Synthesis of Pyrroles, Indoles, and Carbazoles through Transition-Metal-Catalyzed C–H Functionalization

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Abstract: Pyrroles, indoles, and carbazoles are among the most important families of nitrogen-containing heterocycles that occur frequently in natural products, pharmaceuticals, agrochemicals, and other functional molecules. Consequently, improved syntheses of these compounds continue to interest synthetic chemists. This Focus Review describes recent advances in synthetic methods for producing these privileged heterocycles that feature transition-metal-catalyzed C–H activation approaches. Because of the common five-membered pyrrole core, some of the C–H activation approaches are applicable to two or more of the pyrrole, indole, and carbazole skeletons. The reactions discussed here not only serve as atom- and step-economical alternatives to the existing synthetic methods, but also show the latest developments in organometallic chemistry and homogeneous catalysis.

Keywords: C–H activation · heterocycles · homogeneous catalysis · palladium · rhodium

1. Introduction

Pyrrole and its benzo-fused analogues indole and carbazole are extremely common structural units in biologically active natural and unnatural compounds, as well as in dyes, pigments, and other functional materials (Scheme 1). Consequently, the development of synthetic methods for producing these privileged heterocyclic scaffolds has received considerable attention from synthetic chemists.[2,3] Whereas classical synthetic methods, such as the Paal–Knorr pyrrole synthesis and the Fischer indole synthesis, have been important methods for more than a hundred years, transition-metal-catalyzed reactions have emerged and evolved into practical alternatives over the past several decades. The preparation of a tryptamine-based gonadotropin-releasing hormone (GnRH) antagonist through Larock, Fischer, and Castro indole syntheses is an illustrative example that shows the practical utility of such well-established synthetic methods (Scheme 2).[4]

Scheme 1. Examples of biologically active and other functional molecules that contain pyrrole, indole, or carbazole moieties.

thermore, the diversity of commercially available aryl hydrazines and 2-haloanilines is relatively limited and much narrower than that of simple anilines. This limited availability poses a serious obstacle when one wishes to access a diverse array of indoles with various substituents on the benzene ring.

In the above context, over the last several years, remarkable progress has been made in the syntheses of pyrroles, indoles, and carbazoles through transition-metal-catalyzed C–H bond functionalization, which is summarized in this Focus Review. Herein, such emerging synthetic methods are classified based on the key bond disconnection (Scheme 3). Thus, transition metal-catalyzed C–H activation has proven effective for forging C–C bonds through dehydrohalogenation or dehydrogenation (disconnection a), C–C and C–N bonds simultaneously through annulation with an alkyne (disconnections a and b), or C–N bonds through oxidative amination or (formal) nitrene insertion (disconnection b or c).

2.1. C–H/C–X Coupling

In the early 1980s, Ames and Opalko reported that diaryl ethers and diaryl amines with a 2-bromo or 2-iodo substituent underwent palladium-catalyzed dehydrohalogenative cyclization to afford dibenzofurans and carbazoles, respectively. This seminal work on biaryl synthesis through C–H arylation, however, was scarcely revisited for a long time. In 2002, Bedford and Cazin reported a palladium-catalyzed one-pot synthesis of N-alkylcarbazole from 2-chloro-N-alkylaniline and aryl bromides by sequential Buchwald-Hartwig amination and C–H arylation (Scheme 4). Modification of the original catalytic system later allowed the synthesis of N–H carbazoles from unprotected 2-chloroanilines in either a one-pot or stepwise manner. Indole derivatives were also synthesized from 2-chloroanilines and bromoalkenes.
In 2004, Fagnou and co-workers published the first major contribution of their group in the area of C–H functionalization, that is, palladium-catalyzed intramolecular biaryl synthesis through direct arylation, which allowed efficient formation of six- and seven-membered rings.[11] The power of their Pd–PCy3 catalytic system was also demonstrated for the synthesis of carbazole derivatives.[12] For example, the carbazole natural product Mukonine was readily synthesized with the intramolecular C–H arylation as the key step (Scheme 5).

In 2007, Ackermann and Althammer reported an alternative strategy for one-pot carbazole synthesis through sequential C–N and C–C bond formations (Scheme 6). Thus, a variety of carbazole derivatives, including the natural product Murrayafoline A, were assembled from simple aniline derivatives and dihalogenated arenes/olefins.

Oxidative linkage of two C–H bonds is one of the ideal strategies for C–C bond formation.[13] This strategy becomes particularly attractive if the process is catalytic and requires only a harmless and inexpensive oxidant. In 1975, Åkermark et al. found that a stoichiometric amount of Pd(OAc)2 effected cyclization of diarylamines to carbazoles (Scheme 8a).[16] Subsequent studies by the groups of Åkermark and Knöller significantly improved the reaction and demonstrated its utility in the synthesis of naturally occurring carbazole alkaloids.[17] Most importantly, the reaction was made catalytic in Pd(OAc)2 by using an oxidant such as Cu(OAc)2 or molecular oxygen (Scheme 8b). On the other hand, the acidic reaction medium (acetic acid) and harsh reaction conditions often caused undesirable side reactions and, thus, limited the substrate scope. Notable modifications have been made, including the one-pot N-arylation/oxidative coupling protocol by Fujii and co-workers,[18] the use of pivalic acid as a superior solvent by Fagnou et al.,[19] and the use of Pt/C instead of a palladium catalyst in hydrothermal water by Yamamoto and Matsubara.[20]
In 2008, Glorius and co-workers brought about a significant breakthrough in the scope of the oxidative palladium catalysis by introducing a new substrate class and modified reaction conditions. They showed that N-aryl enamines, which can be readily prepared from anilines and β-dicarbonyl compounds, are efficiently cyclized into indoles in the presence of catalytic Pd(OAc)$_2$ and a stoichiometric amount of Cu(OAc)$_2$, with K$_2$CO$_3$ and DMF as the base and the solvent, respectively (Scheme 9). A variety of indole derivatives with electron-withdrawing substituents on the C3 position were synthesized and the reaction tolerated a remarkably broad range of functional groups.

The follow-up study by the same group led to an improved catalytic system with K$_3$PO$_4$ instead of K$_2$CO$_3$, which proved effective on a preparatively useful scale. The reaction was proposed to begin with electrophilic palladation of the enamine and subsequent deprotonation, which led to a vinylpalladium(II) species (Scheme 10). This species then undergoes intramolecular aromatic C/H activation, and a subsequent reductive elimination affords the product and palladium(0), which is then reoxidized to palladium(II) with the aid of Cu(OAc)$_2$. Based on the results of mechanistic studies, which included a large H/D kinetic isotope effect (KIE), the intramolecular C/H activation step was proposed to involve σ-bond metathesis or base-assisted deprotonation rather than electrophilic palladation.

Glorius and co-workers’ discovery of the enamine cyclization was followed by the development of several alternative reaction systems for the same type of transformation. Cacchi and co-workers developed a copper-based system with air as an oxidant (Scheme 11a). Zhao and co-workers reported a metal-free reaction system with iodobenzene diacetate as a stoichiometric oxidant (Scheme 11b). Liang and co-workers reported a catalytic system comprising FeCl$_3$ as a catalyst and Cu(OAc)$_2$·CuCl$_2$ as an oxidant (Scheme 11c).

Building on the chemistry pioneered by Åkermark, Knölker, and Glorius, in 2012 we disclosed a palladium-catalyzed aerobic oxidative cyclization reaction of N-aryl imines to indoles (Scheme 12). A variety of N-aryl imines derived from anilines and ketones, including acetophenones, 2-arylacetonaphenones, and aliphatic methyl ketones, for example, cyclopropyl methyl ketone, were effi-

![Scheme 9. Palladium(II)-catalyzed, copper(II)-mediated cyclization of N-arylenamines to give indoles. EWG = electron-withdrawing group; Piv = pivaloyl.](image)

![Scheme 10. Proposed mechanism for palladium(II)-catalyzed indole formation from an enamine.](image)

![Scheme 11. Several reaction systems for oxidative cyclization of N-arylenamines to give indoles. DCE = 1,2-dichloroethane.](image)

![Scheme 12. Palladium(II)-catalyzed aerobic cyclization of N-aryl imines to give indoles.](image)
ciently converted into indole products in the presence of catalytic Pd(OAc)$_2$ and molecular oxygen (1 atm.) with Bu$_4$NBr and dimethyl sulfoxide (DMSO) as the crucial additive and solvent, respectively, under mild conditions.

The catalytic cycle shown in Scheme 13 was proposed. Palladation of the $N$-aryl enamine generated through tautomerization of the imine and subsequent elimination of HOAc gives an $\alpha$-palladated imine. This intermediate undergoes intramolecular aromatic C–H activation then reductive elimination to afford the 3$H$-indole and palladium(0). The former quickly tautomerizes to the indole product and the latter is oxidized to palladium(II) by molecular oxygen and HOAc. The mechanism of the intramolecular C–H activation step appears similar to that involved in Glorius and co-workers’ enamine cyclization because the H/D KIE is similar in magnitude.

As a major limitation of the imine cyclization reaction, imines with $\beta$-hydrogen atoms underwent dehydrogenation rather than oxidative cyclization, presumably through rapid $\beta$-hydride elimination of the putative $\alpha$-palladated imine (Scheme 14). This reactivity could be used for the preparation of arylamines from amines and cyclohexanones through dehydrogenative aromatization of the imine intermediates.

2.3. C–H/N–H/Alkyne Annulation

Annulation of $\alpha$-haloaniline derivatives and alkynes, known as the Larock indole synthesis, offers a highly reliable method for the synthesis of indoles that is compatible with various functional groups. On the other hand, this method suffers from the high cost and limited availability of $\alpha$-haloanilines. In this context, the rhodium(III)-catalyzed oxidative annulation reaction disclosed by Fagnou and co-workers in 2008, is a highly attractive alternative (Scheme 15). Thus, a cationic rhodium(III) catalyst, which is generated from [Cp*RhCl$_2$]$_2$ and AgSbF$_6$, in combination with a stoichiometric copper(II) oxidant, allowed direct coupling of $N$-acetyl anilines and internal alkynes to form a variety of $N$-acetyl indoles.

A subsequent investigation by the same group led to a significant improvement of the catalytic system. With a preformed cationic rhodium(III) complex [Cp*Rh(MeCN)$_2$][SbF$_6$]$_2$ as a catalyst, the reaction was made much milder and catalytic in copper(II) with molecular oxygen (1 atm.) as a terminal oxidant. The improved catalytic system enabled a concise synthesis of Paullone (Scheme 16a) and extended the scope of the reaction to the synthesis of pyrroles from enamides and alkynes (Scheme 16b). The regioselectivity of the reaction with unsymmetrical alkynes was primarily governed by electronic effects, and moderately affected by steric factors.

Extensive mechanistic studies led to the proposal of the catalytic cycle outlined in Scheme 17, which involves deprotonative ortho-rhodation assisted by the amide-oxygen atom, insertion of the alkyn into the Rh–aryl bond then deprotonation to form a six-membered rhodacycle, and C–N reductive elimination to generate the indole product and a rhodium(I) species that is oxidized to rhodium(III) with the aid of Cu(OAc)$_2$/O$_2$. Whereas the ortho-rhodation step is intrinsically reversible, its reversibility in the annulation reaction depends on the rate of the subsequent alkyn insertion step. Therefore, it is reversible and irreversible with the original and the improved catalytic systems, respectively. The importance of precoordination of the alkyn

Scheme 13. Proposed mechanism for palladium(II)-catalyzed indole formation from $N$-aryl imines.

Scheme 14. Dehydrogenative aromatization of an $N$-aryl imine derived from tetralone.

Scheme 15. Rhodium(III)-catalyzed, copper(II)-mediated oxidative annulation of acetonilides and alkynes to give indoles. Am = amyl.
A significant limitation of the annulation reaction was poor regioselectivity with unsymmetrical dialkylalkynes. Fagnou and co-workers solved this problem by combining oxidative annulation of enynes and hydrogenation of the resulting indole/pyrrole products (Scheme 18).\[36\] Thus, the regiochemistry of the final dialkylindole/pyrrole products can be secured by the regioselective annulation of enynes, in which C–N bond formation takes place at the carbon atom that is proximal to the alkenyl group.

Glorius and co-workers discovered a different type of rhodium(III)-catalyzed oxidative annulation reaction to produce pyrroles (Scheme 19).\[37\] Enamides with methyl and ester groups at the α and β positions, respectively, underwent annulation with an alkyne at the N/C0H and methyl C/C0H bonds, presumably through C(sp3)/C0H bond activation. Interestingly, when the β substituent R1 was H, the rhodium catalyst appeared to reversibly activate the β-C–H position, but no pyrrole product arising from such a process was obtained.

Since a study by Ackermann et al. in 2011,\[38\] ruthenium(II) catalysts have proven to serve as inexpensive alternatives to rhodium(III) catalysts in a series of oxidative C–H functionalization reactions. They developed an annulation reaction of N-pyrimidylindoles with alkynes to form indole products with a [RuCl2(μ-cymene)]2 catalyst and Cu(OAc)2 as the oxidant (Scheme 20a).\[39\] The pyrimidyl group on the indole product was readily removed by using NaOEt. They further demonstrated the feasibility of the ruthenium-catalyzed annulation reaction for the synthesis of pyrroles from enamines and alkynes (Scheme 20b).\[40\]

Whereas the above annulative indole syntheses require enamines with directing groups on the nitrogen atom, Jiao and co-workers achieved oxidative annihilation by using unprotected anilines. Thus, simple anilines underwent oxidative coupling with dimethyl acetylenedicarboxylate (DMAD) in the presence of catalytic Pd(OAc)2 and molecular oxygen (1 atm., Scheme 21a).\[41\] Although the scope of
the alkyne was largely limited to DMAD and its analogues, the catalytic system allowed some intriguing transformations, such as formation of carbazole from \( \text{O-silylphenyl triflate} \) (Scheme 21b) and formation of a tricyclic indole derivative from tetrahydroquinoline (Scheme 21c). The reaction was thought to involve initial formation of an enamine intermediate then sequential palladation/reductive elimination processes as proposed for Glorius and co-workers/C29 enamine cyclization (Scheme 10). However, a small intramolecular KIE suggested that the aromatic C\(-/C0\)H activation occurred through electrophilic palladation.

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Wang and co-workers recently developed an oxidative annihilation reaction of simple anilines with diarylalkynes by using \( \text{PdCl}_2 \) and \( \text{Cu(OAc)}_2 \) as a catalyst and an oxidant, respectively, to afford 2,3-diarylindoles (Scheme 22a). \(^{[42]}\) With modifications of the reaction conditions, the same starting materials afforded pentaarylpyrroles (Scheme 22b). The proposed mechanisms for these reactions involve aminopalladation of diarylalkyne as a common initial step.

In 2005, Buchwald and co-workers reported the first example of carbazole synthesis through oxidative aromatic C\(-/C0\)H bond amination. \(^{[43]}\) In the presence of a Pd(OAc)\(_2\) catalyst, Cu(OAc)\(_2\), and molecular oxygen (1 atm.), 2-acetoaminobiphenyl derivatives efficiently cyclized to afford \( \text{N-acetylcarbazoles} \) (Scheme 23). The loading of Cu(OAc)\(_2\) could be reduced to a catalytic amount. This oxidative amination reaction in combination with the Suzuki–Miyaura coupling opened a convenient route to carbazoles starting from 2-haloacetanilides and arylboronic acids. Shortly after this report, Matsubara and co-workers reported \( \text{N/C0} \)H carbazole synthesis from 2-aminobiphenyls with a Pt/C catalyst under hydrothermal conditions. \(^{[20]}\)

The follow-up studies of Buchwald and co-workers improved the catalytic system, expanded the substrate scope, and demonstrated the utility of the reaction in the synthesis of carbazole alkaloids, such as Mukonidine. \(^{[44]}\) Notably, the reaction did not require Cu(OAc)\(_2\) when DMSO was used as the solvent instead of toluene. Although the reaction was initially considered to involve intramolecular aromatic C\(-/C0\)H palladation of an amidopalladium(II) species, such a mechanism was not consistent with the substituent effects. Alternatively, a mechanism involving Heck-like or Wacker-like amidopalladation was suggested (Scheme 24).

In 2008, Gaunt and co-workers reported that the same type of carbazole-forming reaction could be achieved with 2-aminobiphenyls that contain N-alkyl, benzyl, and allyl groups in the presence of catalytic Pd(OAc)\(_2\) and PhI(OAc)\(_2\) (Scheme 25). \(^{[45]}\) Remarkably, the reaction took place at room temperature and tolerated various functional groups.
groups on the aryl groups of the starting material. Amino-
biphenyls with a protected glycosyl group on the nitrogen
atom also underwent the reaction.

The stoichiometric reaction of 2-(N-benzyl)aminobiphen-

yl with \( \text{Pd(OAc)}_2 \) affords a trinuclear palladium complex

that features two six-membered palladacycle moieties and

four bridging acetate ligands (Scheme 26). The reaction is

believed to go through oxidation of such a pallada(II)cycle

with the hypervalent iodine oxidant to give a palladium(IV)

intermediate, and a C–N reductive elimination follows.

Note that oxidative palladium catalysis also allowed cycliza-
tion of 2-hydroxybiphenyls to dibenzofurans with the ap-
propriate choice of ligand, oxidant, and other conditions.[46,47]

2-(N-sulfonylamino)biaryls and 1,1-diaryl-2-(N-sulfonyla-
mino)ethenes were used as precursors for N-sulfonylcarba-
zoles and N-sulfonylindoles through palladium-catalyzed

oxidative C–H amination by Youn et al. and Inamoto/Doi

et al., respectively (Scheme 27).[48,49] The palladium(II)/

oxone system of Youn et al. was proposed to involve a palla-
dium(II)/palladium(IV) catalytic cycle, whereas the palla-
dium(II)/copper(II) system of Inamoto/Doi et al. appears

mechanistically more related to the Buchwald system (see

above).

More recently, Chang and co-workers devised copper-
based and metal-free systems for carbazole synthesis

through intramolecular oxidative C–H amination of 2-sul-
fonylamino-biphenyl and related substrates under mild con-
ditions (Scheme 28).[50] Whereas the copper-based system

consisted of \( \text{Cu(OTf)}_2 \) and \( \text{PhI(OAc)}_2 \) as the catalyst and

oxidant, respectively, the use of a stronger oxidant, phenyl

iodonium bis(trifluoroacetate), \( \text{PhI(OTFA)}_2 \), allowed metal-free cyclization. Mechanistic experiments suggested

that the reaction involves a radical intermediate, and that

the copper(II) catalyst activates the hypervalent iodine re-

gent.

Whereas the above examples used a free N–H bond and

an external oxidant for C–H amination, Tan and Hartwig

introduced a conceptually different strategy for indole syn-

thesis.
thesis, where an oxime N=C=O bond serves as an “internal oxidant” for C−H amination (Scheme 29).[51,52] Thus, O-acetyl oximes derived from 1,1-diarylacetone derivatives and a few other ketones cyclized into indole products in the presence of Pd(dba)₂ catalyst and Cs₂CO₃.

The reaction was proposed to proceed through a catalytic cycle consisting of four elementary steps, that is, oxidative addition of the oxime N=C=O bond to palladium(0) to form an iminylpalladium(II) species,[53] tautomerization to a palladium(II) enamide, intramolecular C=C palladation, and C=N reductive elimination (Scheme 30). The viability of the first step was confirmed by a stoichiometric experiment with O-pentafluorobenzoyloxime as a substrate, which allowed the first isolation of a product of N−O oxidative addition with palladium(0) (see inset in Scheme 30). This isolated complex afforded the indole product upon heating with Cs₂CO₃.

2.5. C−H Amination through (Formal) Nitrene Insertion

Intramolecular C−H amination through thermal decomposition of azide precursors is one of classical methods for the synthesis of indoles and carbazoles. This method, however, suffers from harsh conditions and limited scope. This (formal) nitrene insertion chemistry has received renewed attention in recent years.[54] In 2006, Taber and Tian demonstrated the utility of thermal rearrangement of 2H-azirines, which can be readily prepared by a Neber reaction of oximes derived from α-arylketones (Scheme 31a).[55] Shortly after this report, Narasaka and co-workers reported that the same cyclization reaction was efficiently catalyzed by a rhodium(II) catalyst, presumably through a rhodium-nitrenoid species (Scheme 31b).[56]

In 2007 and 2008, Driver and co-workers reported rhodium(II)-catalyzed denitrogenative C−H amination reactions for the synthesis of indoles from α-azidocinnamates and 2-azidostyrenes, respectively (Scheme 32a and b).[57–59] These reactions serve as complementary methods for the preparation of 2-substituted indoles, wherein the substituents at the C2 position are the ester and aryl/alkyl substituents from the former and the latter reactions, respectively. The same amination strategy was also applicable to carbazole synthesis from 2-azidobiphenyl derivatives.[60] Furthermore, ZnI₂ alone was shown to efficiently catalyze denitrogenative cyclization of dienyl azides to pyroles (Scheme 32c).[61]

The rhodium(II)-catalyzed reactions most likely involve rhodium-nitrenoid species as reactive intermediates, which should form through denitrogenation of the starting materials. Whereas the C−H amination could a priori take place in a concerted or a stepwise manner, pieces of experimental evidence point to the latter pathway, in which electrophilic attack of the nitrogen atom is followed by C−C bond cleavage.[62] Notable among these pieces of evidence are the absence of an H/D KIE in intramolecular competition between C−H and C−D cleavage (Scheme 33a) and the formation of 2,3-diphenylindole from 2-azidostyrene having β,β-diphenyl groups, which can be rationalized by a 1,2-
phenyl shift of the electrophilic amination intermediate (Scheme 33b).

Driver and co-workers further extended the latter observation to achieve the synthesis of 2,3-disubstituted indoles from a series of β,β-disubstituted 2-azidostyrenes (Scheme 34). Most notably, with aryl and alkyl substituents on the β position, the aryl group preferentially underwent 1,2-migration with high selectivity (> 95:5). Mechanistic studies, including Hammett analysis of the intramolecular competition of the migration of different aryl groups, suggested the formation of a phenonium ion intermediate.

Another notable finding in the rhodium-catalyzed cyclization of 2-azidostyrene derivatives is 1,2-migration of an electron-withdrawing group on the β position (Scheme 35). This phenomenon occurs with nitro, ketone, and sulfonyl groups with high selectivity, whereas no significant migration occurs with less electron-withdrawing groups, such as esters and amides.

Transition-metal-catalyzed reduction of a nitro group with carbon monoxide is an alternative method to generate a nitrene species. This chemistry was successfully implemented for the synthesis of carbazoles and indoles through reductive C–H amination. Thus, Smitrovich and Davies as well as Hsieh and Dong achieved conversion of 2-nitrobisaryl and 1,1-diaryl-2-nitroethenes into carbazoles and 3-aryl indoles, respectively, by using a catalytic system consisting of Pd(OAc)2 and 1,10-phenanthroline (Scheme 36).

**2.6. Miscellaneous**

Takemoto and co-workers recently developed a palladium-catalyzed reaction between aryl isocyanides that have ortho-methyl groups and aryl halides, which affords 2-aryl indole derivatives (Scheme 37). The reaction is thought
to involve oxidative addition of the aryl halide to palladium(0), isocyanide insertion into the palladium–aryl bond, benzyl C–H activation with the resulting imidoylpalladium species, and reductive elimination. For the benzyl C–H activation to take place, the isocyanide substrate must have two ortho-methyl groups.

Shibata and co-workers reported an iridium-catalyzed direct cyclodehydration reaction of α-arylamino ketones to afford 4-acetyldiones (Scheme 38).[90] The reaction likely involves aromatic C–H metatlation directed by the acetyl group, intramolecular addition of the resulting aryliridium species to the carbonyl moietly, and dehydration.

3. Conclusion

Synthetic chemists have become fully aware of the power and potential of using C–H bonds as “functional groups” for organic synthesis.[70] The synthesis of nitrogen-containing heterocycles is no exception. The last several years have witnessed the development of a variety of new catalytic reactions for the synthesis of pyroles, indoles, and carbazoles that feature transition-metal-mediated C–H activation as the key step, as summarized in this Focus Review. These new reactions are not only practically attractive as atom- and step-economical synthetic methods, but are also fundamentally interesting and show the latest innovations in organometallic chemistry as well as homogeneous catalysis. Whereas conventional synthetic methods will play major roles for the time being, the importance of the C–H activation approaches will continue to grow, with prospective applications in academia as well as in industry.

Acknowledgements

This work was supported by the National Research Foundation, Singapore (NRF-RF-2009-05) and Nanyang Technological University.


