C–H amination in the synthesis of N-heterocycles

Jipan Yu
Hua Fu
Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing, People’s Republic of China

Correspondence: Hua Fu
Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, People’s Republic of China
Fax +86 10 6278 1695
Email fuhua@mail.tsinghua.edu.cn

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.
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 al.17 used substituted 3-iodochromones (3) and amidines (4) as the substrates, and the reactions underwent subsequent intermolecular Ullmann-type N-arylation of amidines and intramolecular aerobic oxidation in air to afford chromenotetraimidazole-9(1H)-ones (5) in moderate to good yields (Figure 3).

In 2011, Cho et al.18 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 al.19 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 al.20 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).

In 2013, Li et al.21 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 al.22 established synthesis of 4-aryl-2-quinolones (17) from 3,3-diarylacylamides (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 KOtBu as the base, and the reactions were performed in o-xylene under air atmosphere. Gui et al.23 developed a similar procedure for the synthesis of phenanthridinone derivatives (19) by using 2-phenylbenzamides (18) as the substrates (Figure 7B).

The synthesis of isoquinolin-1(2H)-ones via copper-mediated amination has been developed by Chary et al.24 (Figure 8). Reaction of 2-iodobenzamides (20) with alkynes in PEG 400 afforded N-substituted isoquinolin-1(2H)-ones (21) in moderate to good yields. The reaction undergoes sequential Sonogashira-type coupling and intramolecular cycloaddition process.

In 2012, Wang et al.25 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-(1H-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 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 phenanthridine-6(5H)-ones.

Figure 8 Copper-catalyzed synthesis of isoquinolin-1(2H)-ones.

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

Figure 10 Copper-catalyzed synthesis of imidazooxquinolinolines.
described copper-catalyzed synthesis of imidazo[1,2-α] 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 Chemler30 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).31 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-Cu-L 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, 10α,11-dihydro-10H-indolo[1,2-α]indoles (36) with high enantiosel ectivity were prepared (Figure 15).32

In 2011, Lu et al33 established the efficient copper-catalyzed aerobic oxidative intramolecular alkene C–H amination leading to N-heterocycles (38) (Figure 16). The protocol used substituted 3-methylenesindolin-1-ones (37) as the starting materials, Cu(O2CCF3)2 as the catalyst, and air.

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

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

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

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

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

Figure 16 Copper-catalyzed synthesis of fused N-heterocycles.
as the oxidant, and the corresponding N-heterocycles were obtained in good to excellent yields.

The copper-catalyzed C–H bond amination of alkenes 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 amides (39) and terminal alkynes (Figure 17). The protocol used 20 mol% CuCl$_2$ $\cdot$ H$_2$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 C(sp$^3$)-H bond amination is effective for the synthesis of heterocyclic compounds. In 2013, Huang et al. described the Cu(I)-catalyzed intramolecular aerobic oxidative C–H bond 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 al. described the amination of aliphatic C–H bonds in N-alkylamidines (43), in which Cu(OAc)$_2$ was used as the catalyst, PhI(OAc)$_2$ as the oxidant (Figure 20). The intramolecular C–H amination was performed in the presence of K$_3$PO$_4$ at room temperature. As shown in Figure 21, treatment of 43 with copper catalyst in the presence of PhI(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 al. reported the efficient method for construction of four-membered $\beta$-lactams (46) based on copper-catalyzed C(sp$^3$)-H amination with 8-aminoquinolinolyl as the directing group (Figure 22A). A plausible mechanism is proposed in Figure 22B. Oxidation of Cu(II) by Ag$_2$CO$_3$ affords Cu(III), treatment of Cu(III) with 45 leads to I, and insertion of Cu(III) to C(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 al. 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 Bao independently reported the iron-catalyzed aerobic oxidative synthesis of substituted 1H-indazoles (50) and 1H-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
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 al. described the synthesis of 2-pyrrolines (55) from readily available substrates (53 and 54) under mild conditions (Figure 26). Under FeCl₃ 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 FeCl₃ 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 al. developed synthesis of 4,5-dihydropyroles (58) through iron-catalyzed [4C + 1N] cyclization of 4-acetylenic ketones (56) and primary amines (57) (Figure 28). The protocol used FeCl₃ as the catalyst and 1,5-pentanediol as solvent, and various substituted 4,5-dihydropyroles were obtained in moderate to good yields. The reaction was performed through enamine formation and subsequent cyclization.

In 2014, Liu et al. 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 [Fe(F₂₆ TPP)Cl] (H₂F₂₆ TPP = meso-tetrakis(pentfluorophenyl)porphyrin) as the catalyst and PhI(OAc)₂ as the oxidant. The protocol can be applied

**Figure 20** Copper-catalyzed synthesis of dihydroimidazoles.

**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.
to both intra- and intermolecular amination of sp² and sp³ C–H bonds, affording the amination products 60 and 62 in moderate to high yields. A possible mechanism was proposed (Figure 30). Under catalysis of [Fe(F₂₀TPP)Cl]/Ph(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 FeCl₃ and FeCl₂ 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-aminooarylazides (65) and arylaldehydes (Figure 32).⁴³ The procedure was divided into two steps: reaction of o-aminooarylazides and arylaldehydes firstly produced imines in the presence of MgSO₄, 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, CF₃, C–F, and C–Cl bonds.

**Figure 26** Iron-catalyzed synthesis of 2-pyrrolines.

**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 al. developed the FeCl₃-catalyzed synthesis of 2,3-disubstituted indoles (71) from 2H-azirines (70) (Figure 34). The reactions underwent the sequential ring opening of 2H-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 Betley developed the iron-dipyrinato 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 al. 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 al. 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 cycloalkyl C(sp³)-H amination with PhI=NR was also effective.
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.\(^a\) 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.\(^a\) also reported a similar procedure (Figure 43A). They used Ph(OAc)\(_2\) as the oxidant. It is worthwhile to note that the reactions were 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).\(^b\)

In 2012, Yang and Zhang\(^c\) reported an efficient palladium-catalyzed intramolecular aerobic aza-Wacker cyclization for the synthesis of isoindolinones (87) and isooquinolin-1(2H)-ones (88) from N-Ts-2-arylanilines (84) under different catalytically active conditions (Figure 44). Isoindolinones (87) were prepared using Pd(OAc)\(_2\) as the catalyst and Phen as the ligand, and isooquinolin-1(2H)-ones were obtained by using (MeCN)\(_2\)PdCl\(_2\) as the catalyst and Et\(_2\)N as the base.

In 2010, Shi et al.\(^d\) 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 39** Possible mechanism for iron-catalyzed synthesis of 2,3-disubstituted indoles.

**Figure 40** Iron-catalyzed C(sp\(^3\))-H amination of sulfamate esters.

**Figure 41** Palladium-catalyzed synthesis of carbazoles.

**Figure 42** Proposed mechanism for 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 al. 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 al. developed a convenient and practical one-pot method for the synthesis of 2H-indazoles (100) 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 al. 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 al. 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 al. 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. reported an efficient difunctionalization of alkenes (110) through intramolecular C—N and
aromatic C–H bond formation (Figure 53). The reactions were performed using palladium dichloride as the catalyst, PhI(OAc), as the oxidant, and MeCN as the solvent. The products (111) containing spirooxindole unit were prepared in moderate yields.

In 2014, Jeong and Youn⁶⁹ 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 oxygen as the oxidant, and the reactions were carried out in the presence of powered 4Å 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 Yu⁶⁶ 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.⁶³ reported the palladium-catalyzed intramolecular oxidative dianimation of alkenes (118) (Figure 56). Cyclic ureas (119) were prepared through this strategy by using Pd(OAc)₂ as the catalyst and PhI(OAc), 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.
Rhodium-catalyzed synthesis of N-heterocycles

Rhodium-catalyzed C–H amination is effective for the synthesis of N-heterocycles. In 2008, Stuart et al. 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, AgSbF6 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 al. reported the synthesis of indole[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 intramolecular 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). 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 good yields.

In 2010, Hyster and Rovis 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 al. 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 al. reported the rhodium(III)-catalyzed synthesis of isoquinolones (137) from amides (135) and cyclopropanes (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 Ackermann 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 55](images/figure55.png)

**Figure 55** Palladium-catalyzed synthesis of lactams.

![Figure 56](images/figure56.png)

**Figure 56** Palladium-catalyzed intramolecular deamination.

![Figure 57](images/figure57.png)

**Figure 57** Proposed mechanism for palladium-catalyzed intramolecular deamination.
proved to be key for the synthesis of products in high yields with excellent chemoselectivity, site-selectivity, and regioselectivities under an air atmosphere.

In 2012, Li et al. developed a ruthenium-catalyzed oxidative C–H bond olefination for the synthesis of 3,4-dihydroisoquinolinone derivatives (143) from readily available N-methoxybenzamides (144) and styrenes (142) (Figure 67). The corresponding products were obtained in good yields with broad substrate scope. A proposed mechanism is shown in Figure 68. Treatment of 141 with Ru catalyst provides 1, addition of 1 and 2 leads to 2, and reductive elimination of 2 affords the target product (143).

In 2013, Reddy et al. 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% [RuCl\(_2\)(p-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 [RuCl\(_2\)(p-cymene)]\(_2\) provides a Ru-N intermediate (IV) with extrusion of HOAc. Cycloaddition of IV to alkene (145) forms seven-membered intermediate (V), and reductive elimination of V affords the target product (146).

Ackermann et al. developed the ruthenium-catalyzed synthesis of 2-pyridone derivatives (149) via the oxidative
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 annihilation to synthesis of indoles (152) from anilines (150) and alkynes (151) (Figure 72). 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.14 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 oxyavicene (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.

**Acknowledgments**

The authors thank the National Natural Science Foundation of China (grant nos 21172128, 21372139, and 21221062) and the Ministry of Science and Technology of China (grant no 2012CB722605) for financial support.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**

1. DeSimone RW, Currie KS, Mitchell SA, Darrow JW, Pippin DA. Privileged Structures: applications in drug discovery. Comb Chem High Throughput Screen. 2004;7(5):473–493.

2. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medical chemistry. Nat Rev Drug Discov. 2007;6(11):881–890.

3. Jia CG, Kitamura T, Fujiwara Y. Catalytic functionalization of arenes and alkanes via C–H bond activation. Acc Chem Res. 2001;34(8):633–639.

4. Hassan J, Sevignon M, Gozzi C, Schulz E, Lemaire M. Aryl-aryl bond formation one century after the discovery of the Ullman reaction. Chem Rev. 2002;102(5):1359–1470.

5. Davies HML, Beckwith REJ. Catalytic enantioselective C–H activation by means of metal-carbenoid induced C–H insertion. Chem Rev. 2003;103(8):2861–2904.

6. Davies HML, Beckwith REJ. Catalytic enantioselective C–H functionalization via nickel-catalyzed annulation using heteroaromatic compounds. Chem Soc Rev. 2007;36(7):1173–1193.

7. Park YJ, Park JW, Jun CH. Metal-organic cooperative catalysis in C–H and C–C bond activation and its concurrent recovery. Acc Chem Res. 2008;41(2):222–224.

8. Lewis JC, Bergman RG, Ellman JA. Direct functionalization of nitrogen heterocycles via Rh-catalyzed C–H bond activation. Acc Chem Res. 2008;41(8):1031–1025.

9. Daugulis O, Do HO, Shabashov D. Palladium- and copper-catalyzed arylation of carbon-hydrogen bonds. Acc Chem Res. 2009;42(8):1074–1086.

10. Lyons TW, Sanford MS. Palladium-catalyzed ligand-directed C–H functionalization reactions. Chem Rev. 2010;110(2):1147–1169.

11. Collet F, Dodd RH, Dauban P. Catalytic C–H amination: recent progress and future directions. Chem Commun (Camb). 2009;34:5061–5074.

12. Thomas A, Ramirez TA, Zhao B, Shi Y. Recent advances in transition metal-catalyzed sp3 C–H amination adjacent to double bonds and carbonyl groups. Chem Soc Rev. 2012;41(2):931–942.

13. Dauban P, Dodd RH. In Amino Group Chemistry. Ricci A Ed. Wiley-VCH: Weinheim, Germany, 2008:55–92.

14. Collet F, Lescot C, Dauban P. Catalytic C–H amination: the stereoselectivity issue. Chem Soc Rev. 2011;40(4):1926–1936.

15. Brasche G, Buchwald SL. C–H functionalization/C–N bond formation: copper-catalyzed synthesis of benzimidazolides from amidines. Angew Chem Int Ed. 2008;47(10):1932–1934.

16. Sheng J, Chao B, Chen H, Hu Y. Synthesis of chromeno-[2,3-d] imidazol-9(1H)-ones via tandem reactions of 3-iodochromones with amidines involving copper-catalyzed C–H functionalization and C–O bond formation. Org Lett. 2013;15(17):4508–4511.

17. Cho SH, Yoon J, Chang S. Intramolecular oxidative C–N bond formation for the synthesis of carbazoles: comparison of reactivity between the copper-catalyzed and metal-free conditions. J Am Chem Soc. 2011;133(15):5996–6005.

18. Takamatsu K, Hirano K, Satoh T, Miura M. Synthesis of carbazoles by copper-catalyzed intramolecular C–H–N–H coupling. Org Lett. 2014;16(11):2892–2895.

19. Zhou W, Liu Y, Yang Y, Deng GJ. Copper-catalyzed intramolecular direct amination of sp2 C–H bonds for the synthesis of Naryl acridones. Chem Commun (Camb). 2012;48(86):10678–10680.

20. Li XW, He L, Chen HJ, Wu WQ, Jiang HF. Copper-catalyzed aerobic C(sp2)-H functionalization for C–N bond formation: synthesis of pyrazoles and indazoles. J Org Chem. 2013;78(8):3636–3646.

21. Berrino R, Cacci S, Fabrizi G, Goggiomiani A. 4-Aryl-2-quinolines from 3,3-diarylacrylalides through intramolecular copper-catalyzed C–H functionalization/C–N bond formation. J Org Chem. 2012;77(5):2537–2542.

22. Gui QW, Yang ZY, Chen X, et al. Synthesis of phenanthridin-6(5H)-ones via copper-catalyzed cyclization of 2-phenylbenzamides. Synlett. 2013;24(8):1016–1020.

23. Chary RG, Dhananjaya G, Prasad KV, et al. A simple access to N-(un)substituted isoquinolin-1(2H)-ones: unusual formation of regioisomeric isoquinolin-1(4H)-ones. Chem Commun (Camb). 2014;50(51):6797–6800.
25. Wang QX, Jin YH, Zhao YF, Zhu L, Fu H. Copper-catalyzed aerobic oxidative intramolecular C–H amination leading to imidazobenzimidazoles. *Org Lett.* 2012;14(2):452–455.

26. Xu H, Fu H. Copper-catalyzed one-pot synthesis of imidazo[2,1-β]benzimidazoquinolinolones by sequential Ullmann-type coupling and intramolecular C–H amidation. *Chem. Eur. J.* 2012;18(4):1180–1186.

27. Chen DB, Chen QF, Liu MC, et al. Cascade synthesis of azoquinolino- nes by Cu(I)-catalyzed C–N coupling/C–H activation/C–N formation reactions under O2. *Tetrahedron.* 2013;69(1):6461–6467.

28. Wang HG, Wang Y, Liang DD, Liu LY, Zhang JC, Zhu Q. Copper- catalyzed intramolecular dehydrogenative amino-oxygenation: direct access to formyl-substituted aromatic N-heterocycles. *Angew Chem Int Ed.* 2011;50(25):5678–5681.

29. Zeng W, Chemler SR. Copper(II)-catalyzed enantioselective intramolecular carboamination of alkenes. *J Am Chem Soc.* 2007;129(43):12948–12949.

30. Sherman ES, Chemler SR. Copper(II)-catalyzed aminooxygenation and carboamination of N-aryl-2-ethyl anilines. *Adv Synth Catal.* 2009;351(3):467–471.

31. Miao L, Haque I, Manzoni MR, Tham WS, Chemler SR. Diastereose- and enantioselective copper-catalyzed intramolecular carboamination of alkenes for the synthesis of oxahydro-1H-benz[f]indoles. *Org Lett.* 2010;12(21):4739–4741.

32. Lu JY, Jin YB, Liu HX, Jiang YY, Fu H. Copper-catalyzed oxidative intramolecular alkene C–H amination leading to N-heterocycles. *Org Lett.* 2011;13(14):3694–3697.

33. Li JH, Neuville L. Copper-catalyzed oxidative amination of terminal alkynes by amidines: synthesis of 1,2,4-trisubstituted imidazoles. *Org Lett.* 2013;15(7):1752–1755.

34. Huang PC, Gandeepan P, Cheng CH. Cu(I)-catalyzed intramolecular oxidative C–H amination of 2-aminoacetophenones: a convenient route toward isatins. *Chem. Commun.* 2013;49(76):8540–8542.

35. Chen H, Sanjaya S, Wang YF, Chiba S. Copper-catalyzed aliphatic C–H amination with an amidine moiety. *Org Lett.* 2013;15(1):212–215.

36. Wang Z, Ni JZ, Kuninobu Y, Kanai M. Copper-catalyzed intramolecular oxidative C–H amination of 2-aminoacetophenones: a convenient route toward isatins. *Chem. Commun.* 2013;49(76):8540–8542.

37. Wu XS, Zhao Y, Zhang GW, Ge HB. Copper-catalyzed site-selective intramolecular amidation of unactivated (sp2)-H bonds. *Angew Chem Int Ed.* 2014;53(14):3496–3499.

38. Wu XS, Zhao Y, Zhang GW, Ge HB. Copper-catalyzed site-selective intramolecular amidation of unactivated (sp2)-H bonds. *Angew Chem Int Ed.* 2014;53(14):3496–3499.

39. Zhang TS, Bao WL. Synthesis of 1H-Indazoles and 1H-Pyrazoles via FeBr3/O2 mediated intramolecular C–H amination. *J Org Chem.* 2013;78(3):1317–1322.

40. Fan J, Gao L, Wang Z. Facile construction of highly functionalized 2-pyrrolines via FeCl3-catalyzed reaction of azidines with arylalkynes. *Chem Commun.* 2009;33(33):5021–5023.

41. Sun B, Ma Q, Wang Y, Zhao Y, Liao P, Bi X. Iron-catalyzed [4C–4I] cyclization of 4-acetylenic ketones with primary amines: synthesis of 5-(aryl)alkylidene-4,5-dihydropyrroles. *Org Lett.* 2014;16(3):5180–5182.

42. Liu Y, Chen GQ, Tse CW, et al. [(FeF3-TPP)[NAr] ([FeF3-TPP][Ph]-NAr)]. Intermediate assessed by high resolution ESI-MS and DFT calculations. *Chem Asian J.* 2015;10(1):100–105.

43. Karthikeyan I, Sekar G. Iron-catalyzed C–H Bond functionalization for the exclusive synthesis of pyrido-[1,2-α]indoles or triaryl methaneols. *Eur J Org Chem.* 2014;2014(36):8055–8063.

44. Shen MH, Driver TG. Iron(I) bromide-catalyzed synthesis of benzimidazoles from aryl azides. *Org Lett.* 2008;10(15):3367–3370.

45. Bonnamour J, Bolm C. Iron(II) triflate as a catalyst for the synthesis of indoles by intramolecular C–H amination. *Org Lett.* 2011;13(8):2012–2014.

46. Jana S, Clements MD, Sharp BK, Zheng N. Fe(II)-catalyzed amination of aromatic C–H bonds via ring opening of 2H-azirines: synthesis of 2,3-disubstituted indoles. *Org Lett.* 2010;12(17):3736–3739.
67. Guimond N, Gouliaras C, Fagnou K. Rhodium(III)-catalyzed isoquinolone synthesis: the N–O bond as a handle for C–N bond formation and catalyst turnover. *J Am Chem Soc*. 2010;132(20):6908–6909.
68. Hyster TK, Rovis T. Rhodium(III)-catalyzed C–H activation mediated synthesis of isoquinolones from amides and cyclopropanes. *Synlett*. 2013;24(14):1842–1844.
69. Li J, Ackermann L. Ruthenium-catalyzed oxidative alkyne annulation by C–H activation on ketimines. *Tetrahedron*. 2014;70(20):3342–3348.
70. Li B, Ma J, Wang N, Feng H, Xu S, Wang B. Ruthenium-catalyzed oxidative C–H bond olefination of N-methoxybenzamides using an oxidizing directing group. *Org Lett*. 2012;14(3):736–739.
71. Reddy MC, Manikandan R, Jegannohan M. Ruthenium-catalyzed aerobic oxidative cyclization of aromatic and heteroaromatic nitriles with alkynes: a new route to isoquinolones. *Chem Commun*. 2013;49(54):6060–6062.
72. Ackermann L, Lygin AV, Hofmann N. Ruthenium-catalyzed oxidative synthesis of 2-pyridones through C–H/N–H bond functionalizations. *Org Lett*. 2011;13(12):3278–3281.
73. Ackermann L, Lygin AV. Cationic ruthenium(II) catalysts for oxidative C–H/N–H bond functionalizations of anilines with removable directing group: synthesis of indoles in water. *Org Lett*. 2012;14(3):764–767.
74. Liu CC, Parthasarathy K, Cheng CH. Synthesis of highly substituted isoquinolone derivatives by nickel-catalyzed annulation of 2-haloazobenzenes with alkynes. *Org Lett*. 2010;12(15):3518–3521.