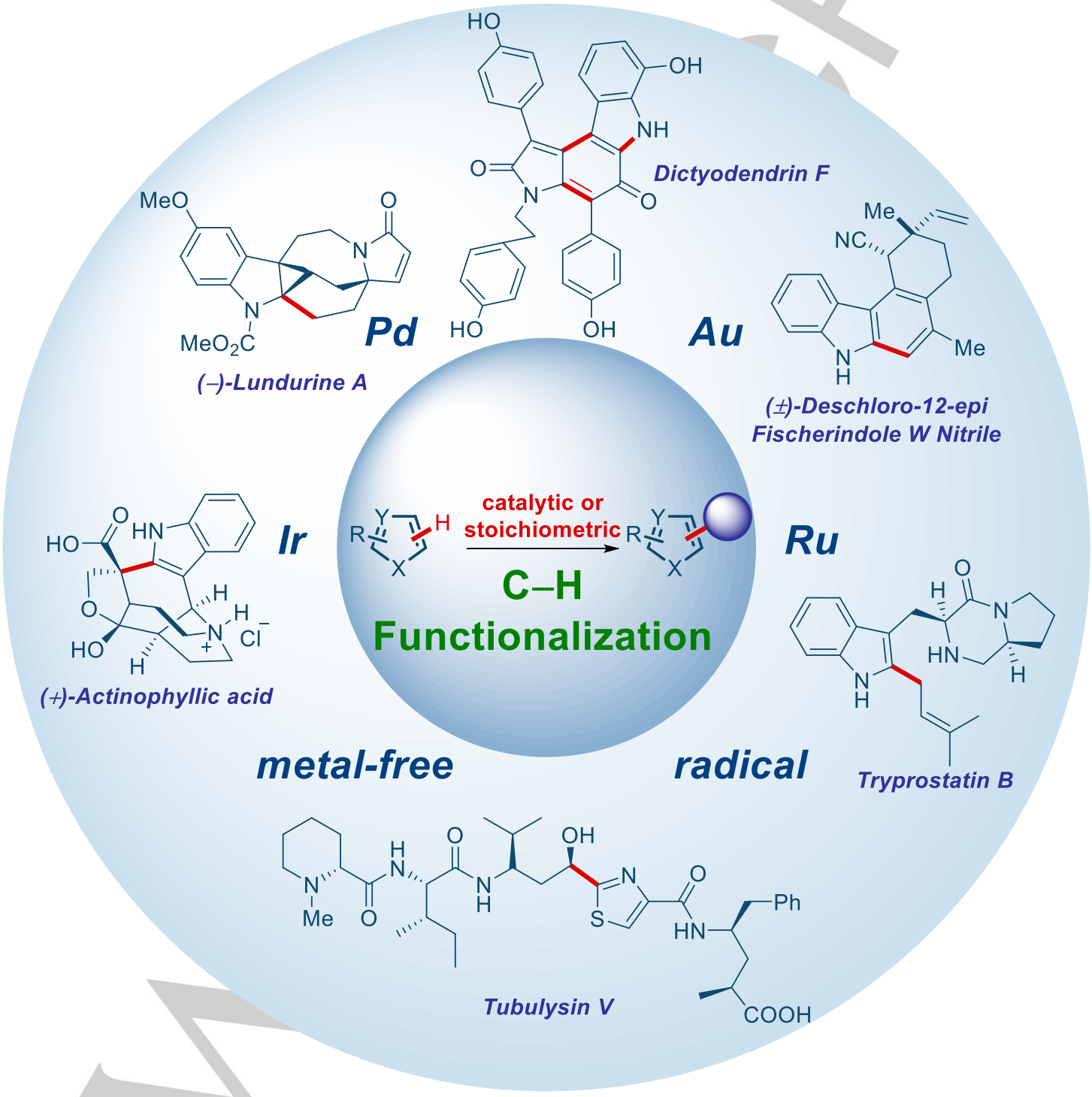
REVIEW

Synthesis of Natural Products by C–H Functionalization of Heterocycles

Yang Zhang[a] and Michal Szostak*[a]



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Abstract: *Total synthesis is considered by many as the finest combination of art and science. During the last decades, several concepts were proposed for achieving the perfect vision of total synthesis, such as atom economy, step economy, or redox economy. In this context, C–H functionalization represents the most powerful platform that has emerged in the last years, empowering rapid synthesis of complex natural products and enabling diversification of bioactive scaffolds based on natural product architectures. In this review, we present an overview of the recent strategies towards the total synthesis of heterocyclic natural products enabled by C–H functionalization. Heterocycles represent the most common motifs in drug discovery and marketed drugs. The implementation of C–H functionalization of heterocycles enables novel tactics in the construction of core architectures, but also changes the logic design of retrosynthetic strategies and permits access to natural product scaffolds with novel and enhanced biological activities.*

1. Introduction

Total synthesis is considered by many as the finest combination of art and science.[1] During the last decades, potent biological activity and pharmacological properties of a plethora of natural products have provided a staple motivation to chemists to devise and implement increasingly more creative, more concise, and ultimately more efficient synthetic methods and strategies enabling total synthesis of complex natural products.[2] Diverse synthetic approaches have been developed driven by biosynthesis, divergent total syntheses, chemoenzymatic total synthesis, cascade reactions, protecting-group-free synthesis and biomimetic total synthesis.[3–7] During the last decades, several concepts were proposed for achieving the perfect vision of total synthesis, such as atom economy, step economy, or redox economy.[8–10] Furthermore, the concepts of achieving ideality as well as time and pot economy were introduced to evaluate the efficiency of total synthesis of natural products.[11,12]

Over the decades, natural products have significantly contributed to medicinal chemistry, especially for the treatment of cancer and infectious diseases.[13] In particular, many bioactive natural products feature heterocyclic architectures that are essential for their biological properties. To complete total synthesis of natural products, various synthetic methods have been developed.[3–13] Undoubtedly, the most powerful reactivity platform that has emerged over the past years is the direct functionalization of C–H bonds, empowering rapid synthesis of complex natural products as well as enabling diversification of bioactive scaffolds based on natural product architectures.[14,15]

In this context, direct C–H functionalization of heterocycles offers several distinct advantages over traditional C–H functionalization of arenes, driven by the inherent electronic properties of heterocycles rendered by heteroatom substitution.[16] Heterocycles represent the most common motifs in drug discovery and marketed drugs.[17] The implementation of C–H

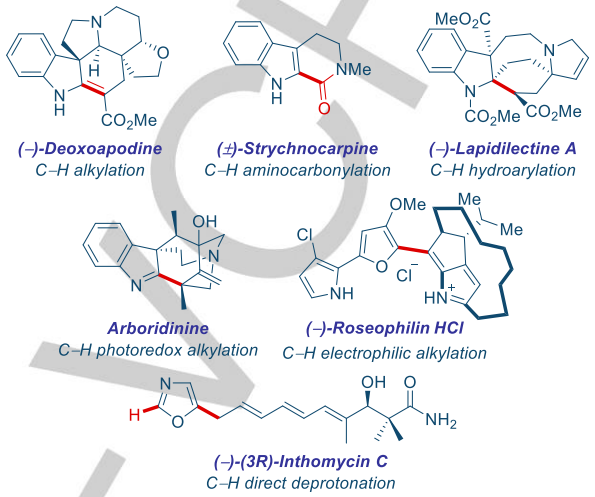


Figure 1. Selected Natural Products Synthesized by C–H Functionalization of Heterocycles.

functionalization of heterocycles enables novel tactics in the construction of core architectures,[14,15] while changing the logic design of retrosynthetic strategies[3–12] and permitting access to natural product scaffolds with novel and enhanced biological activities.[13]

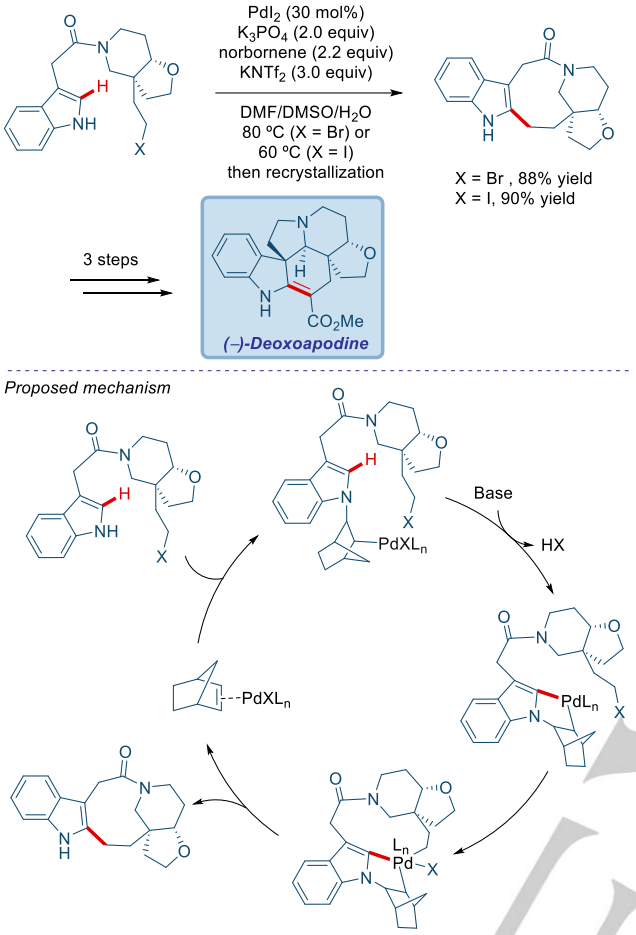
In this review, we present an overview of the recent strategies towards the total synthesis of heterocyclic natural products enabled by C–H functionalization. While the review is focused on transition-metal-catalyzed approaches, such as palladium catalysis (Section 2), gold catalysis (Section 3), iridium and ruthenium catalysis (Section 4), we also present transition-metal-free radical strategies (Section 5) as well as electrophilic-type metal-free C–H functionalization reactions (Section 6) and direct deprotonation approaches driven by the properties of heterocycles (Section 7). The processes cover transition-metal-catalyzed reactions, Friedel-Crafts mechanisms, radical-based abstractions and enolate-type functionalizations. These reactions are characterized by a replacement of a carbon–hydrogen bond by a functional group. This selection is based on the processes that cover the most common carbon–hydrogen functionalizations that are facilitated by the presence of heterocycles.

The review focuses on the recent literature from the last five years. We hope that the review will provide a timely overview of the most common strategies used for the C–H functionalization of heterocycles as an enabling method for the synthesis of natural products and motivate chemists to establish more effective and reliable C–H functionalization methods. Figure 1 presents a selection of heterocyclic natural products synthesized by C–H functionalization.

2. Palladium-Catalyzed C–H Activation

Palladium catalysis is the predominant direction in the development of new C–H functionalization reactions.[15] In the last years, the majority of Pd-catalyzed C–H functionalization

reactions in the synthesis of heterocyclic natural products natural involved electrophilic palladation facilitated by electron-rich heterocycles.[18]

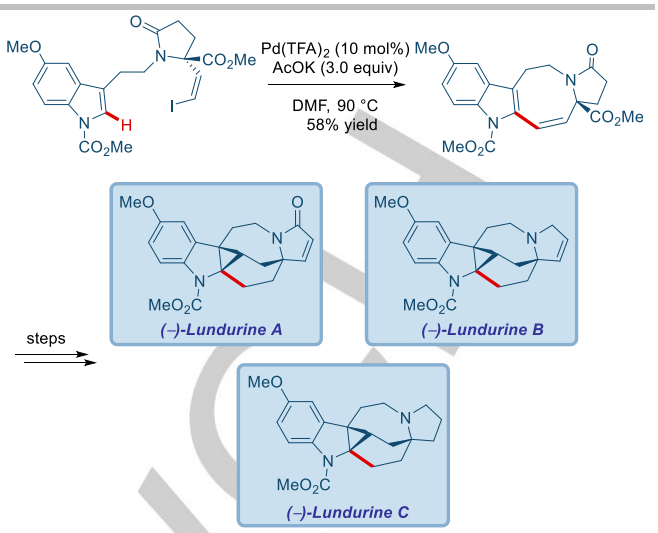


Scheme 1. Synthesis of (–)-Deoxoapodine by Pd-catalyzed C–H Alkylation of NH-Free Indoles by Tokuyama.

In 2020, Tokuyama and co-workers reported a concise synthetic route for the enantioselective total synthesis of (–)-deoxoapodine, which is a hexacyclic Aspidosperma alkaloid (Scheme 1).[19] The key step involved palladium-catalyzed C–H activation/cyclization cascade to rapidly construct the pentacyclic core of the alkaloid.

A palladium-catalyzed direct 2-alkylation reaction of free N-H indoles based on a norbornene-mediated regioselective cascade C–H activation was envisioned. First, an alkyl bromide was tested in Bach intermolecular alkylation conditions ($PdCl_2$, K_2CO_3, norbornene, 80 °C).[20] However, the nine-membered lactam was formed in low yield due to bromo-to-chloro substitution. Then, they found that the combined use of $PdBr_2$ to limit the direct substitution and K_3PO_4 as base significantly increased the yield. Furthermore, the combination of an alkyl iodide with PdI_2 and halide scavengers further increased the yield. The optimized conditions (PdI_2, K_3PO_4, $KNTf_2$, norbornene, 60°C) afforded the cascade product, featuring a bridged lactam moiety,[21] in an impressive 67% yield. Control experiments showed this reaction could not proceed without norbornene, which suggests that this reaction started from a norbornene-induced aminopalladation.

The formation of a nine-membered bridged lactam by a catalytic C–H palladation/alkylation cascade at the indole 2-position facilitated the construction of the Aspidosperma skeleton. The C–H activation at the indole C2-position was effective to reduce the number of chemical steps and eliminate protection/deprotection sequence, expanding the protecting-group-free synthesis concept pioneered by Baran.[6]



Scheme 2. Synthesis of (–)-Lundurines A–C by Pd-catalyzed C–H Vinylation of Indoles by Zhai.

Zhai and colleagues reported the asymmetric total synthesis of lundurines A–C using L-pyroglutamic acid in 2018 (Scheme 2).[22] In their synthetic route, the palladium-catalyzed intramolecular direct C–H vinylation of indole at the C2 position enables facile construction of the crucial polyhydroazocine ring. Thus, a direct ring-closing C–H bond vinylation of indole was proposed to convert a vinyl iodide precursor to the key tetracyclic intermediate. Initially, the reaction was tested with $Pd(OAc)_2$ as a catalyst and AcOK as a base in DMF at 65 °C, however the desired

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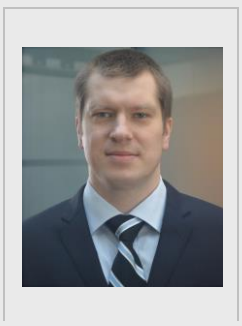
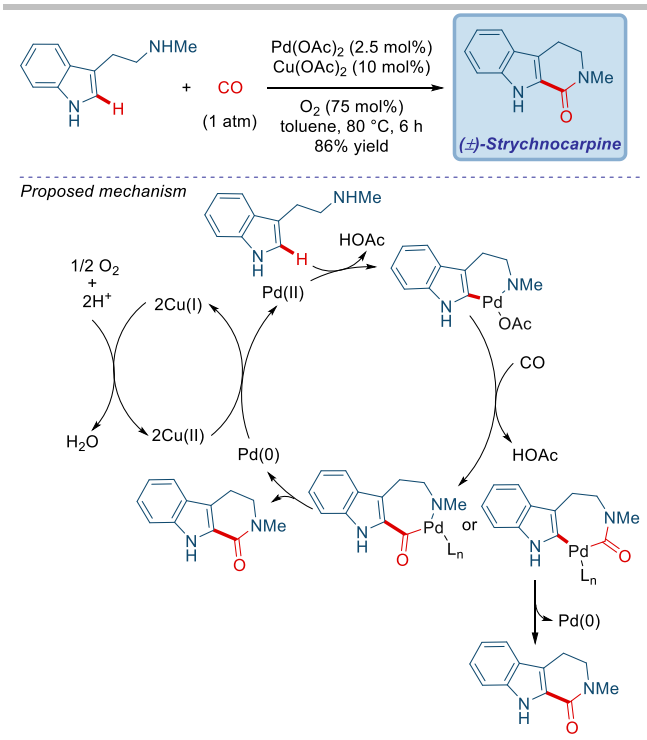
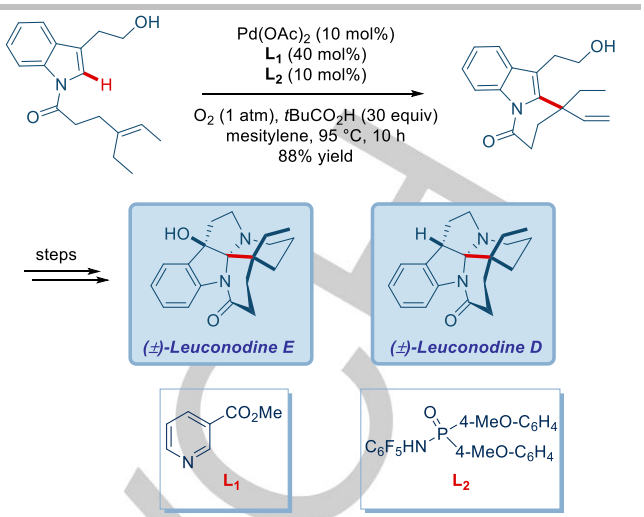


Michal Szostak received his Ph.D. from the University of Kansas in 2009. After post-doctoral stints at Princeton University and University of Manchester, in 2014, he joined the faculty at Rutgers University, where is currently Professor of Chemistry. His research group is focused on the development of new synthetic methodology based on transition-metal-catalysis, amide bonds, NHC ligands, C–H activation, decarbonylative coupling and application to the synthesis of biologically active molecules. He is the author of over 200 peer-refereed publications.



Scheme 3. Synthesis of (±)-Strychnocarpine by Pd-catalyzed C–H Aminocarbonylation of Indoles by Xia.



Scheme 4. Synthesis of (±)-Leuconodines D and E by Pd-catalyzed Oxidative Heck C–H Functionalization of Indoles by Han.

tetrahydroazocine was obtained in low yield. After optimization, they found that the reaction temperature of 90 °C was optimal. Furthermore, in the extensive screening of palladium catalysts, $Pd(TFA)_2$ afforded the highest yield (58%). Interestingly, screening of different ligands and bases could not improve the yield of this reaction, while addition of phosphine ligands, such as PPh_3, completely shut down the reaction. In the stratefy reported by Zhai, the central eight membered ring was constructed directly through a palladium(II)-catalyzed direct C–H vinylation of indole, which facilitated the completion of the total synthesis of lundurines A–C rapidly. The method exemplifies C2-electrophilic palladation of the electron-rich indole ring in the synthesis of challenging eight-membered rings.

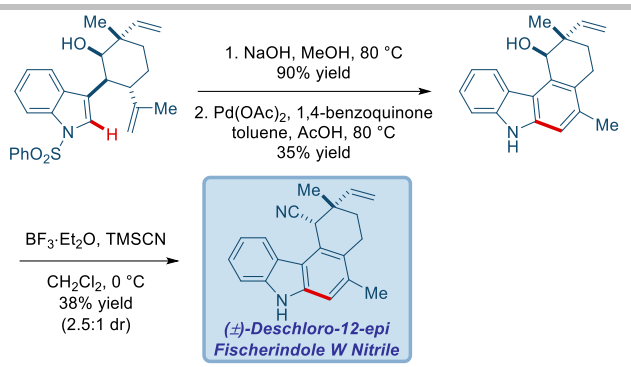
Xia and colleagues reported a concise total synthesis of strychnocarpine by Pd/Cu co-catalyzed oxidative tandem C–H aminocarbonylation and dehydrogenation (Scheme 3).[23] The strategy is notable for the facile access to the natural product strychnocarpine and its analogues by exploiting C2–H selective carbonylative indole functionalization.

For optimization of the reaction conditions, N-methyltryptamine was selected as a model substrate. When using $Rh(PPh_3)_3Cl$ as a catalyst and $Cu(OAc)_2$ as an oxidant in diglyme at 110 °C under an atmospheric pressure of CO, the target compound was formed in low yields (up to 25%). Subsequently, much improved results were obtained when Rh catalyst was replaced by Pd. The target product was formed in 81% with $Pd(OAc)_2$ as a catalyst in toluene. Interestingly, it was noted that an extended reaction time resulted in a further conversion to β-carbolinone by tandem C–H aminocarbonylation and dehydrogenation. Further optimization focused on oxidant and solvent screening established that the yield of the desired carboline was improved by lowering the reaction temperature to 80 °C, while $Cu(OAc)_2$ was identified as the optimal oxidant. Furthermore, solvent screening indicated that toluene was the best choice, while the use of molecular oxygen as a terminal oxidant permitted for a catalytic amount of $Cu(OAc)_2$. Mechanistically, the key step involves amine-directed C2–H activation of indole using Pd(II), followed by CO insertion and reductive elimination. Pd(0) is re-oxided by Cu(II)/O_2 couple to regenerate the catalyst.

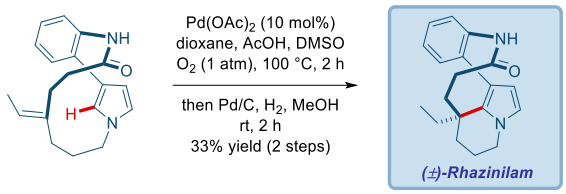
The reaction developed by the Xia group exemplifies the cooperative Pd/Cu catalysis using CO as attractive C1 synthon in indole functionalization, enabling an efficient and direct total synthesis of strychnocarpine and its analogues under mild reaction conditions.

Han and coworkers developed a highly concise synthetic route for the synthesis of (±)-leuconodines D and E, which are the members of Aspidosperma family of monoterpene indole alkaloids (Scheme 4).[24] Both of the natural products feature an atypical diaza[5.5.6.6]-fenestrane core, which represents a rare class in indole alkaloids. The approach by Han embodies an efficient construction of the key indole δ-lactam by the means of Pd(II)-catalyzed oxidative Heck C–H activation.

This approach relies on the combination of two different ligands, namely methyl nicotinate and a phosphinamide type ligand, to promote the Pd-catalyzed C–H activation. In an initial study, a Tf-protected tryptamine was used as the substrate to investigate the synthesis of leuconodine E. Thus, the desired δ-lactam was obtained in 78% yield under the conditions of oxidative Heck cross-coupling previously reported by the same group ($Pd(OAc)_2$, 10 mol%, methyl nicotinate, 40 mol%, phosphinamide, 10 mol%, $pivCO_2H$, 30 equiv, mesitylene, O_2, 130 °C). Although the 6-exo-trig intramolecular C–H cyclization was successful (78% yield), the authors encountered problems with the removal of N-Tf protecting group. Thus, substrates bearing different NH-protecting group, such as CBz, Boc and Ts, were examined in the key C–H cyclization; alas, replacement of the protecting groups made the oxidative Heck C–H cyclization less effective. Finally, the authors resorted to the use of an alcohol derivative, which underwent smooth intramolecular oxidative Heck cross-coupling under the developed conditions in an impressive 88% yield. The alcohol product embedded in a [6.5.6]-tricyclic indole δ-lactam was then elaborated to leuconodine D and leuconodine E.



Scheme 5. Synthesis of (±)-Deschloro-12-epi-fischerindole W Nitrile by Pd-catalyzed Oxidative Heck C–H Functionalization of Indoles by Maji.



Scheme 6. Synthesis of (±)-Rhazinilam by Pd-catalyzed Oxidative Heck C–H Functionalization of Pyrroles by Blanc.

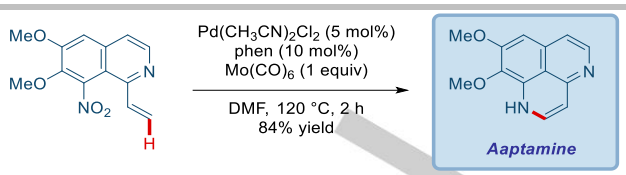
Overall, the application of a Pd-catalyzed aerobic oxidative Heck cross-coupling provided an efficient way for the construction of an atypical diaza[5.5.6.6]fenestrane core. The strategy of using indole C2–H functionalization vastly simplified the synthesis and permitted a concise assembly of (±)-leuconodines D and E, furnishing 100 mg of the complex alkaloid in a single run.

In 2018, Maji and coworkers reported a concise synthetic route to (±)-deschloro-12-epi-fischerindole W nitrile, an indole alkaloid from Hapalindole family (Scheme 5).[25] The challenge in the synthesis of (±)-deschloro-12-epi-fischerindole W nitrile is a trans-1-indolyl-2-isopropenylcyclohexane framework, wherein the indole core is attached to the functionalized cyclohexane unit through the C2/C3-positions in a carbazole framework.

In this study, the authors constructed the key carbazole benzene ring through palladium-catalyzed intramolecular oxidative cyclization of 3-(3'-alkenyl)-indole. This challenging reaction proceeded in 35% yield using $Pd(OAc)_2$ in the presence of 1,4-benzoquinone as an oxidant. In this reaction, the benzene ring is constructed by Pd(II)-catalyzed endo-type cyclization, followed by oxidation of the formed cyclohexadiene moiety with benzoquinone, which is also used to regenerate the active Pd(II) catalyst. A mechanism involves C2–H activation of indole to give the C2-palladated indole intermediate, which then undergoes olefin insertion. β-Hydride elimination generates the diene product, which is further aromatized under the reaction conditions to give the carbazole product. After the key cyclization, the total synthesis of deschloro-12-epi-fischerindole W nitrile was completed in in 38% yield.

Overall, the elegant use of oxidative Heck coupling established the challenging carbazole ring at the final stages of the synthesis by exploiting electronic properties of the indole at C2–H position.

In 2019, Blanc and co-workers reported the total synthesis of (±)-rhazinilam, a monoterpenoid pyrrole alkaloid, using an intramolecular oxidative Heck cyclization in combination with Pd-catalyzed C–O cross-coupling to build the key architecture of the natural product (Scheme 6).[26] In this reaction, they successfully applied selective Pd(II)-catalyzed C5-alkenylation of 3-substituted pyrroles (cf. C2-alkenylation) to efficiently form the quaternary center by using dioxygen as the terminal oxidant. The mechanism of this C5-alkenylation involves pyrrole palladation, olefin insertion and β-hydride elimination. The key species formed is pyrrolyl–Pd(II), while the selectivity originates from the steric hindrance of the 3-substituted pyrrole. The use of pyrroles is particularly efficient in this C–H activation manifold due to electrophilic palladation by Pd(II) favored by electron-rich heterocycles, a process which is complementary to the classical Heck reaction.



Scheme 7. Synthesis of Aaptamine by Pd-catalyzed Reductive Cyclization of Nitroarenes with 1-Vinyl-Quinolines by Lin.

In this approach, the total synthesis of rhazinilam was completed concisely by Pd-catalyzed cross-coupling/oxidative Heck reaction, highlighting the complementary power of C–H functionalization and cross-coupling methodologies.

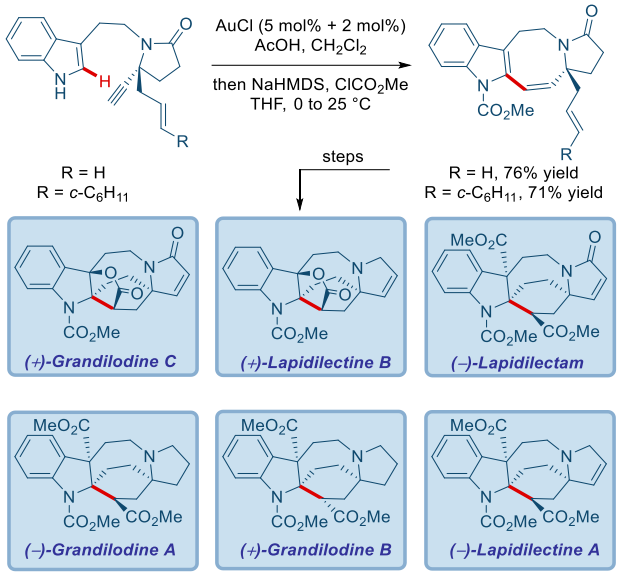
In 2019, Lin and co-workers reported a concise synthetic route to aaptamine, an important member of the aaptaminoids bearing a novel benzonaphthyridine framework (Scheme 7).[27] The key step is a novel palladium-catalyzed intramolecular reductive cyclization of nitroarenes with olefins, which allowed for the direct formation of a new pyridine ring onto the isoquinoline scaffold. After careful optimization of the reaction conditions by screening different palladium catalysts, reductants, and ligands, the best yield was achieved in the presence of $Pd(CH_3CN)_2Cl_2$ (5 mol%) and phenanthroline as a ligand (10 mol%) with $Mo(CO)_6$ as a stoichiometric reductant. A mechanism may involve a radical pathway, with the formation of a radical anion by single-electron transfer from the palladium complex to the nitroalkene as the initial step. Then the intermediate could be reduced to afford nitrosoalkene that undergoes cyclization.

This intriguing approach proved an efficient way to generate aaptamine directly by reductive cyclization of nitroarenes by palladium catalysis. It may be expected that this novel reductive cyclization will be applied to the synthesis of other classes of pyridine alkaloids.

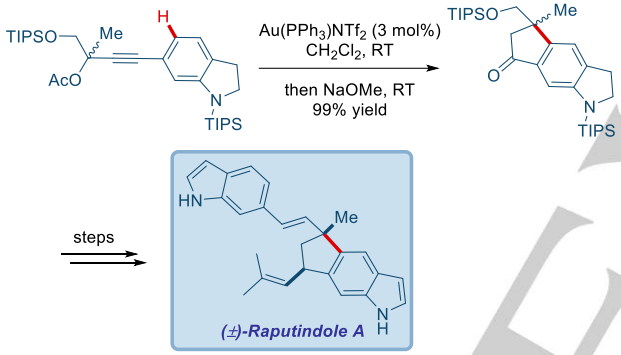
3. Gold-Catalyzed C–H Activation

Over the last two decades gold-catalysis has emerged as an increasingly modular platform for electrophilic functionalization reactions of π-systems under mild conditions.[28] The majority of recent applications of gold catalysis in C–H functionalization for the synthesis of heterocyclic natural products involve electrophilic hydroarylation reactions of electron-rich nitrogen heterocycles.

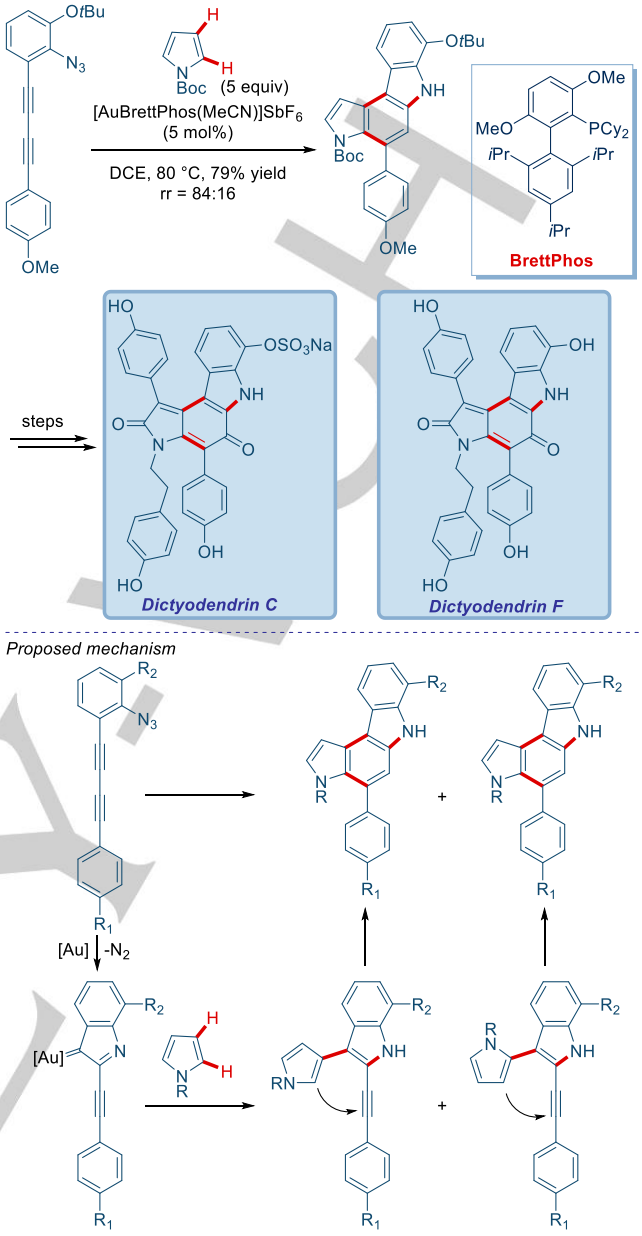
In 2018, Echavarren and co-workers reported an impressive total synthesis of Lapidilectine and Grandilodine natural products from the Kopsia family of indole alkaloids without the use of protecting groups (Scheme 8).[29] In this total synthesis, the key



Scheme 8. Synthesis of Lapidilectine and Grandilodine Natural Products by Au-catalyzed C–H Hydroarylation of Indoles by Echavarren.



Scheme 9. Synthesis of (±)-Raputindole A by Au-catalyzed C–H Hydroarylation of Indolines by Lindel.



Scheme 10. Synthesis of Dictyodendrins by Au-catalyzed C–H Hydroarylation Cascade of Pyrroles by Ohno.

step is 8-endo-dig hydroarylation of the electron-rich C2–H position of the indole ring catalyzed by gold(I), an inventive reaction that permits for the efficient assembly of pyrroloazocine tetracyclic indole core. At the outset, the authors found that the reaction is inefficient in the presence of AuCl catalytic system due to decomposition of the catalyst. Remarkably, the use of a cationic gold complex $[Au(IPr)(CH_3CN)]SbF_6$ with gold stabilized by N-heterocyclic carbene ligand[30] promoted the desired 8-endo-dig hydroarylation with excellent 8-endo selectivity and in high yields. Subsequently, they found that the stability of AuCl catalyst could be improved in the presence of acetic acid, and this system was used as the preferred Au(I) promoter for the reaction.

This concise total synthesis of lundurines A–C highlights the utility of Au(I)-hydroarylation of electron-rich heterocycles to enable highly efficient cyclization building the pyrroloazocine indole core.

In 2018, Lindel and co-workers reported total synthesis of (±)-Raputindole A, an alkaloid from Raputia simulans tree (Scheme 9).[31] The key step exploits Au(I)-catalyzed cyclization of propargylic acetate with the electron-rich C6–H position of the indoline to directly furnish the cyclopenta[*f*]indole tricyclic core of the alkaloid. In this case, the preferred catalyst is cationic $[Au(PPh_3)_4(NTf_2)]$, which delivered the desired cyclization product in quantitative yield after methanolysis, thus highlighting the utility of electrophilic Au(I)-catalyzed cyclizations guided by nitrogen heterocycles.

In 2017, Ohno and coworkers reported concise total synthesis of dictyodendrins B, C, E, and F, intriguing marine indole alkaloids isolated from Japanese sponge Dictyodendrilla verongiformis (Scheme 10).[32] The key step involved Au(I)-catalyzed annulation of a conjugated diyne with pyrrole, a remarkable process which forged three bonds and two aromatic rings in a single transformation, allowing for a rapid construction of the tetracyclic pyrrolo[2,3-*c*]carbazole core of the alkaloids. This gold-catalyzed annulation is promoted by a cationic Au(I) complex $[Au(BrettPhos)(CH_3CN)]SbF_6$ using biarylphosphine as a

supporting ligand. The reaction likely proceeds via a double hydroarylation cascade to form a disubstituted benzene ring. The mechanism involves the following steps: (i) generation of gold carbenoid from the diyne bearing an azido group; (ii) arylation of the carbenoid at the 3- or 2-position of pyrrole; (iii) 6-endo-dig hydroarylation to form the desired pyrrolo-[2,3-*c*]carbazole product and the regioisomeric pyrrolo[3,2-*c*]carbazole derivative. Under the optimized conditions, high selectivity for the formation of the desired pyrrolo-[2,3-*c*]carbazole tetracycle is observed (>90:10). This impressive reaction allows the direct construction of the core structure of dictyodendrins in a single step.

Thus, the total syntheses of dictyodendrins features another variant of Au(I)-catalyzed intramolecular hydroarylations using electron-rich pyrroles to promote the cyclization.

4. Iridium and Ruthenium-Catalyzed C–H Activation

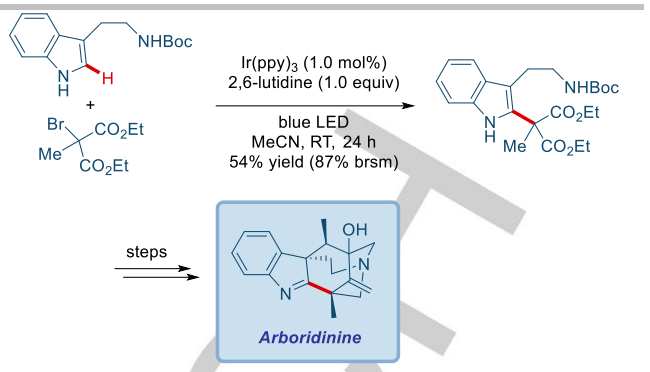
Recently, tremendous progress has been made in transition-metal-catalyzed photoredox catalysis driven by the use of light to promote catalytic generation of radical intermediates.[33] The most common photoredox initiators are based on [Ir(ppy)$_3$] and [Ru(bpy)$_3$]Cl$_2$, enabling generation of electrophilic radicals for C–H functionalization of electron-rich heterocycles. These methodologies have already been successfully implemented in the synthesis of natural products, while more established methods, such as Ir-catalyzed C–H borylation[34] or Ru-catalyzed C–H isomerization[35] have also been recently achieved.

4.1. Photoredox C–H Functionalization

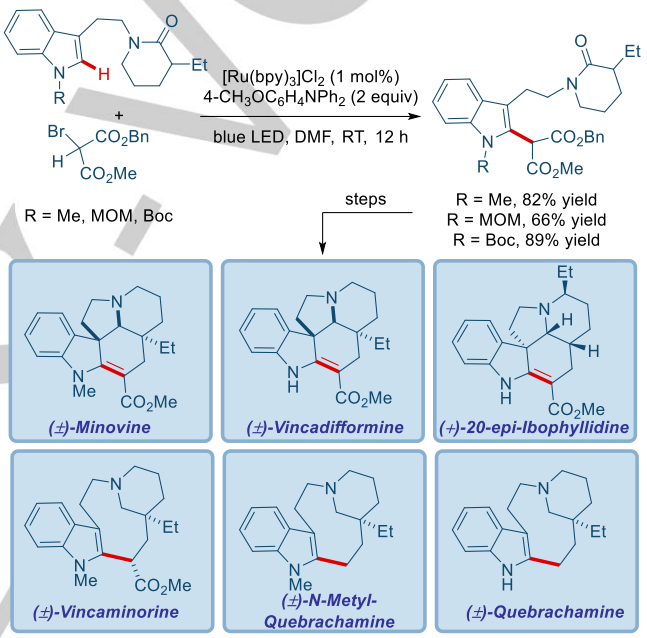
In 2018, Synder and co-workers reported the total synthesis of arboridinine, a cage-containing indole alkaloid featuring a complex tetracyclic indolenine core (Scheme 11).[36] One of the early steps involved Ir-catalyzed intermolecular C–H functionalization at the C2 position of indole using 3° alkyl halides. In this method, photoredox catalysis enables the formation of the reactive tertiary radical intermediate, which undergoes addition to the Boc-protected tryptamine at the electron-rich C2 position to afford substituted malonate esters. The reaction was promoted by [Ir(ppy)$_3$] in the presence of 2,6-lutidine, which directly gave C2 functionalized indole in good yield. Thus, the convenient and efficient C2–H functionalization allowed the further exploration of this total synthesis effort and supported the successful completion of the total synthesis of arboridinine.

It is worth noting that a very similar strategy for C2–H functionalization of indoles by photoredox catalysis has been reported by Dixon and co-workers in the context of the divergent total syntheses of (±)-vincaminorine, (±)-N-methylquebrachamine, (±)-quebrachamine, (±)-minovine, (±)-vincadifformine and (+)-20-epi-ibophyllidine alkaloids (Scheme 12).[37] This mild reaction featured the use of [Ru(bpy)$_3$]Cl$_2$ as a photoredox catalyst to promote C2–H alkylation with 1-benzyl-3-methyl-2-bromomalonate in the presence of C3-linked δ-lactam. This intermediate was subjected to decarboxylation/Eschenmoser methylenation sequence that set the stage for chemoselective Ir-(I)-catalyzed lactam reduction and enamine Michael addition.

Thus, this approach to Aspidosperma alkaloids from a single δ-lacatam intermediate hinged upon the efficient installation of the Michael acceptor by photoredox C2–H activation, allowing the smooth synthesis of these natural products.



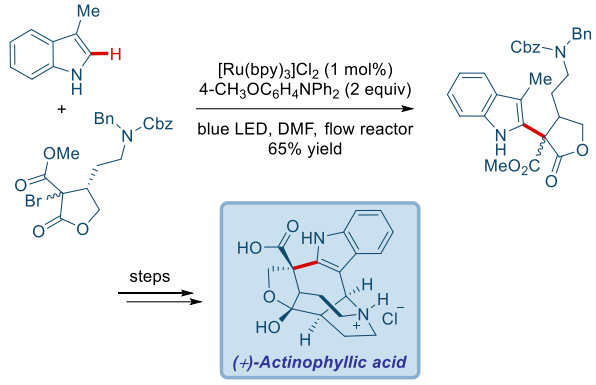
Scheme 11. Synthesis of Arboridinine by Ir-catalyzed Photoredox C–H Alkylation of Indoles by Snyder.



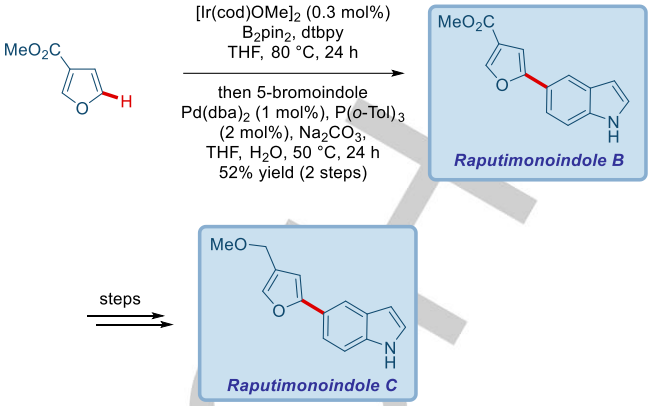
Scheme 12. Synthesis of Aspidosperma Alkaloids by Ru-catalyzed Photoredox C–H Alkylation of Indoles by Dixon.

In 2018, Qin and coworkers reported a concise formal synthesis of both enantiomers of actinophyllic acid (Scheme 13).[38] Their strategy involved efficient construction of the all-carbon quaternary center of the alkaloid by C2–H photoredox functionalization of 3-methylindole with α-methoxycarbonyl-α-bromolactone. Interestingly, this reaction was carried out in a flow reactor using Ru(bpy)$_3$Cl$_2$ as a catalyst to furnish the C2–H alkylation product in 65% yield on an impressive 5 g scale. As in the other photoredox C2–H functionalizations of indoles, a reactive radical intermediate is generated via the reduction of a stabilized C–Br bond. The desired product is formed by coupling of the electron-rich indole with an electrophilic radical. The resultant radical is then oxidized by the excited state of the photocatalyst to afford the final product. The overall sequence is highly efficient to directly install methylenecarbonyl groups at the C2–H position of the indole ring.

Thus, in this formal total syntheses of (–)-actinophyllic acid and its enantiomer, C2–H indole functionalization enabled rapid construction of the congested all-carbon quaternary center,



Scheme 13. Synthesis of (+)-Actinophyllic acid by Ru-catalyzed Photoredox C–H Alkylation of Indoles by Qin.



Scheme 14. Synthesis of Raputimonoindoles B and C by Ir-catalyzed C–H Borylation of Furans by Lindel.

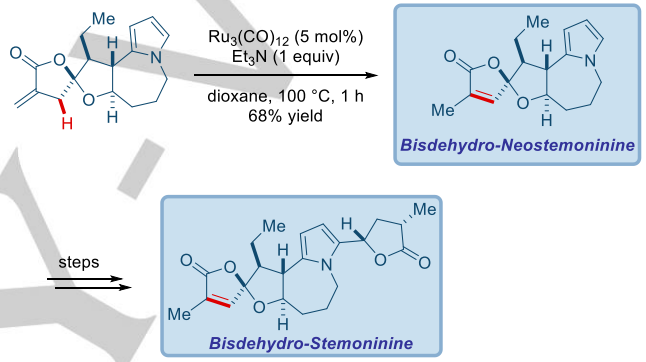
highlighting the power of photredox functionalization of electron-rich heterocycles.

4.2. Non-Photoredox C–H Functionalization

In 2019, Lindel and co-workers reported a concise total synthesis of raputimonoindoles A-C, indole alkaloids isolated from the bark and roots of Amazonian tree Raputia simulans (Scheme 14).[39] In their approach, raputimonoindole B was afforded directly by Ir-catalyzed C–H borylation followed by Pd-catalyzed Suzuki-Miyaura cross-coupling of 3-carbomethoxyfuran. The selective C–H borylation enables the formation of C5 pinacol boronate ester in high yield by sterically-directed C–H borylation. Next, the Suzuki-Miyaura cross-coupling with 5-bromoindole in the presence of $Pd(dba)_2/P(o\text{-}Tol)_3$ catalytic system in THF/H_2O directly afforded the natural product, while avoiding the inconvenience of preparation of boronic acids.

Thus, raputimonoindole B was synthesized efficiently in a single step, highlighting the utility of merging the Ir-catalyzed C–H borylation of heterocycles with the classical Suzuki-Miyaura cross-coupling.

In 2018, Dai and coworkers reported the first total syntheses of *Stemona* alkaloids bisdehydroneostemoninine and bisdehydrostemoninine in racemic forms (Scheme 15).[40] The key step in their synthetic strategy involved C–H isomerization of the exo-methylene group to an endocyclic double bond in the γ-butyrolactone, readily constructed by Eschenmoser methylenation, catalyzed by $Ru_3(CO)_{12}$. This reaction completed the first total synthesis of bisdehydroneostemoninine, whereas the use of a mild Ru-catalyzed C–H bond isomerization protocol[41] streamlined the total synthesis and further enabled the synthesis of the C11 epimer of bisdehydroneostemoninine by the same reaction sequence. The strategy is notable in that is also provides an efficient solution to the installation of γ-butyrolactone motif that is common in many other Stemona alkaloids.



Scheme 15. Synthesis of Stemona Alkaloids by Ru-catalyzed C–H Isomerization of γ-Butyrolactones by Dai.

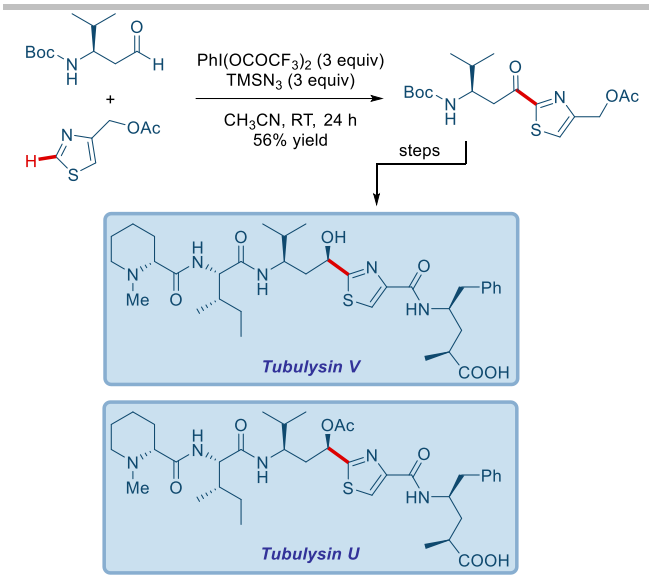
5. Radical Transition-Metal-Free C–H Activation

Generation of the radical intermediates has also been accomplished using transition-metal-free approaches.[42] The reported methods enable C–H functionalization of electron-deficient heterocycles, thus providing a complementary method to photoredox approaches.

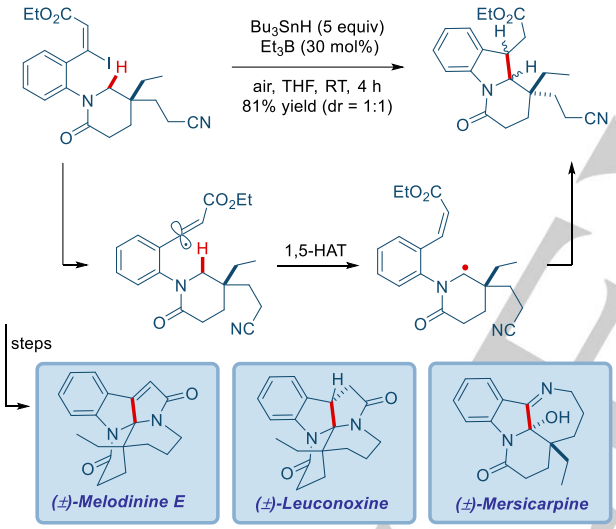
In 2018, Nicolaou and coworkers reported total syntheses of Tubulysins V and U (Scheme 16).[43] The synthetic strategy featured C–H activation of a chiral aldehyde to form formyl radical and coupling with a thiazole derivative at the C2 position. The optimized conditions involve $PhI(OCOCF_3)_2$ and $TMSN_3$,[44] furnishing the ketone coupling product in 81% yield. The mechanism involves ligand exchange between $PhI(OCOCF_3)_2$ and $TMSN_3$ to give $PhI(N_3)(OCOCF_3)$ or $PhI(N_3)_2$ by single or double exchange. Thermal homolytic cleavage of a weak I–N bond generates an azide radical, which reacts with aldehyde to generate nucleophilic formyl radical. The formyl radical reacts with thiazole at the C2 position, which is guided by the electrophilic character of the electron-deficient heterocycle.

Thus, the total synthesis of tubulysins V and U features the power of efficient, mild and scalable direct C–H functionalization of electron-deficient heterocycles with aldehydes under metal-free conditions.

In 2019, Beaudry and coworkers reported the total synthesis of Aspidosperma alkaloids using radical translocation/cyclization cascade via α-aminyl radical (Scheme 17).[45] This key step involves 1,5-hydrogen atom transfer followed by 5-exo-trig cyclization, allowing for the efficient construction of the tricyclic indoline core of the alkaloids. The translocation is initiated by homolysis of the vinyl iodide using Bu_3SnH/Et_3B in air to give benzylic vinyl radical. 1,5-Hydrogen atom transfer is favored by the geometry of the vinylic radical with the ester group pointing



Scheme 16. Synthesis of Tubulysins V and U by Transition-Metal-Free Radical C–H Acylation of Thiazoles by Nicolaou.



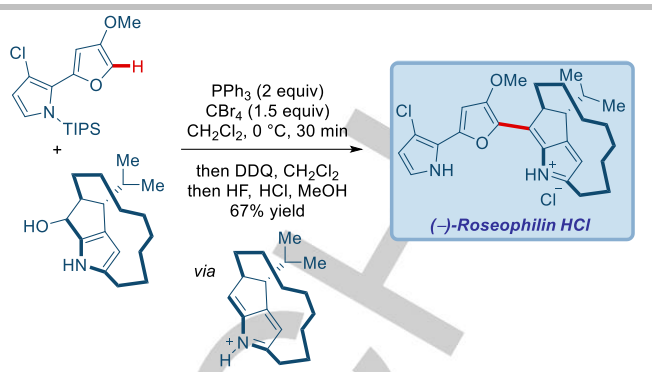
Scheme 17. Synthesis of Aspidosperma Alkaloids by 1,5-Hydrogen Atom Transfer of Piperidin-2-ones by Beaudry.

away from the quaternary carbon. Subsequently, 5-exo-trig cyclization affords the desired tricyclic indolines in excellent yield, as an inconsequential mixture of diasteroisomers.

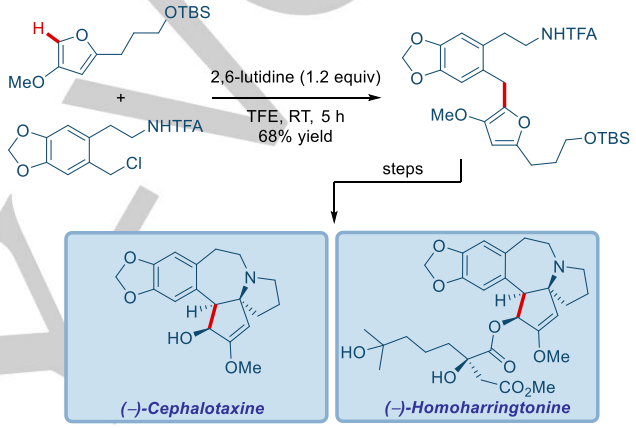
This total synthesis of Aspidosperma alkaloids highlights the utility of α-aminyl radicals[46] in intramolecular cyclization reactions towards complex natural products.

6. Electrophilic Metal-Free C–H Activation

The inherent electronic properties of electron-rich heterocycles permit for facile C–H functionalization by electrophilic metal-free methods.[16] Recent impressive examples include complex alkylation of five-membered heterocycles and polarity reversal by functional group substitution.



Scheme 18. Synthesis of (–)-Roseophilin by Electrophilic C–H Alkylation of Furans by Liang.



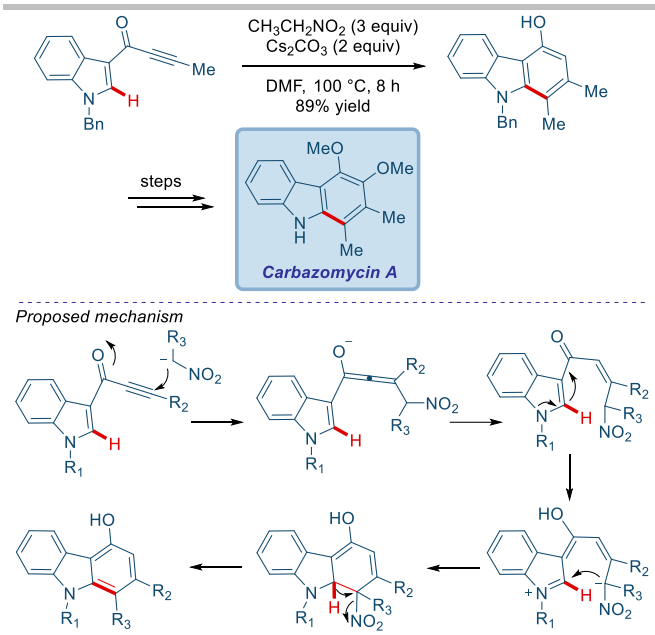
Scheme 19. Synthesis of (–)-Cephalotaxine and (–)-Homoharringtonine by Electrophilic C–H Alkylation of Furans by Beaudry.

In 2019, Liang and co-workers reported a concise total synthesis of either enantiomer of roseophilin (Scheme 18).[47] Their synthetic approach featured an effective coupling of a furan-pyrrole unit with a macrocyclic fragment via intermolecular C–H alkylation under mild conditions. This formal C–H functionalization at the C2–H position of the furan ring proceeded directly between the fully functionalized furan-pyrrole unit and the macrocyclic carbocation generated in situ from the corresponding alcohol using Ph_3P/CBr_4 activation. Impressively, the final natural product was obtained directly after oxidation/desilylation sequence, which allowed the completion of the total synthesis conveniently.

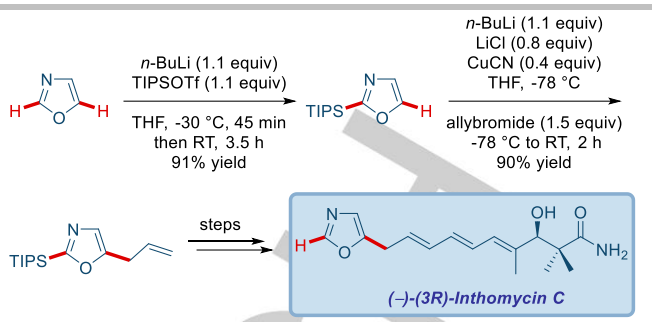
This robust total synthesis of roseophilin features the efficiency of electrophilic C–H alkylation reactions as an alternative method to C–H functionalizations using electrophilic transition metals with electron-rich heterocycles.

It is worth noting that in 2019, Beaudry and co-workers reported total synthesis of (–)-homoharringtonine and (–)-cephalotaxine (Scheme 19).[48] The synthesis featured a similar C–H functionalization of the furan ring at the C2 position via intermolecular C–H alkylation. In this case, the alkylated furan ring was converted into the cyclopentanone ring in the final natural product, thus demonstrating that this general strategy of C–H alkylation of electron-rich heterocycles can be used in conjunction with ring opening reactions to furnish diverse ring systems.

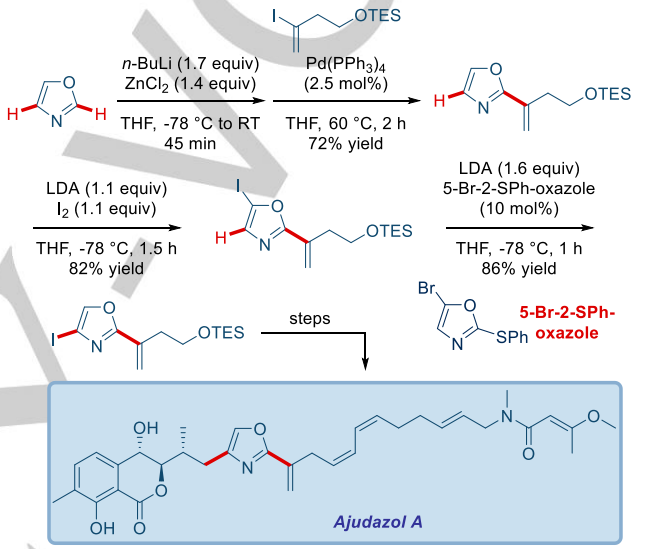
In 2019, Metha and co-workers reported an efficient strategy for the total synthesis of Carbazomycins, bioactive natural products



Scheme 20. Synthesis of Carbazomycin A by Electrophilic C–H Annulation of Indoles by Mehta.



Scheme 21. Synthesis of (–)-(3*R*)-Inthomycin C by Direct C–H Deprotonation of Oxazoles by Donohoe.



Scheme 22. Synthesis of Ajudazol A by Direct C–H Deprotonation of Oxazoles by Menche.

isolated from Streptoverticillium and featuring carbazole ring (Scheme 20).[49] The approach featured a one-pot, domino benzannulation sequence engaging electron-rich C2–H position of the indole ring to set up the tetrasubstituted carbazole moiety between indole-3-ynones and nitromethane derivatives. The optimized conditions use Cs_2CO_3 as a base in DMF as a solvent to furnish the desired functionalized carbazole ring in excellent yield. The mechanism involves the following steps: (i) Michael addition of nitromethane anion to ynone; (ii) tautomerization to enaminoketone; (iii) intramolecular addition of the nitromethane anion to iminium; and (iv) elimination of the nitro group, driven by rearomatization.

This novel one-pot strategy for the synthesis of Carbazomycins underscores the substitution patterns of electron-rich heterocycles, which could be rendered electrophilic by suitable positioning of electron-withdrawing moieties.

7. C–H Activation by Direct Deprotonation

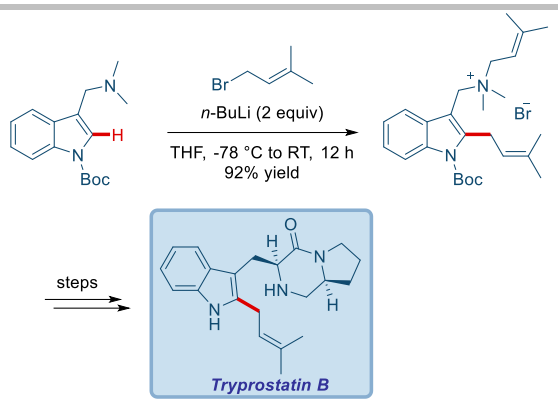
The most classic type of C–H functionalization relies on the direct deprotonation of acidic C–H bonds.[50] In this respect, direct deprotonation of heterocycles is highly attractive owing to the differential acidity of heterocyclic C–H bonds.[51] This approach has been found particularly effective for the C–H functionalization of electron-deficient heterocycles, while directing group effect can be used for their electron-rich counterparts.

In 2018, Donohoe and co-workers reported a concise approach to the synthesis of (–)-(3*R*)-inthomycin C, polyene natural product isolated from Streptomyces and featuring oxazole ring (Scheme 21).[52] The key step involves preparation of C5-substituted oxazoles via sequential C2–H/C5–H lithiation, which permitted for the convenient installation of the methylene-interrupted triene motif of the natural product. The first lithiation is to protect the C2–H position with TIPS group, which is followed by the second lithiation at the C5–H position to furnish C5-allyl-oxazole after transmetalation to copper and addition of allyl bromide.

Thus, the total synthesis of the natural product was completed efficiently from commercially available oxazole by exploiting the concise preparation of the C5-functionalized oxazole intermediate by C–H lithiation of electron-deficient oxazole ring.

In 2020, Menche and co-workers reported another strategy relying on the direct C–H lithiation of oxazole as a key step in the total synthesis of ajudazol A, potent respiratory chain inhibitor (Scheme 22).[53] This synthetic approach hinged upon direct C2–H lithiation of the oxazole ring, followed by transmetallation to $ZnCl_2$ and Negishi $C(sp^2)$–$C(sp^2)$ coupling with vinyl iodide. Interestingly, the oxazole ring was then used as a template for C5–H selective direct lithiation/iodination and LDA-promoted halogen dance reaction to install the halogen atom at the C4–H position, driven by the higher acidity of the C5–H position. The product was then well-poised for another Pd-catalyzed Negishi $C(sp^2)$–$C(sp^3)$ coupling to complete total synthesis of the natural product.

Thus, this total synthesis of ajudazol A was achieved using commercially available oxazole as a template for sequential functionalization by C–H lithiations, exploiting differential acidity of the C–H bonds in electron-deficient heterocycles.



Scheme 23. Synthesis of Tryprostatin B by Direct C–H Deprotonation of Indoles by Hossain.

In 2018, Hossain and coworkers reported an efficient synthesis of tryprostatin B, a prenylated diketopiperazine alkaloid from Aspergillus fumigatus (Scheme 23).[54] The key step of the synthetic strategy is the preparation of a C2-prenylated indole by a direct lithiation directed by N-Boc group. The authors found that N-Boc protected gramine can be subjected directly to excess of n-BuLi and prenyl bromide to produce C2,N-diprenylated N-Boc-gramine in excellent yield. Subsequently, this double-alkylation reaction was also shown to be feasible with other electrophiles, such as benzyl bromide. The total synthesis of tryprostatin B was completed after S_N2 displacement of the benzylic ammonium and formation of the diketopiperazine ring.

Impressively, the total synthesis was accomplished in 35% overall yield by exploiting direct C2–H lithiation of the indole ring. Although C–H lithiations of electron-rich heterocycles are much less common than their electron-deficient counterparts, this total synthesis highlights how the substitution of the heterocyclic ring can change the reactivity patterns and enable smooth synthesis of bioactive natural products.

9. Conclusions

After significant advancements in synthetic methodologies and strategies for several decades, total synthesis of natural products is now accomplished more efficiently and more economically. Evolutionary synthetic approaches were developed and optimized, gradually advanced starting materials and reagents were applied, and the advantage of cascade reactions and tandem catalysis is continually exploited. Among these developments, C–H bond functionalization is undoubtedly one of the most powerful platforms in the total synthesis of natural products.

In this review, we have presented an overview of C–H bond functionalization as a powerful and effective tool for the total synthesis of heterocyclic natural products. Principally, these methods enable rapid and efficient synthetic completion of natural products. Metal-catalyzed C–H functionalization of heterocycles was implemented using electrophilic palladium-catalyzed C–H functionalization, gold-catalyzed C–H hydroarylation as well as iridium- and ruthenium-catalyzed C–H photoredox catalysis. Furthermore, transition-metal-free radical C–H activation, electrophilic metal-free C–H functionalization and direct C–H deprotonation have been demonstrated, facilitating smooth assembly of the core heterocyclic motifs. The C–H bond functionalization of heterocycles provided novel previously unattainable approaches to the total synthesis of natural products, often under mild conditions and with reactivity orthogonal the traditional methods.

To date, the continuous advancements in synthetic methodologies mean that we can complete the synthesis of almost any complex structure. Thus, one of the next targets is achieving higher efficiency and atom economy in total synthesis. Undoubtedly, the use of C–H functionalization allows for a rapid access to complex target motifs in a faster and more atom-economical manner. This approach not only saves time and cost, but also enables the design of innovative and concise synthetic routes without protecting groups. Future studies will likely focus on the design of even better synthetic routes, whereas C–H functionalization will be implemented in an increasingly growing number of steps in a predictable manner.

Acknowledgements

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Keywords: C–H functionalization • natural products • heterocycles • C–H activation • total synthesis

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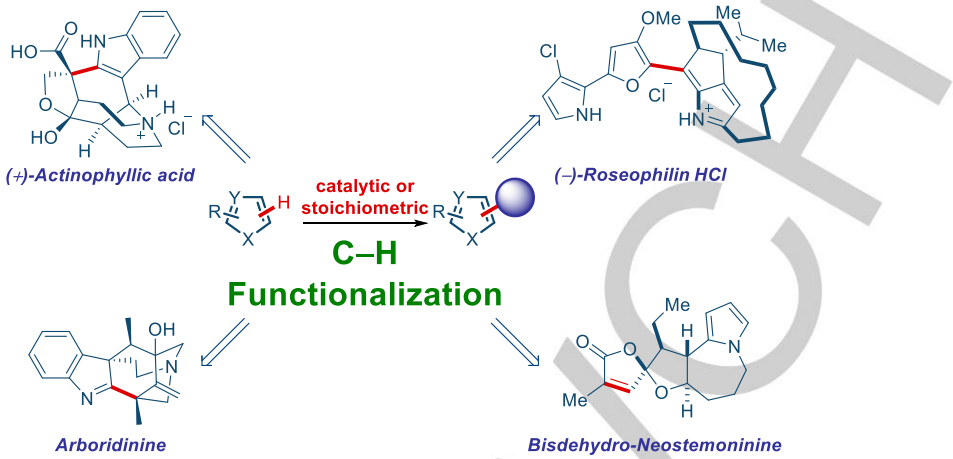

An overview of the recent strategies towards the total synthesis of heterocyclic natural products enabled by C–H functionalization is presented. The review is focused on transition-metal-catalyzed approaches, such as palladium catalysis, gold catalysis, iridium and ruthenium catalysis, and also presents transition-metal-free radical strategies as well as electrophilic-type metal-free C–H functionalization reactions and direct deprotonation approaches driven by the properties of heterocycles. The implementation of C–H functionalization of heterocycles enables novel tactics in the construction of core architectures, while changing the logic design of retrosynthetic strategies and permitting access to natural product scaffolds with novel and enhanced biological activities.

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