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Heterocycle Formation *via* Palladium-Catalyzed C–H Functionalization

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Abstract

Heterocyclic compounds are ubiquitous in natural products, pharmaceuticals, and agrochemicals. Therefore, the design of novel protocols to construct heterocycles more efficiently is a major area of focus in the organic chemistry. In the past several years, cyclization reactions based upon palladium-catalyzed C–H activation have received substantial attention due to their capacity for expediting heterocycle synthesis. This review discusses strategies for heterocycle synthesis *via* palladium-catalyzed C–H bond activation and highlights recent examples from the literature.

Keywords

Heterocycle; C–H activation; amination; carbonylation; olefination

1 Introduction

Due to the unique role of heterocycles in pharmaceuticals, agrochemicals and other biologically active molecular scaffolds, organic chemists have had a long-standing interest in developing reactions to construct heterocycles.¹ In the past decade, transition metal-catalyzed C–H activation reactions for C–C and C–heteroatom bond formation have emerged as a class of promising new transformations.² Applying this technology for the synthesis of heterocycles is appealing because it could improve the overall atom- and step-economy compared to traditional methods.³ Nevertheless, despite significant efforts in the past several years, these methods are still in their infancy.⁴ This short review will focus on new retrosynthetic disconnections based on C–H functionalization and will give an overview of examples from the literature illustrating these principles.

Broadly speaking, there are two types of the heterocyclic ring-forming reactions using C–H activation: (1) intramolecular cyclization and (2) intermolecular annulation. Within each of the general categories, there are several different categories of bond-forming reactions. As one representative example, consider the case of indoline motifs. There are three possible disconnections for indoline synthesis using C–H activation: N1–C2, N1–C8, and C3–C9 (Scheme 1, shown in red). The N1–C2 and C3–C9 bonds can also be disconnected simultaneously. Analogous disconnections exist for a range of N-, O-, and S-containing heterocycles of all different ring sizes.

This short review will focus on Pd-catalyzed C–H functionalization reactions for heterocycle synthesis. Due to space constraints, we are not able to discuss examples using other metals.

2 Intramolecular cyclization *via* C–C formation

Pd-catalyzed intramolecular C–H activation followed by C–C bond formation⁵ has found numerous applications in the construction of heterocycles, which will be discussed in the following order: aryl–aryl (Section 2.1), aryl–alkenyl (Section 2.2), and aryl–alkyl (Section 2.3) coupling reactions.⁶

2.1 Arene/arene coupling

Fused biaryl formation *via* Pd-catalyzed C–H functionalization can be grouped into two distinct categories: C–H/C–X cross-coupling (Type I), and C–H/C–H cross-coupling (Type II) (Scheme 2). It is important to note that the catalytically active species in these two types of reactions are different, Pd(0) in the former case, and Pd(II) in the latter case. The mechanism of the C–H activation step in these processes has been found to vary depending on the nature of the metal center, the substrate, and the reaction conditions. Electrophilic palladation, oxidative addition, as well as concerted metallation/deprotonation have all been invoked.⁷

C–H arylation with aryl halides—In 1982, Ames and coworkers reported a Pd(0)-catalyzed reaction to form benzofuran [3,2-c]cinnoline **2** and indolo[3,2-c]cinnoline **2a** from aryl bromides (Scheme 3).^{8a} The author further developed methodology to synthesize a variety of substituted dibenzofurans and carbozoles with moderate to good yields. The transformation was extended to the preparation of six-membered ring heterocycles (Scheme 4).^{8b,8c} The low yields reported in the synthesis of six-membered ring heterocycles prompted several research groups to further investigate this transformation. For example, Rawal and coworkers developed an arylation reaction of phenols to produce six-membered heterocycles using Herrmann's catalyst (Scheme 5).⁹ Comparing the yields for **10** and **11**, it is clear that the presence of a free hydroxyl group in the aryl ring is crucial; *in situ* deprotonation to generate the phenolate is thought to activate the ring for C–H cleavage

Recently, Fagnou and co-workers developed a collection of practical protocols to obtain six-membered heterocycles by using biarylphosphine ligands. Both electron-donating and electron-withdrawing substituents gave excellent yields (Scheme 6).^{10a} The authors further discovered that aryl chlorides could be used as substrates by employing electron-rich *N*-heterocyclic carbene (NHC) ligands.^{10b} A general and efficient system to synthesize five- or six-membered heterocycles from aryl chlorides, bromides, or iodides was developed using HBF₄-protected tricyclohexanyl phosphine as the ligand.^{10c} It is important to point out that this aryl–aryl coupling reaction is widely used in total synthesis of natural product and other biologically active molecular scaffolds. Indeed, this topic has been extensively reviewed.⁶

C(sp²)–H/C(sp²)–H coupling—Formation of heterocycles through Pd-catalyzed C–H/C–H coupling was first reported by Shiotani and Itatani in the 1974 (Scheme 7).¹¹ However, the dibenzofuran product **3** was obtained in low yield with some dimerized by product.

Recently, DeBoef and coworkers reported an example of oxidative cyclization of *N*-benzoylindole by using stoichiometric amounts of Cu(OAc)₂ under O₂ at elevated pressure (Eq. 1, Scheme 8).¹² An electron-rich arene was found to be necessary for satisfactory yield, which suggests that the C–H activation step proceeds *via* an electrophilic palladation mechanism.¹³ Subsequently, Fagnou and co-workers reported a similar transformation with diarylethers and diarylanilines to construct carbazoles and dibenzofurans (Eq. 2).¹⁴ Interestingly, pivalic acid (PivOH) was found to be an effective solvent for achieving good yields. A variety of naturally occurring electron-rich tricyclic carbazoles could be accessed using this transformation.^{14,15} Interestingly Fujii and co-workers were able to design a one-pot procedure for carbazole synthesis by merging anilines and aryl triflates *via* tandem Buchwald–Hartwig amination/oxidative arylation (Eq. 3).¹⁶

Recently, Liégault and Fagnou reported the first example of six-membered heterocycle formation *via* Pd-catalyzed C–H/C–H coupling, in which the presence of an electron-withdrawing group in the pyrrole ring appears to facilitate the cyclization process (Eq. 1, Scheme 9).¹⁷ Dong and co-workers developed a similar method for lactam formation using persulfate as the oxidant (Eq. 2).¹⁸ Akermann and co-workers have reported a similar reaction between triazoles and arenes, which is thought to proceed *via* initial triazole palladation followed by arene C–H functionalization (Eq. 3).¹⁹ Interestingly, Pintori and Greaney demonstrated that seven- and eight-membered heterocycles could be prepared under similar conditions, by employing tether indoles in which the C-3 position was blocked (Eq. 4).²⁰

2.2 Arene/alkene coupling or arene/alkne coupling Arene/alkene coupling

In 1980, Kibayashi and co-workers disclosed a cyclization reaction of 3-(4-methoxyanilino)cyclohex-2-en-1-one **31** to give carbazole derivatives **32** in 31% yield (Scheme 10).²¹ The arylpalladium species generated from electrophilic palladation was proposed as the key intermediate, which subsequently undergoes intramolecular Heck-type cyclization to give the product.

Following this initial discovery, Akermark demonstrated that TBHP (*tert*-Butyl hydroperoxide) could function as an effective oxidant for this transformation, allowing for the synthesis of a variety of carbazoles in moderate yields (Eq. 1, Scheme 11).²² Recently, Stoltz and co-workers developed an efficient method to construct highly substituted benzofurans from electron-rich arenes (Eq. 2).²³ The use of a pyridine-type ligand and BQ (1,4-benzoquinone) is crucial for catalytic turnover. Thereafter, Oestreich and coworkers applied a similar transformation to synthesize benzolactams. Importantly, the fact that O₂ is the sole terminal oxidant makes this transformation highly atom economical (Eq. 3).²⁴ Wang and co-workers reported an interesting example of benzofuran formation from simple arenes. It was found that the use of both PPh₃ and silver trifluoroacetate is crucial (Eq. 4).²⁵ It is important to note that Pd-catalyzed intramolecular alkenylations of nitrogen-containing heterocycles are well precedented²⁶ and have been applied to total synthesis.²⁷

Arene/alkyne coupling—Fujiwara and co-workers demonstrated the first example of intramolecular arene/alkyne coupling.²⁸ A possible mechanism is depicted in Scheme 12, in

which electrophilic palladation, followed by a *anti* carbopalladation across the C–C triple bond, which gives the resulting alkenyl–Pd species **41b**. Protodepalladation gives the product **42**. Interestingly, deuterium labeling experiments revealed that the alkenyl hydrogen atom of the product comes mainly from the protic solvent.

Later, Zhu and coworkers achieved a highly efficient Pd-catalyzed synthesis of unsymmetrically substituted 3-(diarylmethylenyl)indolinones from the corresponding aryl alkynes. The domino reaction involves oxidative addition of the aryl halide to Pd(0) to generate a [Pd(0)(Ar)(X)] species **43a**, which undergoes intermolecular carbopalladation, followed by C–H activation, and C–C reductive elimination (Eq. 1, Scheme 13).²⁹ Later, Li and coworkers were able to replace the aryl halide by a simple arene to perform a similar domino reaction.³⁰ It is worth noting that the six member lactam product was obtained when the PivOH was used as an additive (Eq. 2).

2.3 Arene/alkane coupling

C(sp²)-H alkylation with alkyl halides—In 2003, Buchwald and Hennessey reported a single pioneering example of Pd(0)-catalyzed alkylation of aryl C–H bonds using a tethered alkyl chloride to construct oxindoles (Scheme 14).³¹ Recently, Wipf and Petronijevic applied this method in the total synthesis of (±)-cycloclaven.³²

C(sp³)-H arylation with aryl halides—In 1992, Dyker discovered an early example of Pd-catalyzed C(sp³)-H arylation, in which a polycyclic ether was formed from 2-iodoanisole *via* a cascade sequence involving multiple C–H activation steps (Scheme 15).³³

Recently, Fagnou and co-workers reported formation of 2,2-dialkyldihydrobenzofurans from the corresponding aryl bromides *via* Pd-catalyzed C(sp³)-H arylation using phosphine ligands (Eq. 1, Scheme 16).³⁴ It is worth noting that the authors also demonstrated that the aryl chlorides were also suitable substrates, although a lower yield (73%) was obtained. Subsequently, Fujii and co-worker developed a similar transformation to construct indolines from 2-chloroaniline-derived substrates.³⁵ The protection of the aniline nitrogen atom is crucial, since the free amine is unreactive. Impressively methylene C–H activation was also found to be possible (Eq. 2). The asymmetric version of this reaction was recently achieved by Kündig and coworkers, in which chiral NHC ligand was used (Eq. 3).^{36a} Concurrently, Kagan and co-workers reported the similar asymmetric cyclization by using chiral diphosphines ligand.^{36b} Recently, Rousseaux and co-workers reported lactam and sulfonamide formation *via* Pd-catalyzed intramolecular arylation of C(sp³)-H bonds adjacent to amides and sulfonamides (Eq. 4).³⁷

Interestingly, by employing a strongly binding auxiliary³⁸ and using Pd(II)/Pd(IV) catalysis, Chen and co-workers achieved intramolecular C(sp³)-H arylation, and a variety of five- and six- membered heterocycles could be formed in good yield (Scheme 17).³⁹

C(sp²)-H/C(sp³)-H coupling—Fagnou and co-workers reported a very rare example of C(sp³)-H/C(sp²)-H coupling.¹⁴ Electrophilic palladation of the pyrrole gives an aryl palladium(II) species, which performs C(sp³)-H bond activation. C–C reductive elimination

gives the heterocyclic product (Scheme 18). Electron-withdrawing substituents are crucial in order to obtain synthetically useful yields.

3. Intramolecular cyclization *via* C–N bond formation

Heterocyclic ring construction *via* Pd-catalyzed C–H amination is complementary approach to intramolecular Buchwald–Hartwig amination.⁴⁰ Buchwald and co-workers reported an intramolecular ring-closing Pd-catalyzed C–H amination reaction of *N*-acetyl-2-phenylaniline **71** to form carbazole ring **72** *via* a presumed Pd(II)/Pd(0) catalytic cycle (Scheme 19).⁴¹ The authors proposed two possible pathways: *syn*- and *anti*-aminopalladation to give intermediates **71a** and **71b**, respectively. These species could undergo β -hydride elimination to provide carbazole **72**. Both electron-rich and electron-deficient substrates gave excellent yields. The utility of this transformation was further demonstrated by making several naturally occurring carbazoles, namely mukonine, mukonidine, and glycosinine.⁴² Subsequently, many protocols have been developed to effect this cyclization including metal-free examples.⁴³

Inamoto and Hiroya devised a protocol for making indazole rings **74** from highly conjugated hydrazones **73** *via* Pd-catalyzed C–H amination (Scheme 20).⁴⁴ In order to achieve satisfactory results, stoichiometric Ag(OAc)₂ and Cu(OAc)₂ were needed. The C–H cleavage step may proceed via electrophilic palladation, since electron-rich arenes were more reactive than electron-deficient arenes. The utility of this Pd(II)/Pd(0) catalytic manifold was further demonstrated in the synthesis of heterocycles such as indoles, benzothiazoles, imidazoles, quinolines, and phenanthridinone.⁴⁵

In 2008, our group developed a method for oxindole synthesis using intramolecular C–H amination (Scheme 21).⁴⁶ Diverse δ - and γ -lactams were prepared by this method and alkenyl C(sp²)–H and allylic C(sp³)–H bonds could also be aminated using this protocol.⁴⁷ Subsequently, Murakami and coworkers reported a similar transformation, in which the *N*-OMe group was replaced by an *N*-Ts group.⁴⁸ One of the fundamental challenges in intramolecular C–H amination is developing reactions that employ readily available substrates and that generate broadly useful product classes. To our delight, we were able to carry out the desired intramolecular C–H amination of phenethyltriflimide **81** in the presence of an F⁺ oxidant **82**,⁴⁹ enabling a highly expedient route to functionalized indoline **83** (Scheme 22).⁵⁰ This work represents the first example in which intramolecular C–H amidation was observed with simple non-substituted phenethylamine substrates—though substituted starting materials give excellent results as well. We also demonstrated that C–N reductive elimination could be promoted by a one-electron oxidant, Ce(SO₄)₂.⁵¹ Recently, many groups have studied this transformation with a variety of phenethylamine derivatives and developed efficient protocols to construct indoline heterocycles (Scheme 23).⁵²

Hartwig and coworkers reported a novel method for indole formation *via* Pd(0)/Pd(II) catalysis. Oxidative addition of the Pd(0) species to *N*-acetyl-oxime substrate **88** gives intermediate **88a**, which undergoes C–H activation to give palladacycle **88b**. After reductive elimination and tautomerization, the indole **89** is obtained in high yield. Interestingly low Pd

loading was used and no external co-oxidant was needed. α,α -Diaryl substitution was necessary for the reaction to take place (Scheme 24).⁵³

While Pd-catalyzed intramolecular C(sp²)-H amination reactions have become more and more established, C(sp³)-H amination remains a challenge where progress has been far slower until recently.⁵⁴ Glorius and coworkers reported indoline formation *via* Pd-catalyzed C(sp³)-H bond amination (Eq. 1, Scheme 25).⁵⁵ The reaction is believed to proceed by amide directed C(sp³)-H activation, giving palladacycle **90a**, which subsequently undergoes reductive elimination to give the product **91**. Subsequently, Daugulis and Chen independently developed a similar transformation with picolinamide (PA) -protected amine derivatives and PhI(OAc)₂ as the oxidant (Eq. 2 and Eq. 3).^{52b,52c} Interestingly, Chen and coworkers demonstrated that a four-membered ring could be achieved through this cyclization protocol (Eq. 4).^{52b}

4 Intramolecular cyclization *via* C–O or C–S bond formation

Oxygen-containing heterocycles are another key class of ubiquitous structural motifs. However, Pd-catalyzed intramolecular C–H activation/C–O cyclization is less developed compared to C–N bond formation. In the context of our group's research on new disconnection for heterocycle synthesis *via* C–H activation, we demonstrated the first example of Pd-catalyzed aliphatic alcohol-directed C–H activation/C–O cyclization for the synthesis of dihydrobenzofuran **100** (Scheme 26).⁵⁶ The reaction presumably proceeds *via* Pd(II)/Pd(IV) catalysis by way of intermediate **98a**. Both NFSI or hypervalent iodine reagents were found to be suitable bystander oxidants.⁵¹ Importantly, this transformation could be applied in the synthesis of natural products and drug molecules containing spirocyclic dihydrobenzofurans.

Recently, Liu and coworkers reported a phenol-directed C–H activation/C–O cyclization reaction as an efficient route to dibenzofurans **103** (Scheme 27) *via* Pd(II)/Pd(0) catalysis.⁵⁷ The use of IPr carbene ligand **102** was crucial for C–O reductive elimination from Pd(II), which was believed to be the rate-determining step. Consistent with this hypothesis, a KIE study revealed $k_H/k_D = 1$.

Similar to Pd-catalyzed C–H activation/C–N or C–O bond formation, analogous methodology for C–S bond formation has also been developed. For instance, Inamoto and co-workers described a novel Pd-catalyzed cyclization of thiobenzanilides **104** through a Pd(II)/Pd(0) catalysis.⁵⁸ The combination of NMP and Bu₄NBr is believed to facilitate reoxidation of Pd(0) to Pd(II) (Eq. 1, Scheme 28). Later, Joyce and Batey developed an efficient protocol to construct thiazole **107** by using O₂ as the terminal oxidant (Eq. 2, Scheme 27).⁵⁹ The presence of MnO₂, which serves as a cooxidant, was found to be crucial. Recently, Antonchick and co-workers reported an interesting route to thiophene **109** *via* Pd-catalyzed C–H activation (Eq. 3, Scheme 27).⁶⁰

4 Incorporation with carbon monoxide/isonitrile

Pd(II)-catalyzed C–H carbonylation is another attractive synthetic tool for the construction of a variety of biologically active heterocycles.⁶¹ For instance, in 2004, Orito and co-

workers developed a novel and efficient process for the preparation of benzolactams *via* C–H activation/carbonylation process (Scheme 29).⁶² Both five and six membered lactams could be prepared, although six-membered lactam formation was found to be favored. Electron-rich substrates gave better yields. Regarding the mechanism, after *ortho*-palladation, key intermediate **110b** is formed. Coordination of CO, followed by 1,1-migratory insertion leads to formation of acylpalladium complex **110c**. After nucleophilic attack of the internal amino group on the carbonyl group, the benzolactam product is formed. The same group also reported the synthesis of *N*-protected staurosporinones and quinolizidine alkaloids by using Pd-catalyzed C–H carbonylation as a key step.⁶³

In context of our work in developing C–H functionalization enabled by weakly coordinating functional groups,⁶⁴ our group developed a Pd(II)-catalyzed C–H carbonylation protocol to convert benzoic acids, such as *o*-toluic acid **112**, to dicarboxylic acids **113** (Scheme 30).⁶⁵ Mechanistically, the substrate undergoes C–H activation to give palladacycle **112a**; CO coordination, followed by 1,1-migratory insertion, and reductive elimination lead the anhydride **112c**. Under the reaction conditions, the anhydride is hydrolyzed *in situ* in the presence of base and adventitious water to give dicarboxylic acid **113** (Scheme 30). Subsequently, the Lloyd-Jones group and our group independently developed C–H carbonylation of anilide-type substrates to construct benzolactams (Eq. 1 and Eq. 2, Scheme 31).⁶⁶ We were further able to isolate and characterize a monomeric palladacycle containing *p*-toluenesulfonate as a ligand.^{66b} Another example of C–H carbonylation under mild conditions was reported by Gaunt (Eq. 3).^{52a} *cis*-Substitution on the side chain in aryethyl amine substrate **118** was necessary. Garcia and Granell demonstrated that unprotected tertiary aryethylamine **120** could undergo C–H carbonylation (Eq. 4).⁶⁷ Zhu and coworkers reported the synthesis of quinazolin-4(3H)-one **123** from *N*-arylamidine **122** by employing a similar transformation (Eq. 5).⁶⁸ Aryl lactones are another important class of heterocycles that we have targeted as desirable targets for synthesis. After extensive optimization, we developed a Pd-catalyzed C–H carbonylation reaction of phenethyl alcohol substrate (Eq. 6).⁶⁹ The use of (+)-Men-Leu-OH, which presumably facilitates C–H cleavage and stabilizes Pd(0) (preventing precipitation of inactive Pd black), **124a** was found to be crucial for high yields.⁷⁰

Despite extensive progress made in Pd-catalyzed C(sp²)–H carbonylation, until recently no examples of C(sp³)–H carbonylation had been reported. Our group reported the first example of such a reaction, enabling a new method for the synthesis of succinimide **127** (Scheme 32).⁷¹

Incorporation with isonitrile

Analogous to the CO chemistry described above, Zhu and co-workers reported a rare example of heterocycle formation with isonitrile insertion to give the product **130** in good yield (Scheme 33).⁷²

5 Incorporation with olefin/alkyne

Pd^{II}-catalyzed C(aryl)–H olefination, one of the oldest classes of Pd^{II}-catalyzed C–H activation reactions, provides an alternative approach to C–C bond formation compared to

the traditional Pd(0)-catalyzed Mizoroki–Heck reaction, which couples aryl halides with olefins.⁷³ An attractive approach for heterocycle formation would thus be to merge this chemistry with a subsequent reaction in which the olefinated product would undergo intramolecular 1,4-conjugate addition or Wacker-type oxidative cyclization.⁷⁴ For instance, Miura and coworkers developed such a sequence to generate phenanthridine derivative **133** (Scheme 34).⁷⁵ The acidity of the sulfonamide N–H bond is quite crucial, since other amides proved to be ineffective. The authors expandws these powerful reactions to benzoic and naphthoic acids, which are structurally related acidic compounds, though low yields were obtained due to the existence of multiple possible pathways.

More recently, the group of Lloyd-Jones and Booker-Milburn reported a similar transformation to construct indoline **136** *via* Pd-catalyzed C–H olefination, followed by intramolecular Tsuji–Trost-type allylic amination (Scheme 35).⁷⁶ It is worth noting that both the use of Pd(OTs)₂(CH₃CN)₂ and anhydrous conditions were crucial to obtain the observed results.

By tuning the acidity of amides through the introduction of electron-withdrawing groups, our group was able to achieve C–H iodination of simple phenethyl amine derivatives.⁷⁷ We envisioned that important heterocycles such as tetrahydroisoquinolines could be formed *via* C–H olefination followed by aza-Michael addition. Indeed, when vinyl ketone **138** was used as the olefin coupling partner, the desired tetrahydroquinolines were achieved with excellent diastereoselectivity (Scheme 36).⁷⁸ Our group also demonstrated alcohol-directed C–H olefination followed by oxidative Wacker-type cyclization to give the cyclic ether **142** (Scheme 37).⁷⁸ It should be pointed out the addition of amino acid ligand⁷⁰ was found to be crucial for high yields. Secondary and primary alcohols were also effective, though they gave lower yields.

Zhu and Falck reported lactam formation *via* a similar transformation using *N*-tosylbenzamide substrate **143** (Scheme 38).⁷⁹ Importantly, a simple alkene could also be used to give annulations products *via* C–H olefination and oxidative Wacker-type cyclization. Phenanthroline ligands were found to be effective in this transformation. Electrophilic palladation was suggested based on the observed relative rates, though a KIE = 3.0 was also observed.

Similar to the case of Pd(II)-catalyzed C(sp³)–H carbonylation, no examples of C(sp³)–H *olefination* had been reported until recently. Using an analogous approach for reaction development, our group was able to achieve a Pd(II)-catalyzed reaction protocol for the direct olefination of *sp*³ C–H bonds (Scheme 39). After C–H olefination, the amide product was observed to undergo 1,4-conjugate addition to give the corresponding lactam compound **149** (Scheme 39).⁸⁰ The reaction conditions could also be applied to effect olefination of cyclopropyl methylene C–H bonds and substrates containing α-hydrogen atoms.

Sanford and coworkers later found that pyridine-directed C(sp³)–H olefination/cyclization could be achieved (Scheme 40).⁸¹

Incorporation with alkyne

In addition to olefins, other unsaturated carbon units can be used for C–H functionalization/annulation sequences. Zhu and coworkers reported a highly efficient Pd-catalyzed synthesis of unsymmetrically substituted 3-(diarylmethylenyl)indolinones from the corresponding aryl alkyne.⁸² The domino reaction involves oxidative addition of an aryl halide to generate an aryl palladium species, which undergoes intermolecular carbopalladation, followed by C–H activation, and C–C bond formation (Scheme 41).

Jiao and coworker recently developed a tandem reaction to construct indoles by reacting anilines with alkynes. The author extended this method to 2-substituted indole substrates to give six-membered lactams or pyridines (Scheme 42).⁸³

6. Conclusions

Due to the importance of heterocycles in all aspects of chemistry, the development of efficient and straightforward methods for their synthesis is of paramount importance. In this short review, we have sought to highlight recent advances in construction of heterocycles *via* Pd-catalyzed C–H activation followed by C–C or C–heteroatom bond formation. This technology not only provides more atom- and step-economical methodology but also provides alternative retrosynthetic disconnections that map bulk chemicals onto valuable heterocyclic building blocks. The development of more reliable and efficient catalysis will make C–H functionalization ever more practical and useful in the heterocycle synthesis.

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Scheme 1.

Retrosynthetic disconnections of indoline based on C-H functionalization. Standard indole/indoline atom numbering is used.

Scheme 2. Two types of arene–arene coupling reactions

Scheme 3. Early examples of heterocycle formation *via* C–H arylation

Scheme 4. Heterocycle formation via C–H arylation

Scheme 5. Formation of six-membered heterocycles via C–H arylation

Scheme 6. Formation of six-membered heterocycles via C–H arylation

Scheme 7.

Early example of C–H/C–H coupling for heterocycle synthesis.

Scheme 8. Formation of five-membered heterocycles via C–H/C–H coupling

Scheme 9. Formation of six- and seven-membered heterocycles *via* C–H/C–H coupling

Scheme 10. Carbazole formation via C–H olefination

Scheme 11. Heterocycle formation *via* intramolecular C–H olefination

Scheme 12. Synthesis of coumarins from aryl alkynoates

Scheme 13. Synthesis of oxindoles from alkynylanilides

Scheme 15. Early example of Pd-catalyzed C(sp³)-H arylation

Scheme 16. Heterocycle formation *via* intramolecular Pd⁰-catalyzed C(sp³)-H arylation

Scheme 17. Quinoline carboxamide directed C(sp³)-H arylation

Scheme 18. An example of heterocycle formation *via* $\text{C}(\text{sp}^2)\text{-H}/\text{C}(\text{sp}^3)\text{-H}$ coupling

Scheme 19. Early example of carbozole formation *via* Pd-catalyzed C–H amidation

Scheme 20. Indazole formation via Pd-catalyzed C–H amidation

Scheme 21. Oxindole formation via Pd-catalyzed C–H activation

Scheme 22. Indoline formation via $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ catalysis

Scheme 24. Indole formation *via* $\text{Pd}^0/\text{Pd}^{\text{II}}$ catalysis

Scheme 25. Indoline formation *via* Pd-catalyzed $\text{C}(\text{sp}^3)\text{-H}$ amination.

Scheme 26. Dihydrobenzofuran formation via $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ catalysis

Scheme 27. Benzofuran formation via Pd-catalyzed C–H activation/C–O bond formation

Scheme 28. Early example of Pd-catalyzed C–H activation/C–S bond formation

Scheme 29. Lactam formation via Pd-catalyzed C–H carbonylation

Scheme 30. Pd-catalyzed C–H carbonylation of *o*-toluic acid

Scheme 31. Annulation with carbon monoxide

Scheme 32. Lone example of Pd-catalyzed C(sp³)-H carbonylation

Scheme 33. Synthesis of quinazoline derivatives *via* C–H activation

Scheme 34. An early example of Pd-catalyzed C–H olefination followed by nucleophilic cyclization

Scheme 35. Indoline formation via C–H olefination

Scheme 36. Tetrahydroquinoline formation via Pd-catalyzed C-H olefination followed by nucleophilic cyclization

Scheme 37.

cyclic ether formation *via* Pd-catalyzed C–H olefination.

Scheme 38. Lactam formation via Pd-catalyzed C–H olefination/cyclization

Scheme 39. Pd-catalyzed C(sp³)–H olefination

Scheme 40. Pd-catalyzed C(sp³)–H olefination

Scheme 41. Pd-catalyzed C–H carbonylation of analide

Scheme 42. Synthesis of indole *via* tandem reaction