\text{Cl}]$ ($\text{H}_2\text{F}_{20}\text{TPP} = \text{meso-tetrakis(pentafluorophenyl)porphyrin}$) as the catalyst and PhI(OAc)_2 as the oxidant. The protocol can be applied

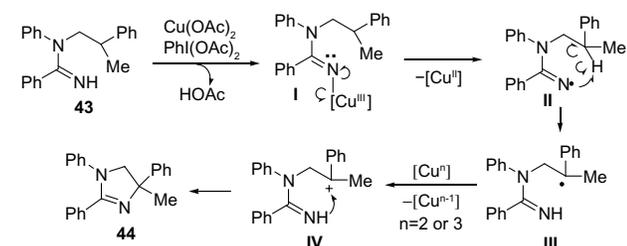


Figure 21 Proposed mechanism for the copper-catalyzed synthesis of dihydroimidazoles.

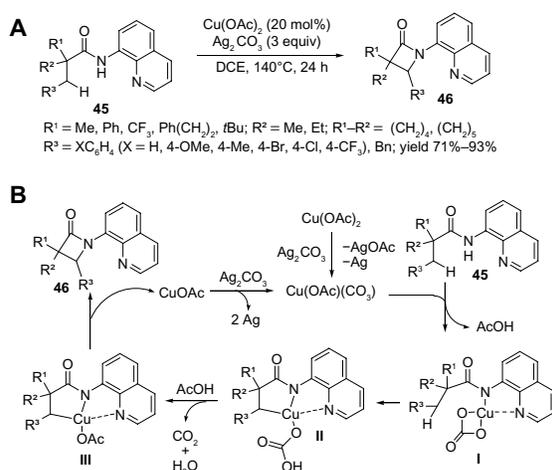


Figure 22 (A, B) Copper-catalyzed synthesis of four-membered β -lactams.

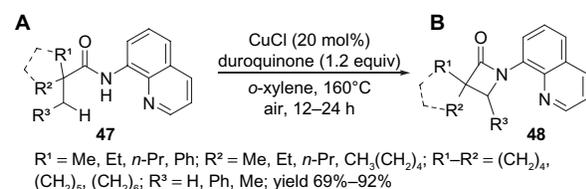


Figure 23 (A, B) Similar copper-catalyzed synthesis of four-membered β -lactams.

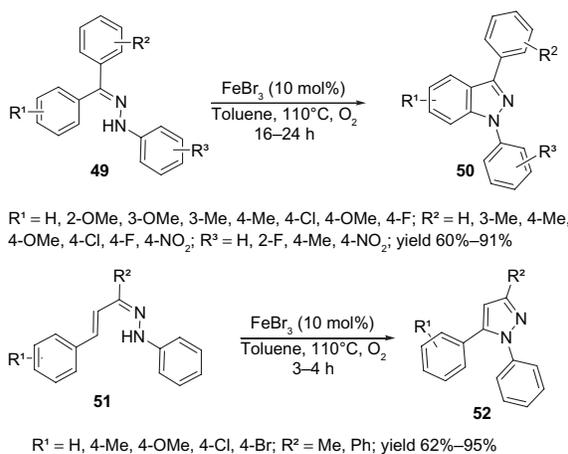


Figure 24 Iron-catalyzed synthesis of substituted 1H-indazoles and 1H-pyrazoles.

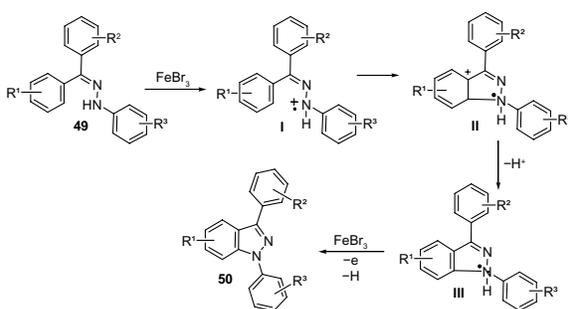


Figure 25 Proposed mechanism for iron-catalyzed synthesis of substituted 1H-indazoles.

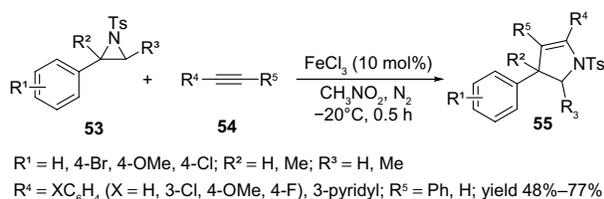


Figure 26 Iron-catalyzed synthesis of 2-pyrrolines.

to both intra- and intermolecular amination of sp^2 and sp^3 C–H bonds, affording the amination products **60** and **62** in moderate to good yields. A possible mechanism was proposed (Figure 30). Under catalysis of $[\text{Fe}(\text{F}_{20}\text{TPP})\text{Cl}]/\text{PhI}(\text{OAc})_2$, arylamine (**59** or **61**) was converted into reactive intermediate (**I**), and then the nitrene/imide insertion to C–H bond provides **59** or **61**.

In 2014, Karthikeyan and Sekar⁴² described the iron-catalyzed intramolecular C–H amination of 2-benzhydrylpyridine derivatives (**63**), and the corresponding pyrido[1,2-*a*]indoles (**64**) were prepared under catalysis of FeCl_3 and FeCl_2 in the presence of molecular oxygen. In the reactions, the pyridine nitrogen atom was a directing group as well as a nucleophile (Figure 31).

The same group reported synthesis of benzimidazoles (**67**) from *o*-aminoarylazides (**65**) and arylaldehydes (Figure 32).⁴³ The procedure was divided into two steps: reaction of *o*-aminoarylazides and arylaldehydes firstly produced imines in the presence of MgSO_4 , and then iron-catalyzed desorption of nitrogen and cyclization provided the target products in the presence of powered 4 Å molecular sieves.

In 2011, Bonnamour and Bolm⁴⁴ described the iron-catalyzed synthesis of indoles (**69**) via intramolecular C–H amination (Figure 33). The protocol used iron(III) triflate as the catalyst, and THF as the solvent, and various 2-substituted indoles were obtained with a broad range of functional groups, including ethers, CF_3 , C–F, and C–Cl bonds.

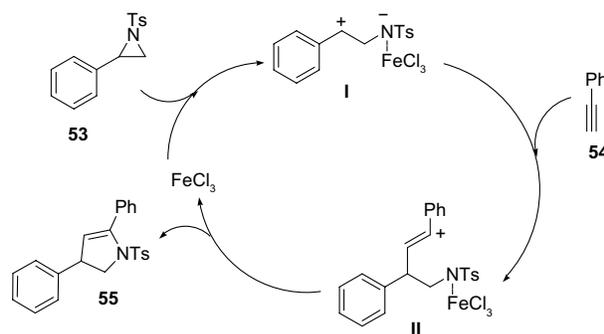


Figure 27 Proposed mechanism for iron-catalyzed synthesis of 2-pyrrolines

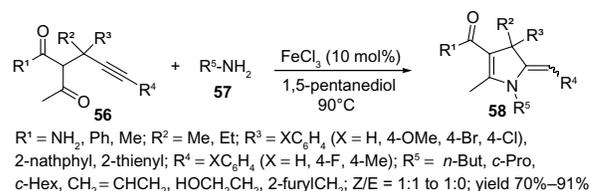


Figure 28 Iron-catalyzed synthesis of 4,5-dihydropyrroles.

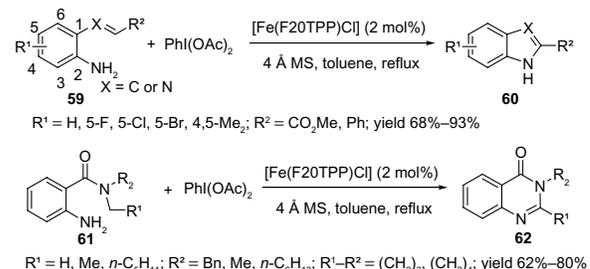


Figure 29 Iron-catalyzed inter- and intramolecular C–H amination.

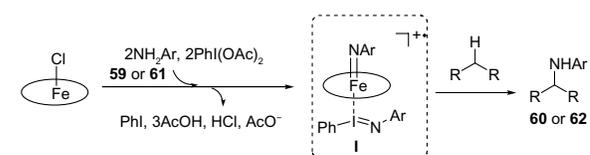


Figure 30 Proposed mechanism for iron-catalyzed inter- and intramolecular C–H amination.

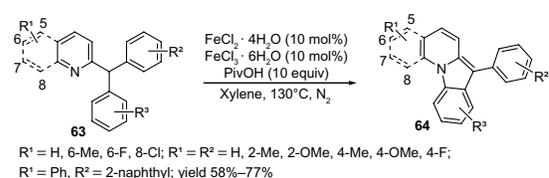


Figure 31 Iron-catalyzed synthesis of pyrido[1,2-*a*]indoles.

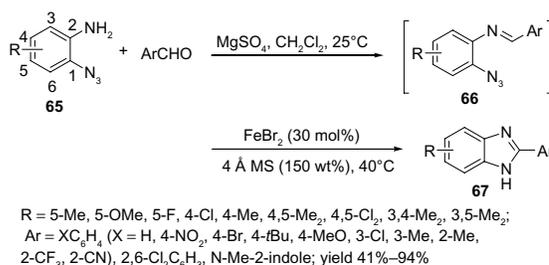


Figure 32 Iron-catalyzed synthesis of benzimidazoles.

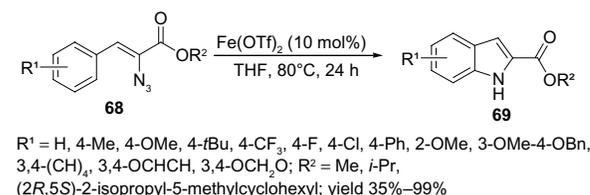


Figure 33 Iron-catalyzed synthesis of indoles.

Jana et al⁴⁵ developed the FeCl₂-catalyzed synthesis of 2,3-disubstituted indoles (**71**) from 2*H*-azirines (**70**) (Figure 34). The reactions underwent the sequential ring opening of 2*H*-azirines (**70**) to lead to the formation of iron vinyl nitrene intermediate (**II**) and intramolecular cyclization to form **III** (Figure 35). The method could tolerate a variety of functional groups such as Br, F, NO₂, OMe, CF₃, OTBS, alkenes, and OPiv.

Hennessey and Betley⁴⁶ developed the iron-dipyrrinato catalyst that promoted the direct aliphatic C–H amination, and various pyrrolidine derivatives (**73**) were obtained in reasonable yields (Figure 36). The reactions were performed under mild conditions, and a free radical intermediate process was proposed. The azetidines and piperidines were also prepared following similar procedures. The authors suggested a possible mechanism (Figure 37). Treatment of **72** with iron catalyst provides **I**, and isomerization of **I** leads to **II**. Cyclization of **II** gives **III**, and freeing of iron catalysts gets the target product (**73**).

In 2012, Nguyen et al⁴⁷ described an interesting iron(II) bromide-catalyzed C–H bond amination 1,2-migration reaction, in which *ortho*-substituted aryl azides (**74**) transformed into 2,3-disubstituted indoles (**75**) in toluene at 140°C (Figure 38). The 1,2-shift component was selective, and the migration aptitude was Me < 1° < 2° < Ph. A possible mechanism is proposed in Figure 39. Reaction of **74** with iron catalyst forms an iron nitrene (**II**), and intramolecular hydride shift in **II** provides an oxocarbenium ion intermediate (**III**). Intramolecular cyclization of **III** leads to **IV**, and desorption of iron catalyst from **IV** affords **V**. Further treatment of **V** with iron catalyst gives **VIII**, and deprotonation of **VIII** provides the desired product (**75**).

Iron catalysts are also used in the C(sp³)-H amination. For example, Liu et al⁴⁸ reported the intramolecular C(sp³)-H amination of sulfamate esters (**76**) (Figure 40). The protocol used nonheme iron complex as the active catalyst and PhI(OAc)₂ as the oxidant, and the reactions were performed well under mild conditions. Furthermore, the benzylic, allylic, and cycloalkylic C(sp³)-H amination with PhI=NR was also effective.

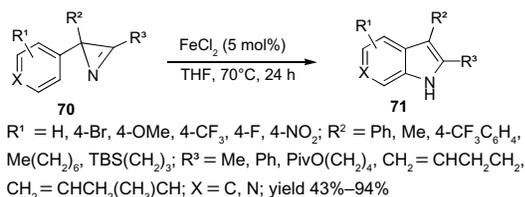


Figure 34 Iron-catalyzed synthesis of 2,3-disubstituted indoles.

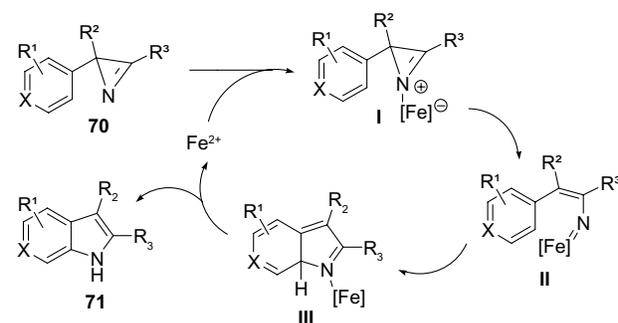
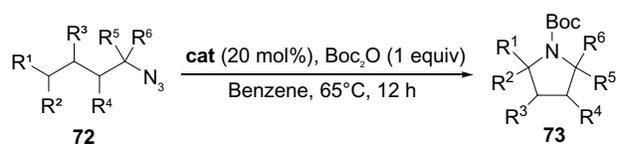


Figure 35 Proposed catalytic cycle for iron-catalyzed synthesis of 2,3-disubstituted indoles.



R¹ = Ph, CH=CH₂, Me, Et, H, CO₂Et; R² = H, Me; R³ = H, Et; R⁴ = H, OTMS, Ph, Me; R⁵ = H, Ph, Me; R⁶ = H, Me; yield 11%–98%

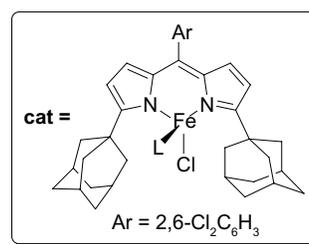


Figure 36 Iron-catalyzed synthesis of pyrrolidines.

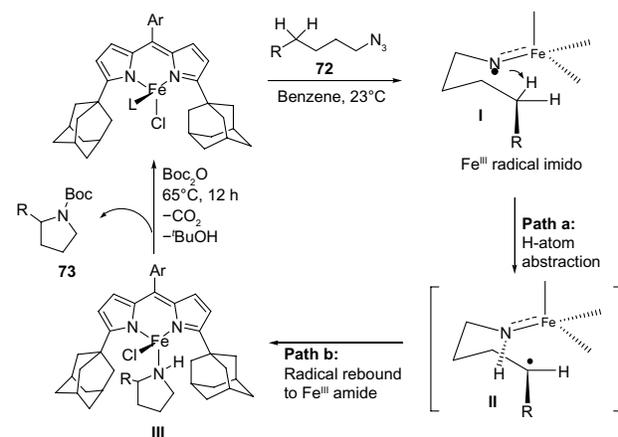


Figure 37 Proposed mechanism for iron-catalyzed synthesis of pyrrolidines.

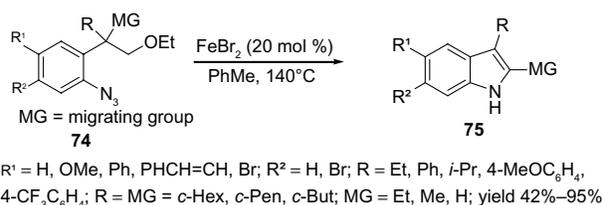


Figure 38 Iron-catalyzed synthesis of 2,3-disubstituted indoles.

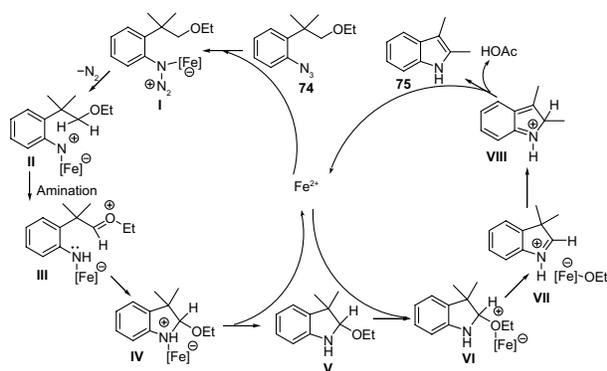


Figure 39 Possible mechanism for iron-catalyzed synthesis of 2,3-disubstituted indoles.

Palladium-catalyzed synthesis of *N*-heterocycles

Palladium catalysts exhibit high catalytic activity, and they are widely applied in C–H activation. In 2008, Tsang et al.⁴⁹ developed the palladium-catalyzed intramolecular C–H amination leading to unsymmetrical carbazoles (**79**) (Figure 41). The protocol used Pd(OAc)₂ as the catalyst and oxygen and Cu(OAc)₂ as the oxidants, and the reactions were performed well in the presence of powered 4-Å molecular sieves with excellent functional group compatibility. A possible mechanism is shown in Figure 42. Coordination of **78** with Pd(OAc)₂ provides a Pd–N intermediate (**I**) with the extrusion of HOAc. Intramolecular electrophilic palladation and subsequent deprotonation generates a six-membered cyclic palladium amide intermediate (**III**) that undergoes reductive elimination to give the target product (**79**).

In the same year, Jordan-Hore et al.⁵⁰ also reported a similar procedure (Figure 43A). They used Ph(OAc)₂ as the oxidant. It is worthwhile to note that the reactions were

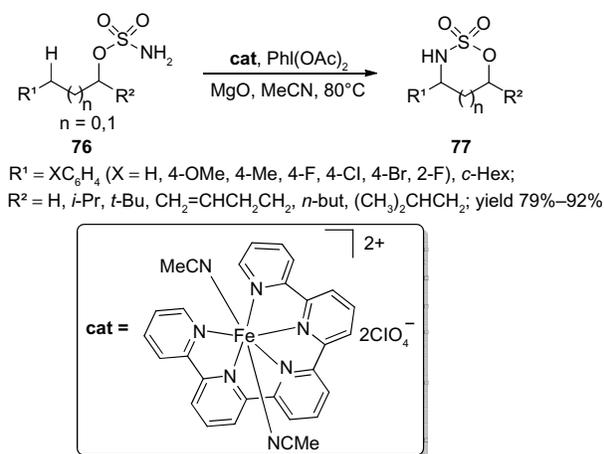


Figure 40 Iron-catalyzed C(sp³)-H amination of sulfamate esters.

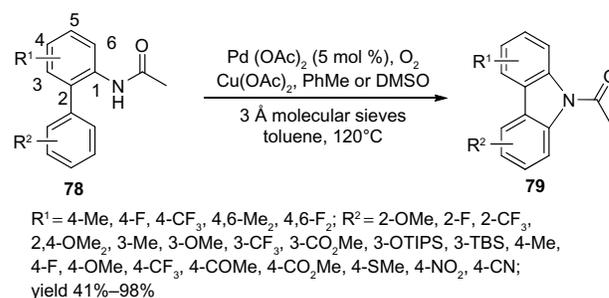


Figure 41 Palladium-catalyzed synthesis of carbazoles.

performed well at room temperature, and the method was applied in the synthesis of *N*-glycosyl carbazoles (**83**) (Figure 43B). In 2011, Youn et al prepared carbazoles (**85**) from *N*-Ts-2-arylanilines (**84**) via palladium-catalyzed intramolecular oxidative C–H amination by using oxone as the oxidant at ambient temperature (Figure 43C).⁵¹

In 2012, Yang and Zhang⁵² reported an efficient palladium-catalyzed intramolecular aerobic aza-Wacher cyclization for the synthesis of isoindolinones (**87**) and isoquinolin-1(*2H*)-ones (**88**) from the same substrates (**86**) under different catalytic conditions (Figure 44). Isoindolinones (**87**) were prepared using Pd(OAc)₂ as the catalyst and Phen as the ligand, and isoquinolin-1(*2H*)-ones were obtained by using (MeCN)₂PdCl₂ as the catalyst and Et₃N as the base.

In 2010, Shi et al.⁵³ described C–H functionalization and C–N bond formation in the Pd-catalyzed synthesis of β- and γ-carbolinones (**91** or **94**) from readily available indole-carboxamides (**89** or **92**) and alkynes (**90** or **93**) (Figure 45). The reactions were performed well under catalysis of palladium(II) acetate in the presence of tetra-*n*-butylammonium-bromide and oxygen. A plausible mechanism is shown in the Figure 46. Palladation of **89** with

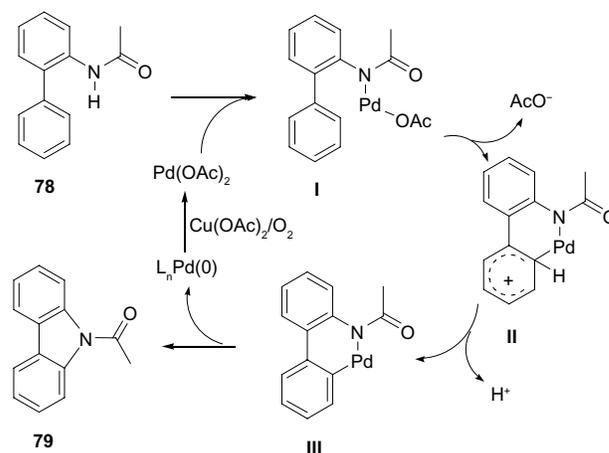


Figure 42 Proposed mechanism for palladium-catalyzed synthesis of carbazoles.

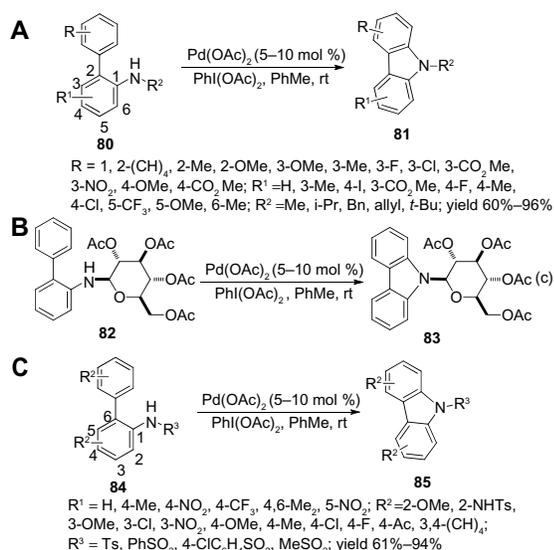


Figure 43 (A–C) Palladium-catalyzed synthesis of carbazoles.

Pd(OAc)₂ affords the Pd(II) intermediate (**I**), and addition of **I** to alkyne (**90**) provides vinylic Pd(II) adduct. Subsequent aminopalladation and reductive elimination generates the β-carbolinones (**91**) leaving Pd(0). Oxidation of Pd(0) regenerates Pd(II) catalyst under air or O₂ atmosphere.

In 2012, Zhang et al⁵⁴ reported the direct palladium-catalyzed synthesis of isoquinolone derivatives (**97**) via C–H and C–N bond oxidative coupling reactions (Figure 47). The protocol used palladium acetate as the catalyst, copper acetate and O₂ as the oxidants, and various substituted isoquinolones (**97**) were obtained in good yields. A proposed mechanism is shown in Figure 48. Treatment of **95** with Pd(II) in the presence of base provides **I**, and reaction of **I** with **96** leads to **II**. Addition of **II** yields **III**, and reductive elimination of **III** gives the target product (**97**) freeing Pd(0). Oxidation of Pd(0) by Cu(OAc)₂ and O₂ regenerates Pd(II) catalyst.

In 2009, Halland et al⁵⁵ developed a convenient and practical one-pot method for the synthesis of 2*H*-indazoles (**100**)

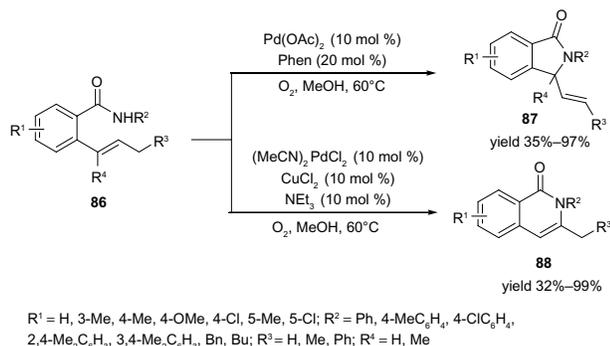


Figure 44 Palladium-catalyzed synthesis of isoindolinones and isoquinolin-1(2*H*)-ones.

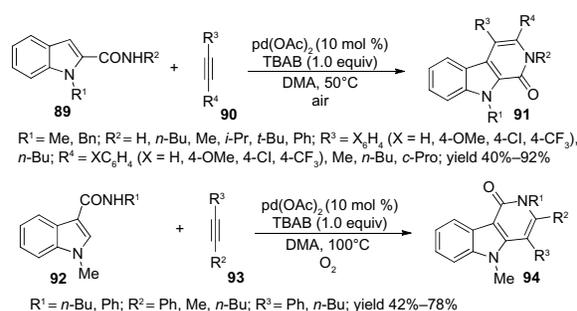


Figure 45 Palladium-catalyzed synthesis of β- and γ-carbolinones.

from readily available 2-halophenylacetylenes (**98**) and hydrazines (**99**) through a regioselective palladium-catalyzed intermolecular C–N coupling and intramolecular addition cascade process (Figure 49). The reaction showed high tolerance to various functionalities, including ester, amide, cyano, carboxylic acid, ether, and ketone groups.

In 2008, Zhang et al⁵⁶ developed the synthesis of pyrroles (**102** and **104**) from simple amino alcohols (**101** and **103**) (Figure 50). The protocol applied palladium(II) acetate as the catalyst, copper(II) triflate as the oxidant and alcohol as the solvent. The reaction was performed well under mild conditions.

In 2010, Majumdar et al⁵⁷ developed the synthesis of pyrrolo-fused heterocycles and carbocycles (**106**) catalyzed by palladium(II) acetate in the presence of IBX as the oxidant (Figure 51). The intramolecular oxidative amination of alkenes (**105**) provides the target product in excellent yields.

In 2009, Kip et al⁵⁸ reported a highly diastereoselective synthesis of fused heterocycles (**108** and **109**) using palladium(II) acetate as the catalyst (Figure 52). The protocol used isoquinoline or quinoline as the ligand and O₂ as the oxidant. The oxidative cascade cyclization reaction constructed three bonds and two chiral centers in one step and provided the target products in moderate yields.

In 2010, Jaegli et al reported⁵⁹ an efficient difunctionalization of alkenes (**110**) through intramolecular C–N and

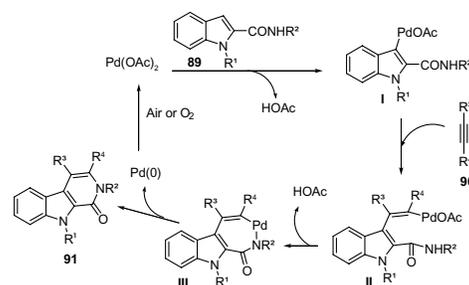


Figure 46 Plausible mechanism for the palladium-catalyzed synthesis of β-carbolinones.

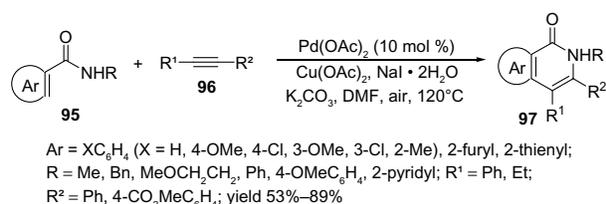


Figure 47 Palladium-catalyzed synthesis of isoquinolones.

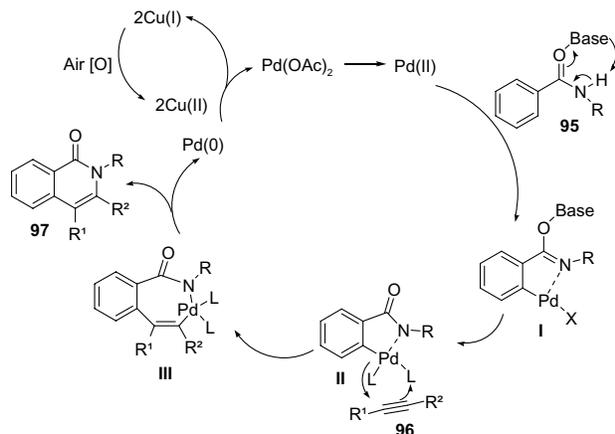


Figure 48 Proposed mechanism for palladium-catalyzed synthesis of isoquinolones.

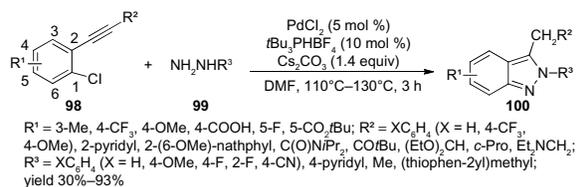


Figure 49 Palladium-catalyzed synthesis of carbazoles.

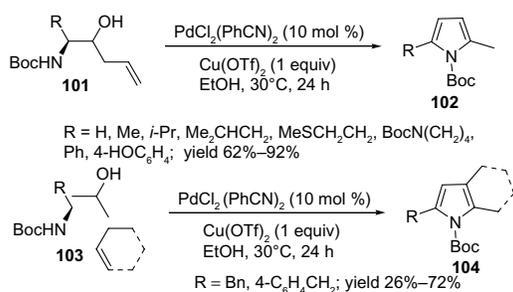


Figure 50 Palladium-catalyzed synthesis of pyrroles.

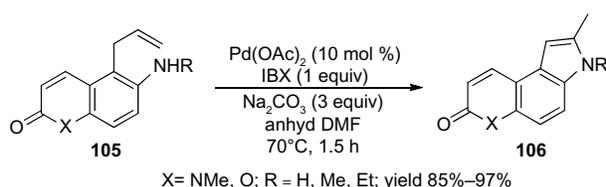


Figure 51 Palladium-catalyzed synthesis of carbazoles.

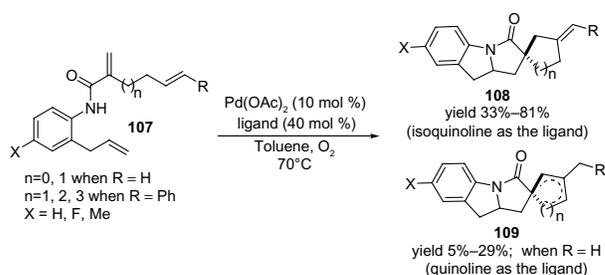


Figure 52 Palladium-catalyzed synthesis of carbazoles.

aromatic C–H bond formation (Figure 53). The reactions were performed using palladium dichloride as the catalyst, PhI(OAc)₂ as the oxidant, and MeCN as the solvent. The products (**111**) containing spirooxindole unit were prepared in moderate yields.

In 2014, Jeong and Youn⁶⁰ reported the palladium-catalyzed oxidative C–H amination from (*Z*)-*N*-Ts-dehydroaminodehydroamino acid esters (**112**), and the protocol used Pd(OAc)₂ as the catalyst and oxone as the oxidant, and the reactions were carried out in the presence of powered 4-Å molecular sieves at 80°C (Figure 54). Furthermore, *N*-Ts-hydrazones were also used as the substrates to prepare indazoles (**113**).

In 2008, Wasa and Yu⁶¹ developed the synthesis of lactams (**115** and **117**) via palladium-catalyzed intramolecular C–H amination using AgOAc and CuCl₂ as oxidants (Figure 55). In the reactions, both *N*-alkoxy-2-phenylacetamides (**114**) and *N*-methoxy-2-phenylacrylamides (**116**) were effective substrates.

Palladium-catalyzed amination of alkenes was also investigated. In 2005, Streuff et al.⁶² reported the palladium-catalyzed intramolecular oxidative diamination of alkenes (**118**) (Figure 56). Cyclic ureas (**119**) were prepared through this strategy by using Pd(OAc)₂ as the catalyst and PhI(OAc)₂ as the oxidant at room temperature. A possible mechanism is proposed in Figure 57. An intermediary vicinal amino palladium compound (**I**) is formed under Pd(II) catalysis, and oxidation of **I** provides the target product regenerating Pd(II) catalyst.



Figure 53 Palladium-catalyzed synthesis of carbazoles.

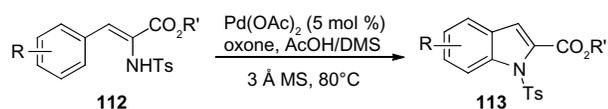


Figure 54 Palladium-catalyzed synthesis of indole-2-carboxylic acid esters.

Rhodium-catalyzed synthesis of *N*-heterocycles

Rhodium-catalyzed C–H amination is effective for the synthesis of *N*-heterocycles. In 2008, Stuart et al⁶³ described the synthesis of indoles (**122**) via rhodium-catalyzed oxidative coupling from readily available acetanilides (**120**) and alkynes (**121**) (Figure 58). The protocol used [RhCp*Cl₂]₂ as the catalyst, AgSbF₅ as the additive, copper acetate as the oxidant, and 2-methyl-2-butanol as the solvent. Various indoles were synthesized in moderate to good yields.

In 2010, Morimoto et al⁶⁴ reported the synthesis of indolo[2,1-*a*]isoquinoline derivatives (**125**) through the rhodium-catalyzed oxidative coupling of 2-phenylindoles (**123**) and alkynes (**124**) (Figure 59). The protocol used [RhCp*Cl₂]₂ as the catalyst and copper acetate as the oxidant in the presence of sodium carbonate under air. The corresponding polycyclic products (**125**) were obtained in good yields. The cascade reaction included an intermolecular C–N bond formation and intramolecular cyclization by C–C coupling. A possible mechanism is shown in Figure 60. Coordination of Cp*Rh(III)X₂ with **123** gives a five-membered intermediate (**I**), addition of **I** to **124** provides **II** or **III**, and reductive elimination of **II** or **III** affords the target product (**125**) releasing Cp*Rh(I). Oxidation of Cp*Rh(I) by copper acetate and air regenerates Cp*Rh(III) catalyst.

In 2009, the same group reported a similar procedure for the synthesis of isoquinoline derivatives (**128**) through rhodium-catalyzed oxidative coupling from aromatic imines (**126**)

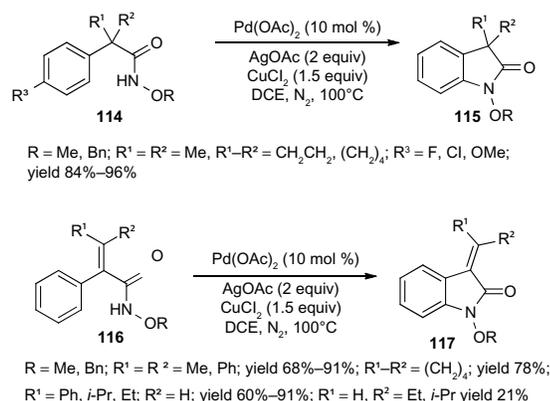


Figure 55 Palladium-catalyzed synthesis of lactams.

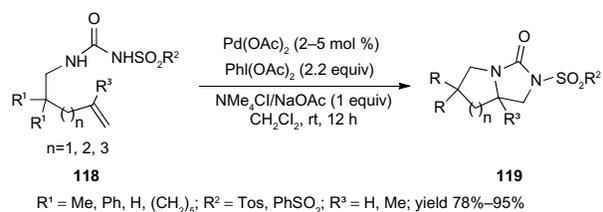


Figure 56 Palladium-catalyzed intramolecular deamination.

and alkynes (**127**) (Figure 61).⁶⁵ The reaction proceeded via cleavage of N–H bond and subsequent C–N/C–C bond formation.

In 2010, Hyster and Rovis⁶⁶ reported the construction of isoquinolone derivatives (**131**) via C–H/N–H activation from benzamides (**129**) and alkynes (**130**) under catalysis of [RhCp*Cl₂]₂ (Figure 62). The cascade reactions could tolerate various functional groups, and the target products were obtained in moderate to good yields.

In 2010, Guimond et al⁶⁷ reported the rhodium(III)-catalyzed synthesis of isoquinolones (**134**) from *N*-methoxylamides (**132**) and alkynes (**133**) (Figure 63). The reaction provided 3,4-disubstituted isoquinolones in moderate to good yields. A postulated mechanism is shown in Figure 64. Treatment of **132** with Rh(III) leads to **I** through C–H cleavage, addition of **I** to **133** provides **II**, and desorption of Rh(III) catalyst affords the target product (**134**).

In 2013, Hyster et al⁶⁸ reported the rhodium(III)-catalyzed synthesis of isoquinolones (**137**) from amides (**135**) and cyclopropenes (**136**) (Figure 65). The protocol used [RhCp*Cl₂]₂ as the catalyst, cesium acetate as the base, and methanol as the solvent. The sequential ring opening and cycloaddition provided the desired product in moderate to excellent yields.

Ruthenium-catalyzed synthesis of *N*-heterocycles

Ruthenium-catalyzed C–H amination is also used in the synthesis of *N*-heterocycles. In 2013, Li and Ackermann⁶⁹ developed a novel and efficient Ru-catalyzed oxidative annulation of ketimines (**138**) with alkynes (**139**) to provide 1-methylene-1,2-dihydroisoquinolines (**140**) (Figure 66). In the reaction, carboxylate-assisted ruthenium(II) catalyst

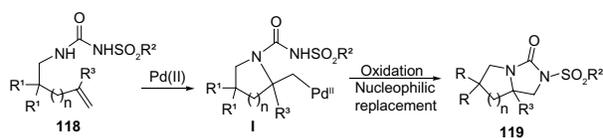


Figure 57 Proposed mechanism for palladium-catalyzed intramolecular deamination.

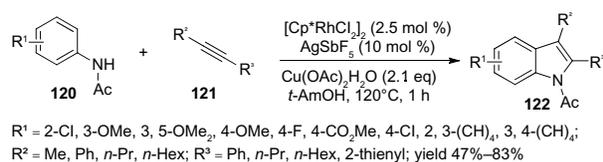


Figure 58 Rhodium-catalyzed synthesis of indoles.

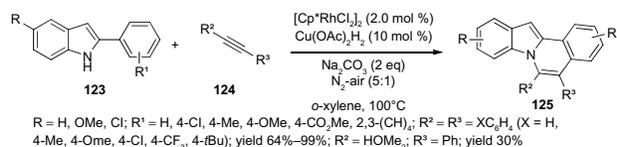
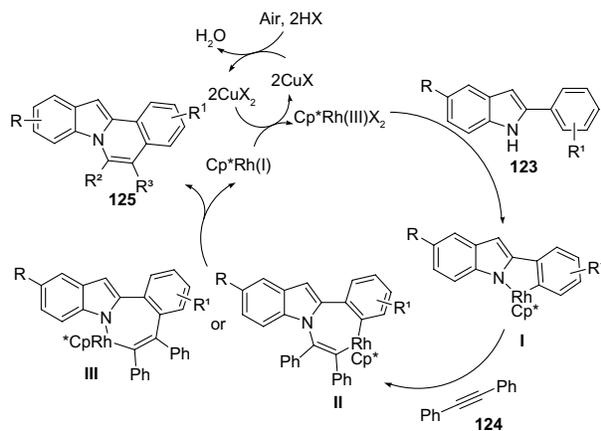
Figure 59 Rhodium-catalyzed synthesis of indolo[1,2-*a*] isoquinolines.Figure 60 Proposed mechanism for rhodium-catalyzed synthesis of indolo[1,2-*a*] isoquinolines.

Figure 61 Rhodium-catalyzed synthesis of isoquinolines.

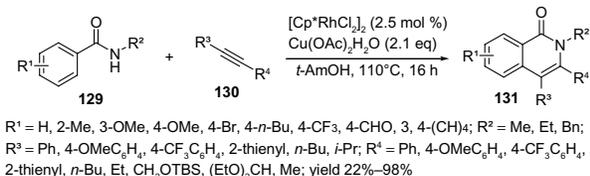


Figure 62 Rhodium-catalyzed intramolecular synthesis of isoquinolones.



Figure 63 Rhodium-catalyzed synthesis of isoquinolones.

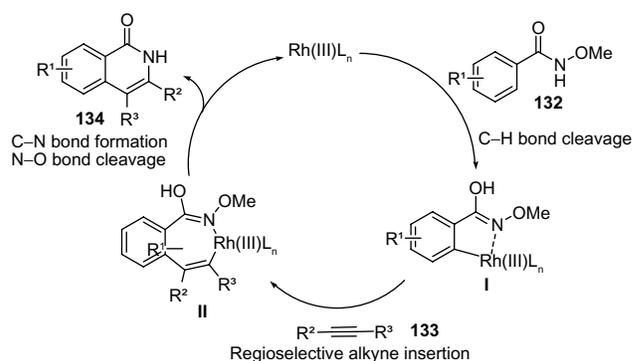


Figure 64 Proposed mechanism for rhodium-catalyzed synthesis of isoquinolones.

proved to be key for the synthesis of products in high yields with excellent chemo-, site-, and regioselectivities under an air atmosphere.

In 2012, Li et al⁷⁰ developed a ruthenium-catalyzed oxidative C–H bond olefination for the synthesis of 3,4-dihydroisoquinolinone derivatives (**143**) from readily available *N*-methoxybenzamides (**141**) and styrenes (**142**) (Figure 67). The corresponding products were obtained in good yields with a broad substrate scope. A proposed mechanism is shown in Figure 68. Treatment of **141** with Ru catalyst provides **I**, addition of **I** to **142** leads to **II**, and reductive elimination of **II** affords the target product (**143**).

In 2013, Reddy et al⁷¹ developed the ruthenium-catalyzed synthesis of isoquinolones (**146**) from readily available aromatic and heteroaromatic nitriles (**144**) and alkynes (**145**) (Figure 69). The protocol used 5 mol% $[\text{RuCl}_2(p\text{-cymene})_2]$ as the catalyst, copper acetate as the oxidant, KPF_6 as the additive, and acetic acid as the solvent. The procedure was useful and attractive for the preparation of biologically relevant isoquinolone derivatives. The proposed mechanism is shown in Figure 70. Treatment of nitriles with acetic acid in the presence of copper acetate gives arylamide (**III**). Coordination of **III** with $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ provides a Ru–N intermediate (**IV**) with extrusion of HOAc. Cycloaddition of **IV** to alkyne (**145**) forms seven-membered intermediate (**V**), and reductive elimination of **V** affords the target product (**146**).

Ackermann et al⁷² developed the ruthenium-catalyzed synthesis of 2-pyridone derivatives (**149**) via the oxidative

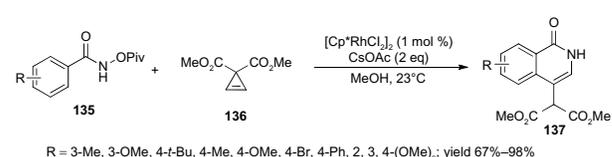


Figure 65 Rhodium-catalyzed synthesis of isoquinolones.

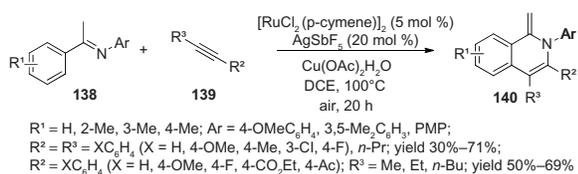


Figure 66 Ruthenium-catalyzed annulation of ketimines and alkynes.

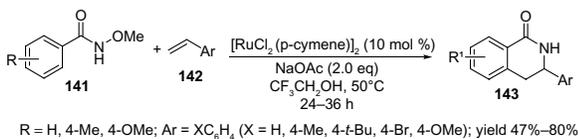


Figure 67 Ruthenium-catalyzed synthesis of 3,4-dihydroisoquinolines.

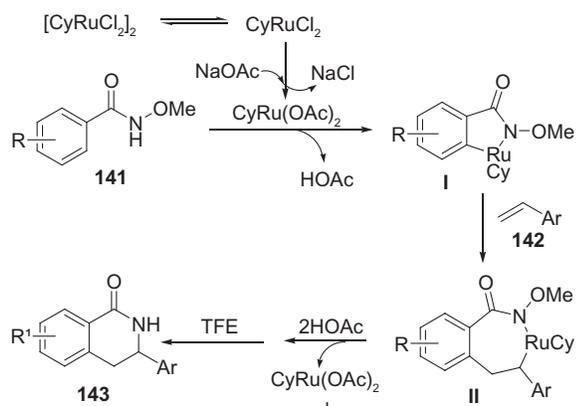


Figure 68 Proposed mechanism for ruthenium-catalyzed synthesis of 3,4-dihydroisoquinolines.

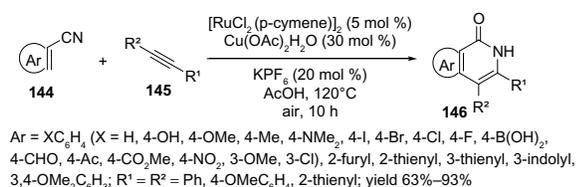


Figure 69 Ruthenium-catalyzed synthesis of isoquinolones.

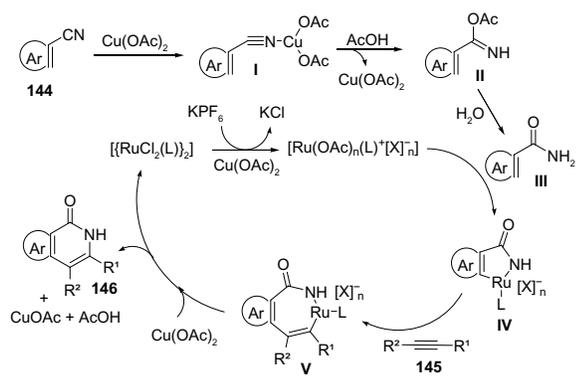


Figure 70 Proposed mechanism for ruthenium-catalyzed synthesis of isoquinolones.

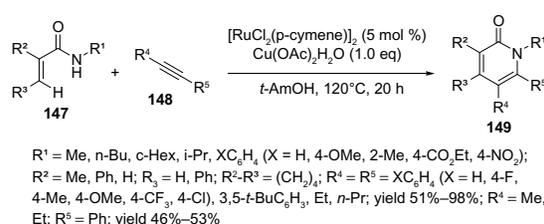


Figure 71 Ruthenium-catalyzed synthesis of 2-pyridones.

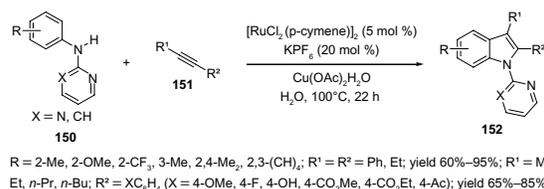


Figure 72 Ruthenium-catalyzed synthesis of indoles.

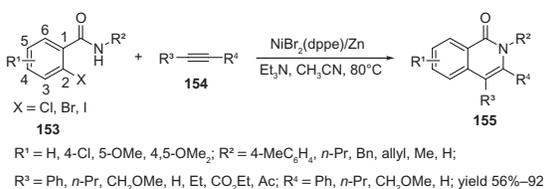


Figure 73 Nickel-catalyzed synthesis of isoquinolone derivatives.

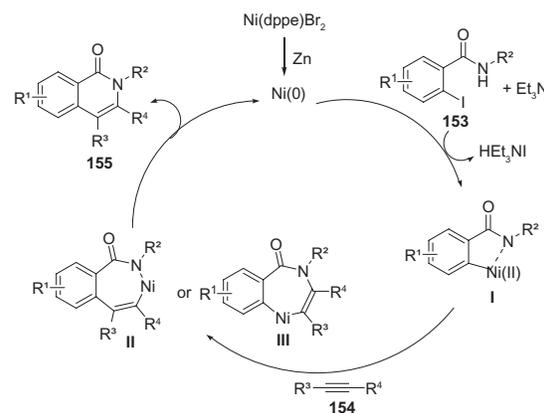


Figure 74 Proposed mechanism for the nickel-catalyzed synthesis of isoquinolone derivatives.

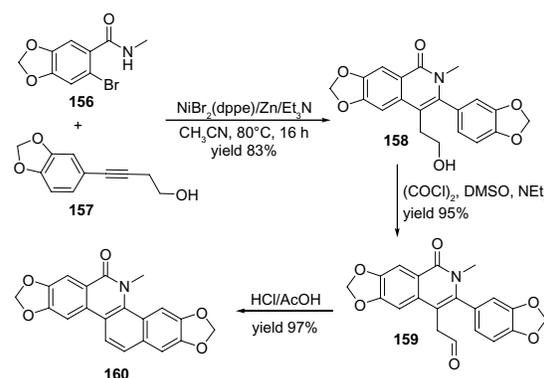


Figure 75 Total synthesis of oxyavicine.

cyclization of acrylamides (**147**) with alkynes (**148**) (Figure 71). The reaction displays a notable chemo- and regioselectivity.

In 2012, the same group reported an example of ruthenium-catalyzed oxidative annulation to synthesis of indoles (**152**) from anilines (**150**) and alkynes (**151**) (Figure 72).⁷³ The reaction was performed by using *N*-2-pyridyl as the directing group.

Nickel-catalyzed synthesis of *N*-heterocycles

Nickel-catalyzed *N*-heterocycles are found via C–H amination. In 2010, Liu et al.⁷⁴ reported the synthesis of isoquinolone derivatives (**155**) via nickel-catalyzed annulation using 2-halobenzamides (**153**) and alkynes (**154**) as the substrates (Figure 73). A possible mechanism is shown in Figure 74. Ni(II) is reduced to Ni(0) by zinc, and oxidative addition of Ni(0) by **153** gives five-membered Ni(II) intermediate (**I**). Subsequently, cycloaddition of **I** to **154** provides **II** or **III**, and reductive elimination of **II** or **III** gets the target product (**155**). Furthermore, the present method was successfully used in the total synthesis of oxyavicine (**160**) (Figure 75).

Conclusion

In this review, copper, iron, palladium, rhodium, ruthenium, and nickel-catalyzed C–H amination leading to *N*-heterocycles have been summarized. The methods show high efficiency, economy, and practicability. It should be noted that the examples for other transition metal-catalyzed construction of *N*-heterocycles through this strategy are existing, and any omissions on this wide topic are unintentional. We believe that the application of transition metal-catalyzed C–H amination leading to *N*-heterocycles is still an active area of research, and more new methods for *N*-heterocyclic synthesis will be discovered in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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