catalysts

MDPI

Review

Synthesis of Indoles via Intermolecular and Intramolecular Cyclization by Using Palladium-Based Catalysts

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Abstract: As part of natural products or biologically active compounds, the synthesis of nitrogen-containing heterocycles is becoming incredibly valuable. Palladium is a transition metal that is widely utilized as a catalyst to facilitate carbon-carbon and carbon-heteroatom coupling; it is used in the synthesis of various heterocycles. This review includes the twelve years of successful indole synthesis using various palladium catalysts to establish carbon-carbon or carbon-nitrogen coupling, as well as the conditions that have been optimized.

Keywords: indole; palladium; cyclization; cross-coupling; transition

Citation: Ayesha; Bilal, M.; Rasool, N.; Khan, S.G.; Rashid, U.; Altaf, H.; Ali, I. Synthesis of Indoles via Intermolecular and Intramolecular Cyclization by Using Palladium-Based Catalysts. *Catalysts* **2021**, *11*, 1018. https://doi.org/10.3390/catal11091018

Academic Editors: Alessandro Di Michele and Carlo Pirola

Received: 23 June 2021
Accepted: 23 July 2021
Published: 24 August 2021

1. Introduction

A.V. Baeyer and Kop discovered indole in 1866 while researching a plant named indigo, which is also known as benzopyrrole. Later, in 1869, Baeyer and Emmering proposed the indole formula, which is generally being used now. A five-membered pyrrole ring and benzene are fused to form indole [1]. Indoles are important heterocyclic compounds because they are an integral part of many alkaloids and biologically active compounds [2–20]. Thus, having enormous activities, indole has always acquired the attention of researchers.

Heterocycles have recently been synthesized in modern research using various transition metals as catalysts. The Pd, Ni, Ru, and Rh are among the most commonly used metals for the synthesis of heterocycles. Metal catalysts have the advantage of constructing heterocycles from readily available starting substrates under mild reaction conditions [21]. Palladium-catalyzed coupling reactions are now regarded as a powerful tool in the synthesis of organic compounds [8,22–38]. About fifty years ago, C-C bond production was once considered one of the most difficult tasks, involving stoichiometric interactions between reactive nucleophiles and electrophiles or pericyclic reactions. However, using palladium-catalyzed synthesis, new gates in C–C bond and C–X bond synthesis are now being opened [39,40]. Palladium exists in three complexes with the following oxidation states: Pd(0), Pd(II), and Pd(IV). These three oxidation states can be easily interconverted, which is one of the reasons for palladium's widespread use in organic synthesis [41]. Palladium-catalyzed couplings are favorable, as they are needed in smaller quantities, have mild reaction conditions and good yields, and are tolerant of a wide range of functional groups [42]. There are various classical methods available for the synthesis of indole and most of them are named after the scientists [25,43–62].

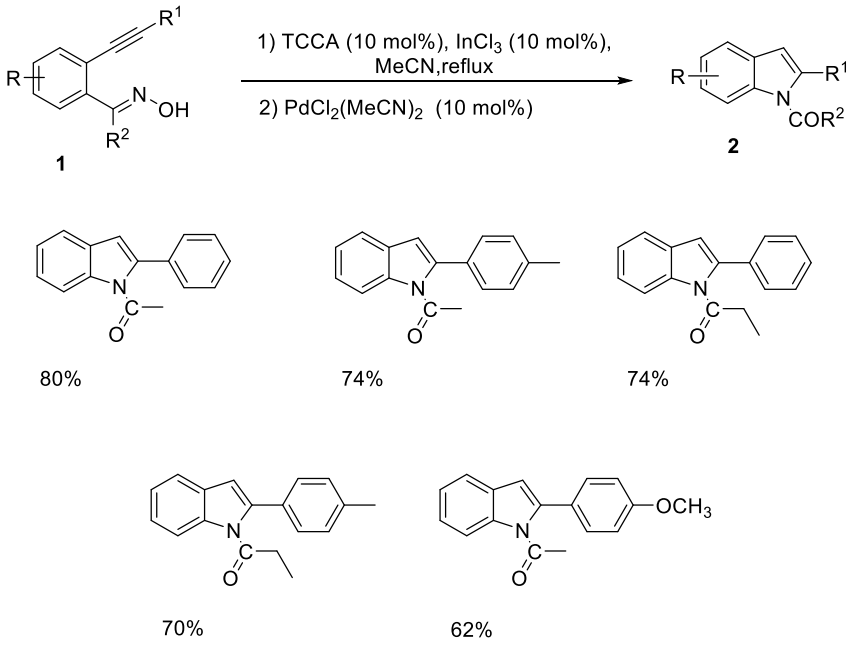
Pd-catalyzed indole synthesis was highlighted in this review. In different reaction conditions, we discuss the role of different Pd Catalysts, for instance, $PdCl_2$, $Pd(PH_3)_4$,

Pd_2dba_3, Pd(OAc), and various others. We also summarized the major factors which affect the yield of reaction for a particular catalyst.

2. Indole Synthesis

2.1. Indole Synthesis via Ortho-Alkynyl Anilines

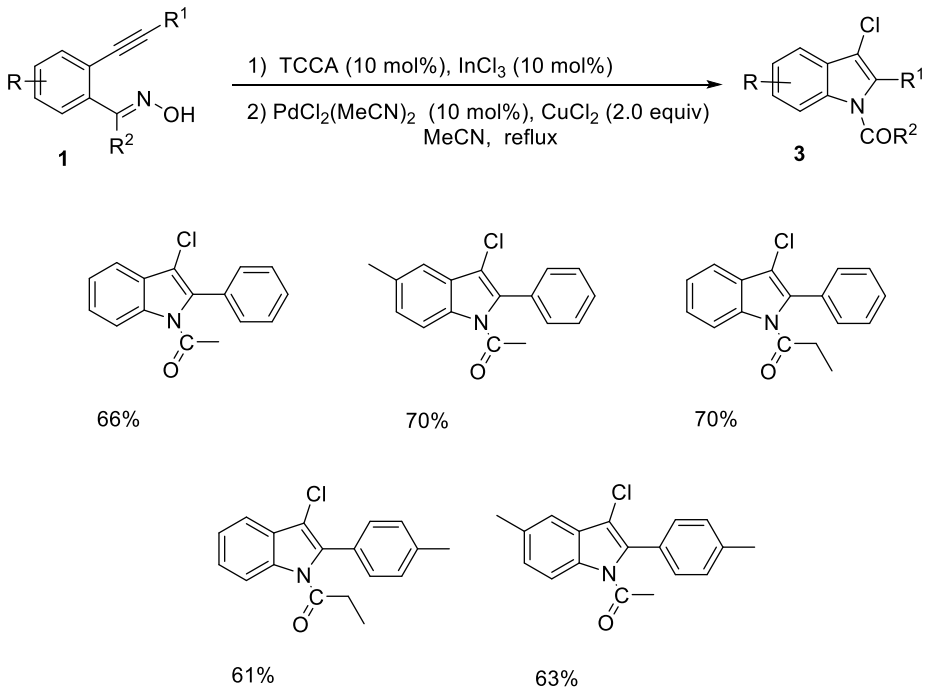
One of the attractive strategies for constructing complex molecules is a tandem reaction [63–71]; by this methodology, N-heterocycles are formed by utilizing 2-alkynyl benzaldoxime in the laboratory for synthesizing compounds resembling natural compounds [72–83]. Moreover, the use of ketoxime in amide production for the Beckmann rearrangement has shown to be a successful and extensively used method [84,85]. In 2010, Qiu and colleagues used a two-step catalytic system for the synthesis of N-substituted indole (**2**). They utilized 1-(2-alkynylphenyl)ketoxime (**1**) as the starting substrate in the tandem reaction using $(NCCl)_3$ in the presence of $InCl_3$ co-catalysts. Their action involved Beckmann rearrangement and subsequent intramolecular cyclization of (**1**) to acquire the desired N-substituted indoles which are fundamental structures in both the therapeutic agents and natural products (Scheme 1). This one-pot multi-catalytic strategy was effective for 1-(2-alkynylphenyl)ketoximes (**1**) having either electron-donating or electron-withdrawing substituents on the aromatic ring.



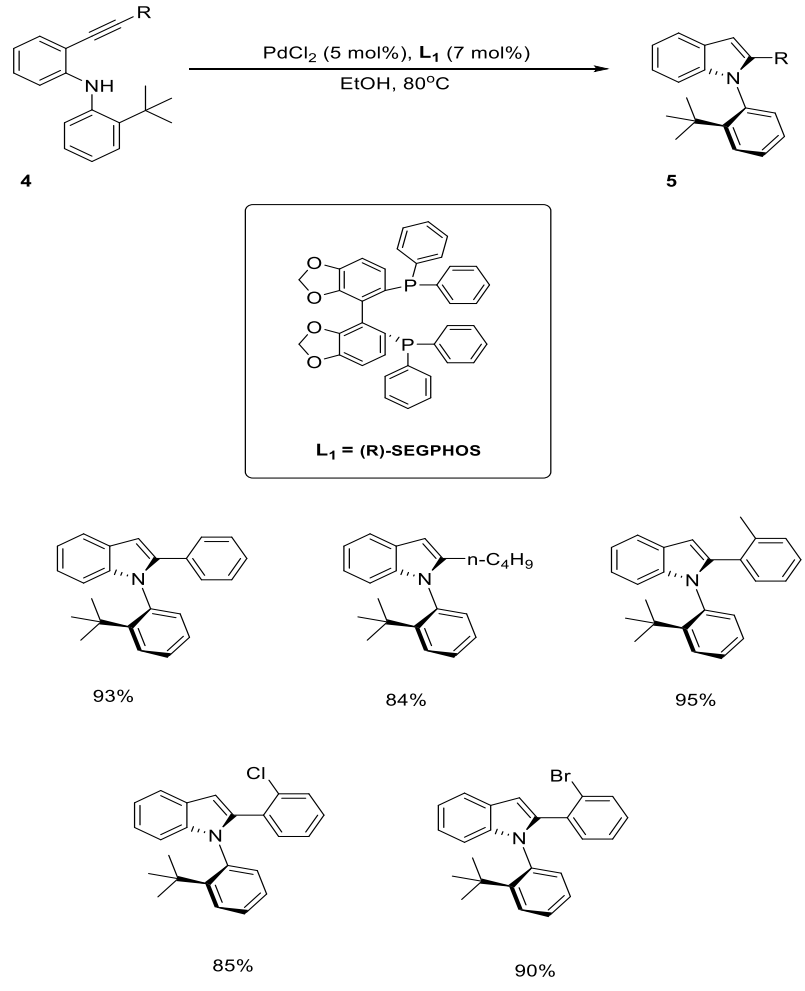
Scheme 1. Synthesis of N-substituted indoles via intramolecular cyclization of ketoxime.

They also reported the formation of the 3-chloroindoles (**3**) by simply adding $CuCl_2$ to the reaction via the following steps: Beckmann rearrangement/intramolecular cyclization/halogenation process (Scheme 2) [86].

Atropisomeric compounds having a chiral N-C axis gained excessive attention as innovative chiral molecules over recent years [87–105]. They are also considered important in the field of advanced organic enantioselective catalytic preparation of the innovative compounds having a chiral Nitrogen-Carbon axis [106–126]. In 2010, Ototake and coworkers stated that the reaction utilizing basic reagents or transition-metal catalysts has been reported as an effective method for constructing indole nuclei [107,127–130]. They firstly synthesized optically active atropisomeric compounds, N-(*o*-tert-butyl phenyl)indole derivatives (**5**) by palladium-catalyzed asymmetric 5-endo-hydroamino cyclization of the achiral N-(*o*-tert-butylphenyl)-2-alkynylanilines (**4**), affording approximately 83% (ee) product (Scheme 3) [131].

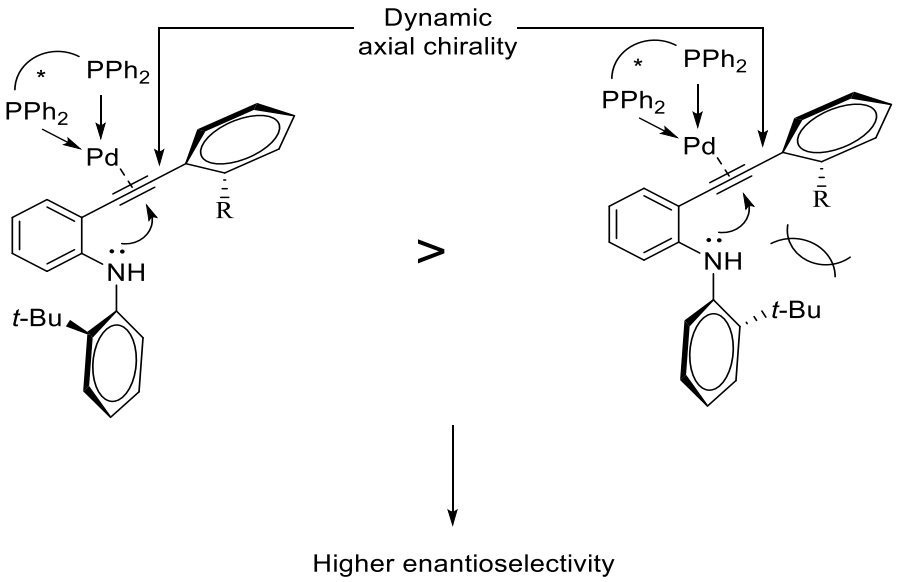


Scheme 2. Synthesis of 3-chloroindoles from ketoxime.



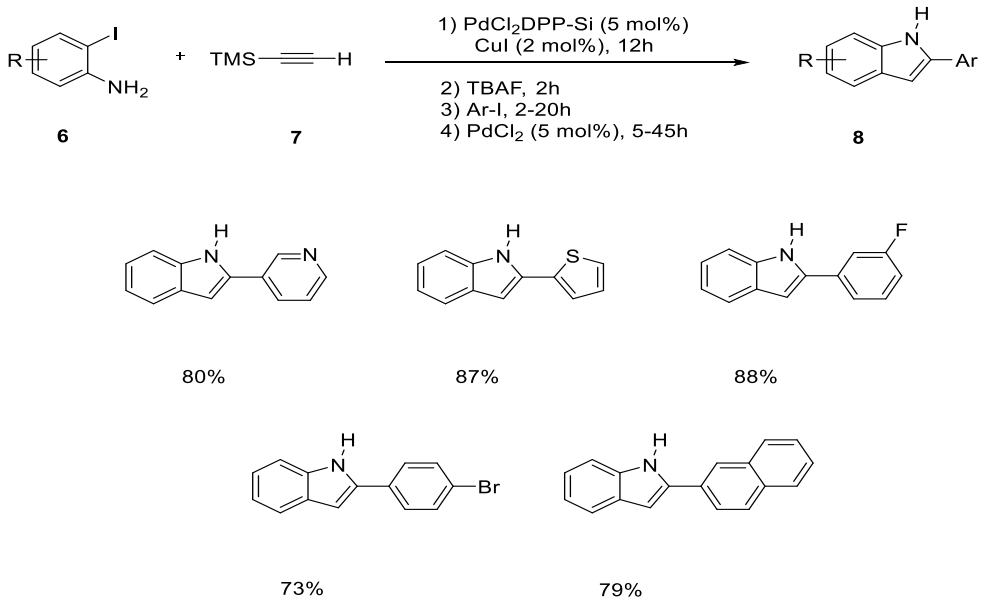
Scheme 3. Synthesis of N-(*o*-tert-butyl phenyl)indoles via intermolecular cyclization of N-(*o*-tert-butylphenyl)-2-alkynylanilines.

It was concluded that enantioselectivity was highly influenced by the electronic crowding in the aryl ethynyl group as well as by the bulkiness of substituents at the ortho position because of the dynamic axial chirality developed by aryl substituent's twisting (Scheme 4) [132].

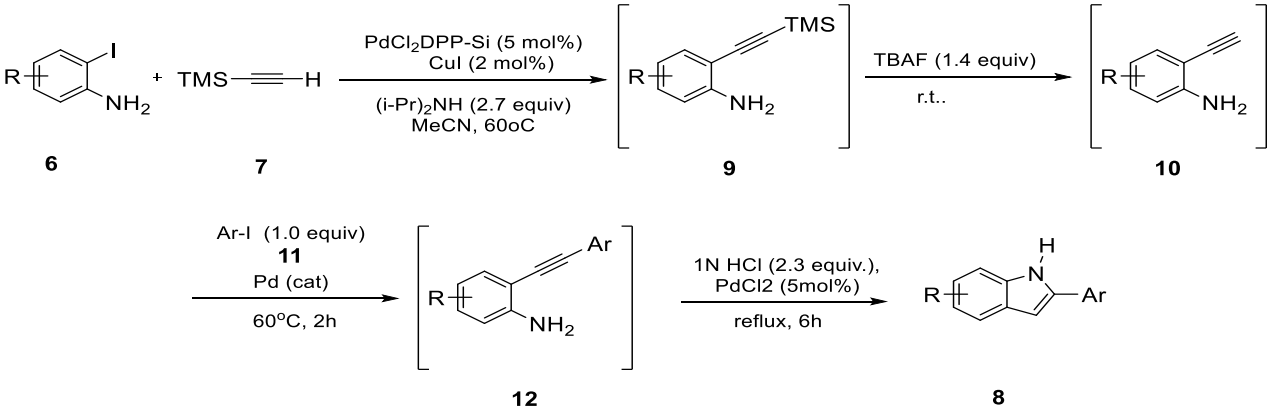


Scheme 4. Effect of electronic crowding and bulkiness on the enantioselectivity.

Due to having unique and effective biological properties and being the essential building element of the many naturally occurring compounds, the reaction for constructing an indole nucleus has gained much attention [127,128]. Currently, one-pot synthesis involving multiple steps have gained attention because of the economic and environmental benefits. The classical separation as well as isolation of the required products needed in every step has been avoided. In 2008, Sakai et al. used one-pot, four-step synthesis for constructing arylated indoles (**8**), utilizing homogeneous as well as heterogeneous solid-supported Pd-catalysts and reagents (Scheme 5). Such a method of using a combination of reagents and two-phase catalysts increased the yield dramatically. The reaction mechanism was initiated with 2-[(trimethyl)ethynyl]aniline (**9**) formation via Sonogashira coupling of trimethylsilylacetylene (**7**) with 2-iodoaniline (**6**). The second step afforded ethynylaniline (**10**) by desilylation. Then, the compound (**10**) in the next step underwent Sonogashira coupling with an aromatic iodide (**11**) to introduce a new functional group in the alkynyl moiety at the terminal position. Lastly, the coupled product (**12**) was cyclized to yield the indole (**8**) (Scheme 6). The combination of $PdCl_2$ and silica-supported Pd-catalyst yielded the best results, in contrast to $PdCl_2(PPh_3)_2$ and all the other heterogeneous catalysts not involving a silica-supported Pd-catalyst. Thus, such results provided a true picture of the potency of using a combination of homogeneous and heterogeneous palladium catalysts [133].

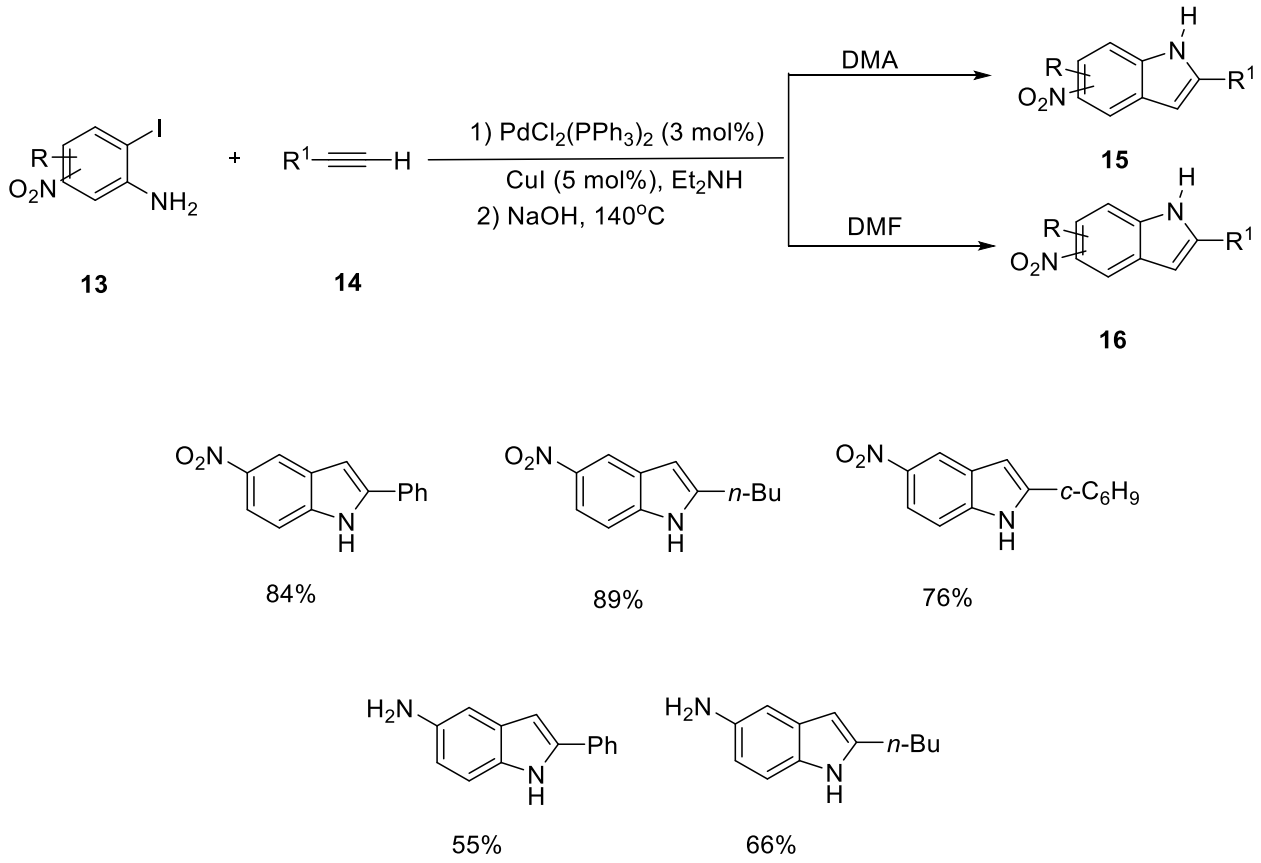


Scheme 5. Synthesis of arylated indoles via Sonogashira cross-coupling.



Scheme 6. The plausible mechanism for the synthesis of arylated indoles involving Sonogashira coupling.

For current interest, indoles having nitrogen substituents over the benzenoid ring are usually found to have biological activities, so there is an urge to develop new methodologies that allow the synthesis of indole-containing nitrogen substituents [134–137]. In 2009, Sanz and co-workers synthesized different derivatives of 2-substituted-nitroindoles from commercially available 2-haloanilines or 2-amino-nitrophenols by cross-coupling hetero-annulation methodology. They reported the synthesis of 2-substituted indoles by treating terminal alkynes (**14**) with 2-haloanilines (**13**), involving 5-endo-dig cyclization in the presence of NaOH. They synthesized 2-substituted indoles having a nitro or an amino substituent selectively on the C–5, C–6, or C–7 position. The desired product formation was accomplished by utilizing different solvents; with DMA, NO_2-indole derivatives (**15**) were obtained effectively, whereas choosing DMF resulted in NH_2-indole derivatives (**16**) selectively (Scheme 7). When DMF was used as a solvent in situ, a derivative of ammonium formate was produced, which acted as a hydrogen source in the presence of palladium salt [138].

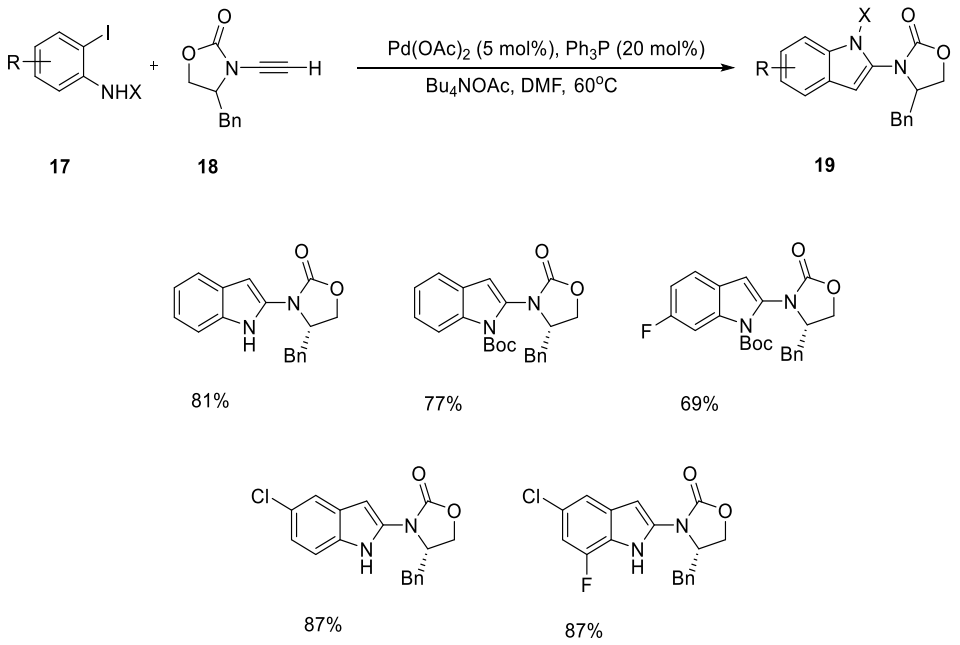


Scheme 7. Synthesis of nitroindoles and aminoindoles via intermolecular cyclization from terminal alkynes and 2-haloanilines.

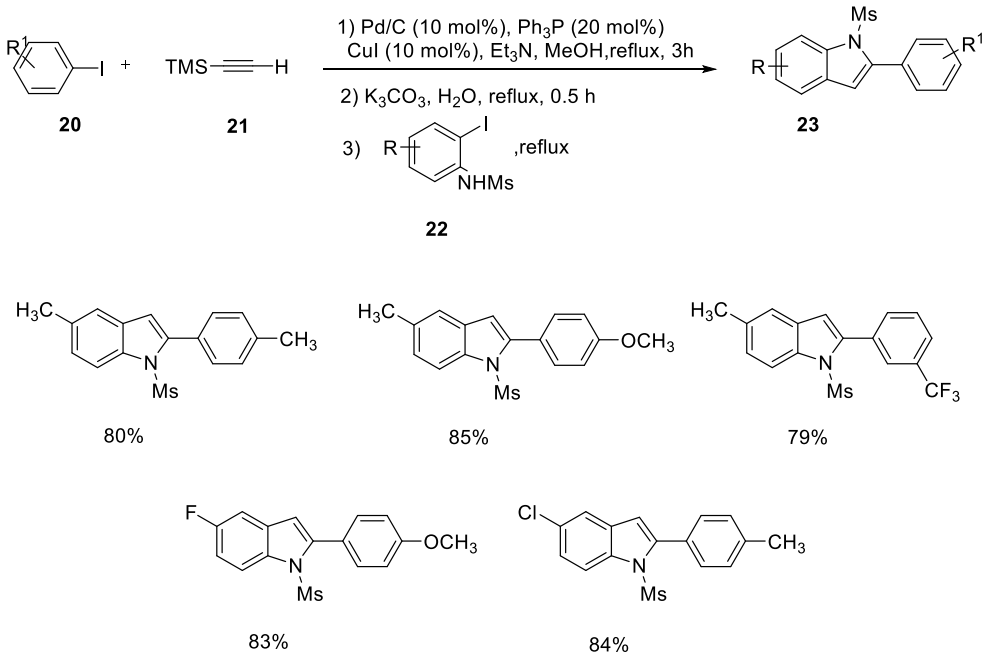
Reactions catalyzed by transition metal have gained an advantage over classical methods for indole synthesis due to their efficient tolerance of functional groups and greater structural diversity [127,139–146]. A viable approach for the synthesis of indole nuclei is a two-step methodology involving a Sonogashira cross-coupling reaction of *o*-halo aniline, followed by the nucleophilic addition of an amine to triple bond. Though the cyclization reaction can proceed on its own, it often needs the assistance of heteroatom to become more nucleophilic, formed either via deprotonation [147,148] or via Lewis acid or metal activation of the alkyne moiety [149–153]. In 2008, Dooleweerdt and co-workers synthesized 2-aminoindoles (**19**) by one-pot, two-step reaction catalyzed by palladium between ortho-iodoanilines (**17**) and ynamides (**18**) (Scheme 8). The reaction mechanism involved a Sonogashira reaction to form a C–C bond. Then, the triple bond spontaneously underwent hydroamination, intramolecularly generating a C–N bond and providing yields up to 87%. In some of the cases, ortho-iodoanilines with electron-withdrawing substituents provided a relatively poor yield of the product, which was due to the reduced nucleophilicity of aniline NH_2 in the step of hydroamination. In comparison with other solvent alternatives, DMF provided the best yield. Additionally, $Pd(dba)_2$ can be used instead of palladium acetate without affecting the yield of indole [140].

In 2011, Rao and colleagues synthesized 2-(hetero)aryl-substituted indoles (**23**) via Pd/C–Cu catalysis involving a cross-coupling reaction. In this reaction, firstly, a coupling reaction between iodoarenes (**20**) and (trimethylsilyl)acetylene (**21**) using Pd/C–CuI–PPh3, Et_3N in CH_3OH took place. Then, the reaction mixture was treated by K_2CO_3 in H_2O/CH_3OH and, lastly, coupled with *o*-iodoanilides (**22**), affording the desired indole derivatives (**23**) (Scheme 9). Here, they utilized K_2CO_3 as a base for desilylation in the presence of $CH_3OH–H_2O$. The reaction mechanism involved the following sequential steps: (i) carbon-carbon coupling reaction followed by (ii) carbon-silicone bond fission followed by (iii) carbon-carbon and (iv) carbon-nitrogen bond formation in a one-pot reaction. The

reaction required only 10% Pd/C–CuI/PPh_3 for a better yield. On the exclusion of any constituent in 10 mol% of the Pd/C–PPh_3–CuI catalytic system, the desired product's yield was decreased. Iodoarene rings having either electron-withdrawing substituents, e.g., $–CF_3$ and $–CO_2Et$, or electron-donation substitutes, e.g., –Me, –OMe, –OH, $–NH_2$, were successfully tolerated in this reaction [154].



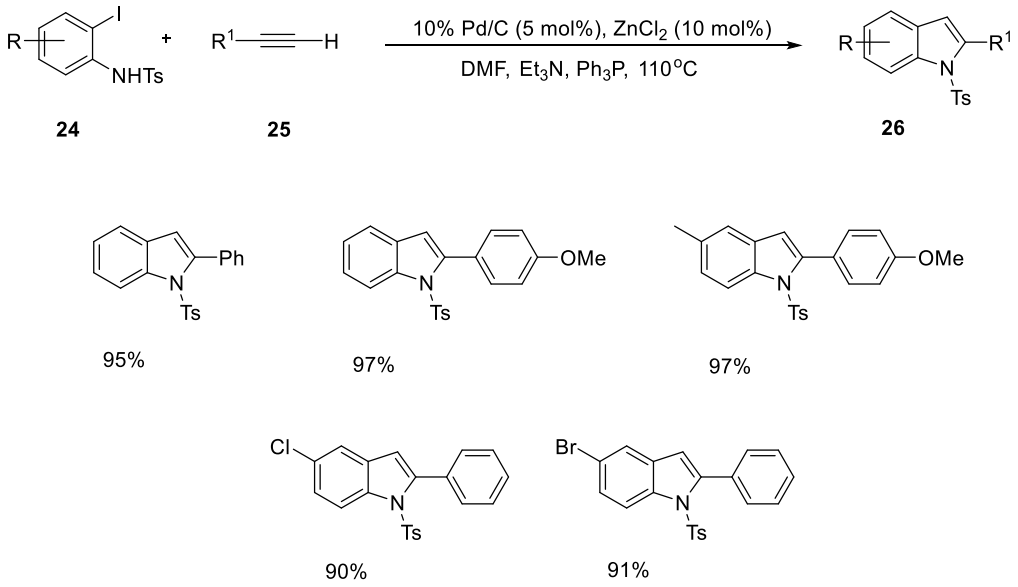
Scheme 8. Synthesis of 2-aminoindoles involving Sonogashira cross-coupling of *o*-iodoanilines and ynamides.



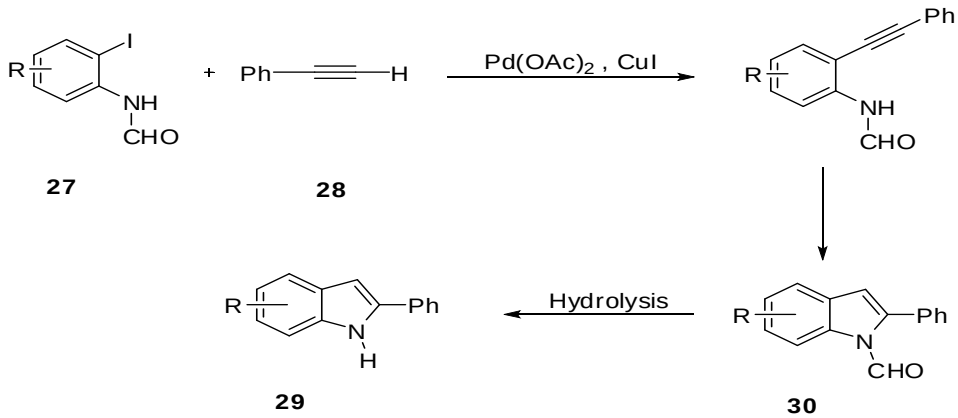
Scheme 9. One-pot synthesis of 2-(hetero)aryl-substituted indoles.

The 2-substituted indoles were synthesized in the presence of economic $ZiCl_2$ that acted as a co-catalyst instead of CuI in the Pd-catalyzed Sonogashira cross-coupling/cyclization. The reactants used in this reaction were terminal alkynes and N-tosyl-2-iodoanilines. In this reaction, terminal alkynes (**25**) were heated with 2-iodoanilines (**24**) using 10% Pd/C,

Et_3N, PPh_3, and moist $ZnCl_2$ at 110 °C in dry DMF for 3 h to afford N-protected indoles (**26**) in higher yields (Scheme 10). At room temperature, the reaction was unable to yield any desired product; while at 110 °C, the desired indole was obtained in a minor quantity together with di-yne produced predominantly by homocoupling of the alkyne. However, after utilizing moist $ZnCl_2$, the only product that was formed was the desired indole without yielding any by-product of homocoupling [155]. Furthermore, they synthesized N-unsubstituted indoles by employing N-formamide-2-iodoanilines rather than N-tosyl-2-iodoanilines. For this reaction, N-(2-iodoaryl)formamides (**27**) were treated with phenylacetylene (**28**) (terminal alkynes) in Pd-catalyzed cross-coupling/cyclization, yielding corresponding indoles (**29**) via an intramolecular cascade C–C/C–N bond generation (Scheme 11). The formamides having electron-donating groups or poor electron-withdrawing groups afforded the desired product in less than 1.5 h in a high yield. In the case of formamides bearing strong electron-withdrawing substituents, a long reaction time was required with the decrease in the yield of the desired product. The reaction was performed by the following sequential steps: Sonogashira cross-coupling, followed by the formation of the intramolecular C–N bond using the exact catalytic system, affording the intermediate substance (**30**), after which hydrolysis afforded the indole derivatives (**29**) (Scheme 11) [156].

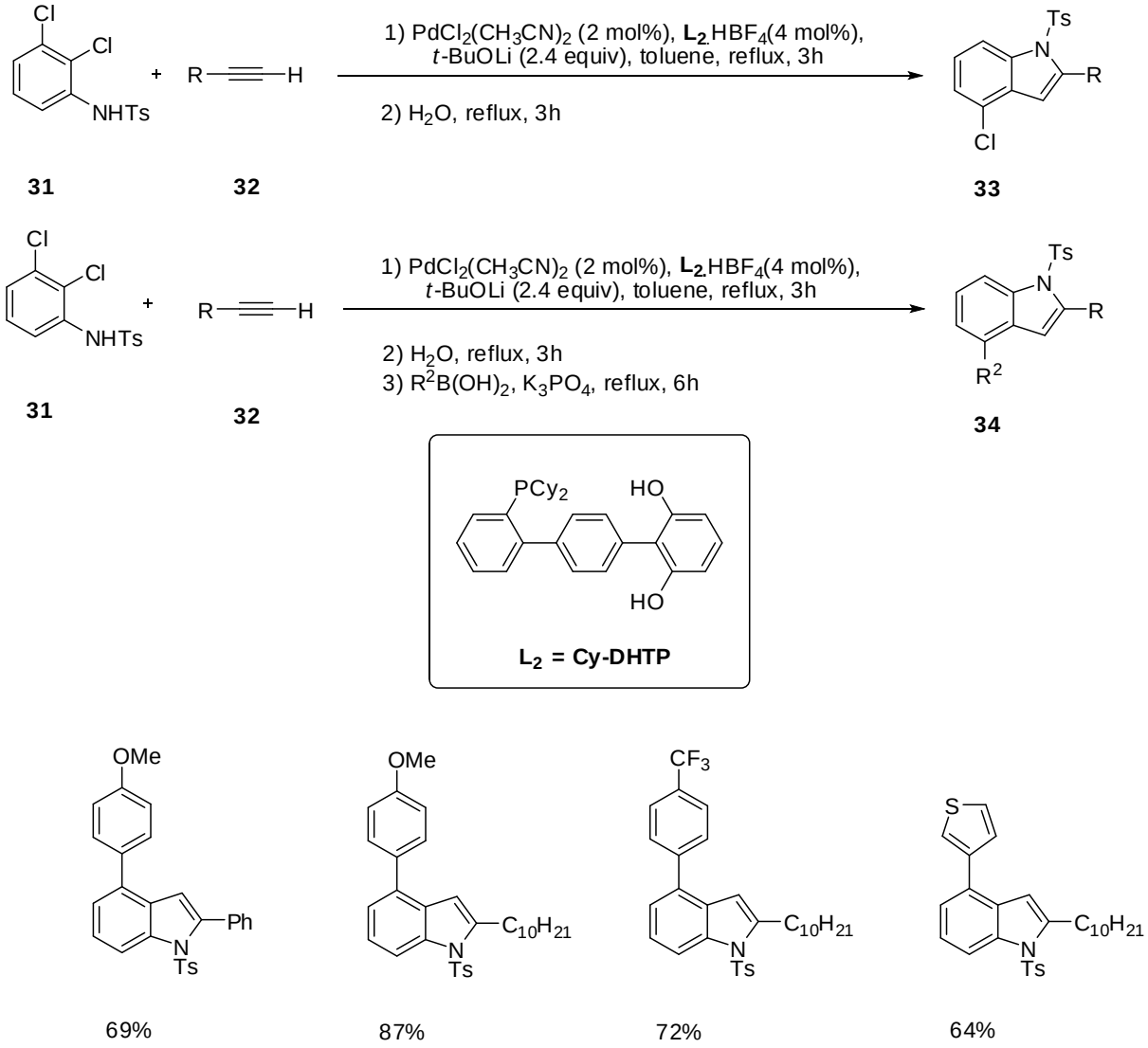


Scheme 10. Synthesis of N-protected 2-substituted indoles via intramolecular cyclization of terminal alkynes and 2-iodoanilines.



Scheme 11. Synthesis of indoles via intramolecular cyclization of terminal alkynes and N-formamide-2-iodoanilines.

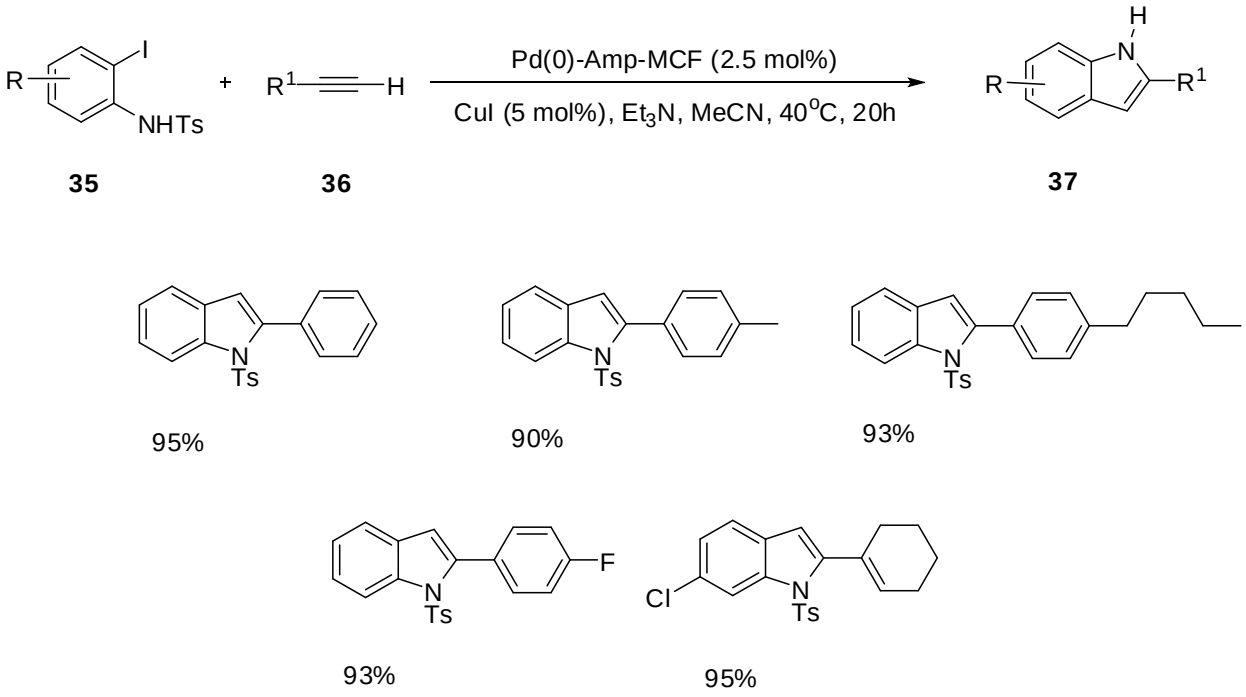
In 2014, Yamaguchi and Manabe synthesized 4-Chloroindoles (**33**) by reacting derivatives of 2,3-dichloroaniline (**31**) with terminal alkynes (**32**) using a catalyst made up of palladium and dicyclohexyl-(dihydroxy terphenyl)phosphine (Cy-DHTP)(**L_2**) (Scheme 12). This catalyst carried out the reaction selectively at the ortho-position involving Sonogashira cross-coupling followed by subsequent cyclization to produce 4-chloroindoles providing high yields. On the contrary, adding the boronic acid to the same reaction conditions yielded 2,4-disubstituted indoles (**34**) by a single-pot reaction involving a Sonogashira cross-coupling reaction followed by subsequent cyclization and a Suzuki–Miyaura reaction (Scheme 12). The Cy-DHTP (**L_2**) provided better results for cross-coupling at ortho-position selectively than Cy-HTP. By increasing the quantity of alkyne, the yield was improved. This reaction did not yield any product by Sonogashira cross-coupling at the meta-chloro substituents because the Sonogashira cross-coupling occurred selectively at the ortho-chloro substituents. These results proved that the Pd-catalyst has potential to increase the reaction rate even in the case of sterically hindered and electronically inactive positions [157].



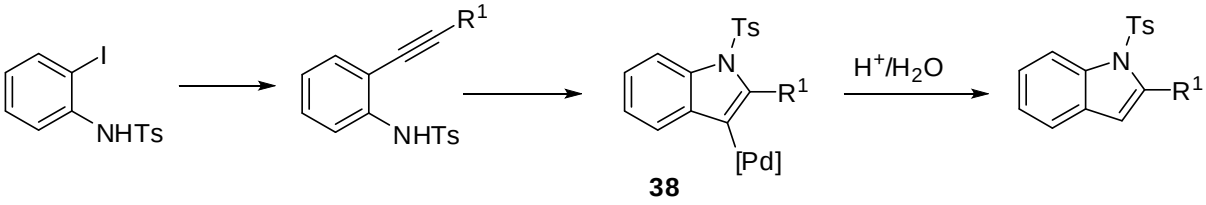
Scheme 12. One-pot synthesis of 4-Chloroindoles and 2,4-disubstituted indoles.

In 2017, Bruneau and co-workers synthesized indoles (**37**) by employing a heterogeneous catalytic system while reacting *o*-iodoanilines (**35**) with terminal alkynes (**36**) (Scheme 13). The catalytic system was composed of nanoparticles of palladium supported on (Pd^0 –AmP–MCF), the siliceous meso-cellular foam. The presence of water even in

a small amount affected the transformation. Moreover, the water increased the yield of indole by accelerating the hydrolysis of vinyl Pd-intermediate (**38**), which was involved in this annulation process (Scheme 14). Under mild reaction conditions, this catalytic protocol enabled good to excellent yields of the desired products without adding any ligand [158].



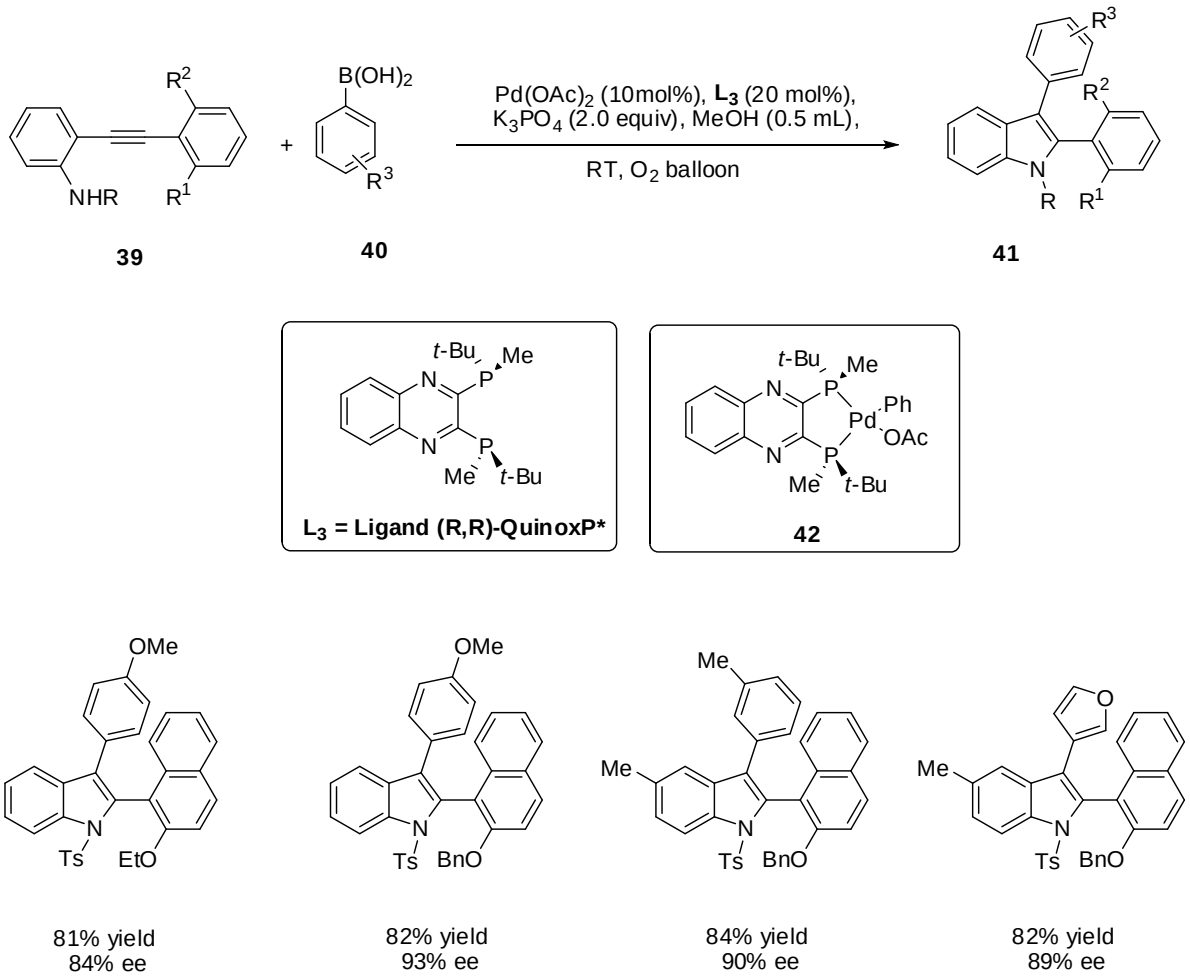
Scheme 13. N-free Indole synthesis via nanoparticles of palladium.



Scheme 14. Hydrolysis of vinyl Pd-intermediate.

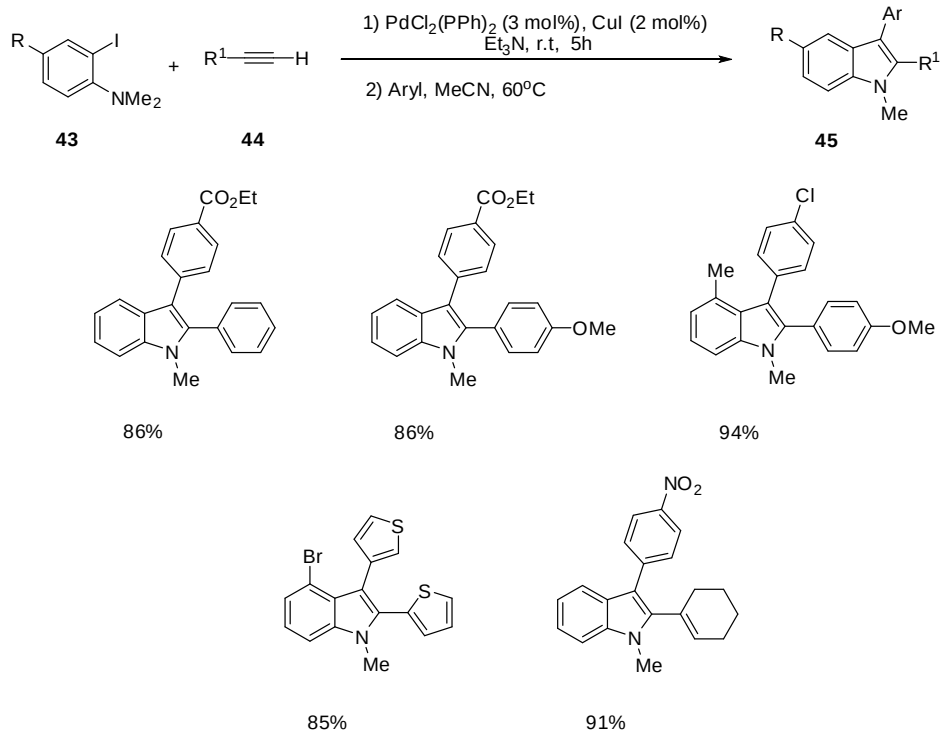
2.2. Indole Synthesis via Cascade Reaction

In 2020, He and colleagues synthesized highly enantioselective 2,3-disubstituted indoles (ee) (**41**) via a Pd-catalyzed Cacchi reaction between N-aryl(alkyl)sulfonyl-2-alkynylanilides (**39**) and aryl boronic acid (**40**). The optimized reaction conditions for the reaction involved $Pd(OAc)_2$ in a catalytic amount, ligand (R,R)-QuinoxP*(**L$_3$**), and the base K_3PO_4 in the presence of solvent MeOH under an O_2 atmosphere (Scheme 15). The experimental studies suggested that the trans-metallation occurred before the amino-palladation in the aryl annulation process. The ligand (**L$_3$**) and PdPh(OAc) complex (**42**) was the vital intermediate in the synthesis. The reaction was remarkably influenced by the size as well as the nature of –OR substituent on the naphthyl moiety, and the presence of -OBn afforded the best results. Aryl boronic acid having electron-donating or electron-withdrawing substituents underwent the reaction smoothly, affording a good to high yield. This reaction also tolerated the presence of many groups as well as heterocyclic substituents such as furan, indole, and quinoline on *o*-alkynylanilines. Ligand (R,R)-QuinoxP* (**L$_3$**) and methanol provided the best results [159].

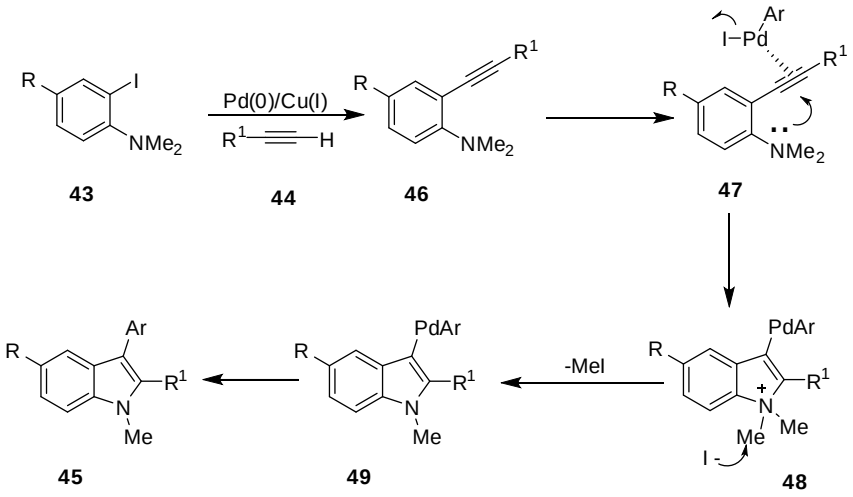


Scheme 15. Synthesis of 2,3-disubstituted indoles by Cacchi reaction.

Larock and co-workers synthesized indoles (**45**) via a one-pot reaction by using microwave radiation and employing three components in this coupling reaction. The reaction involved two steps under Sonogashira cross-coupling standard-reaction conditions. Firstly, N-substituted/N,N-disubstituted 2-iodoaniline (**43**) was treated with terminal alkynes (**44**), followed by the addition of aryl iodide (Ar-I) and acetonitrile (CH_3–CN) (Scheme 16). Mechanistic studies revealed that the first step generated N,N-dialkyl-2-(1-alkynyl)aniline (**46**) via Sonogashira cross-coupling. Then, the aryl iodide was added oxidatively to the $Pd^{(0)}$ which was transformed to an electrophilic Ar-PdI species, which later carried out the activation of the triple bond in alkyne (**46**) of N,N-dialkyl-2-(1-alkynyl)aniline by coordination for forming a pie-palladium complex (**47**). After that, it underwent intramolecular trans-aminopalladation by the 5-endo-dig cyclization, yielding the indolium species (**48**), which then removes a methyl group via the SN_2 mechanism after the iodide anion attack in situ and yielded the indole-Pd(II) intermediate (**49**). Then, after reductive elimination, the 2,3-disubstituted indole derivative was acquired (Scheme 17) [160].

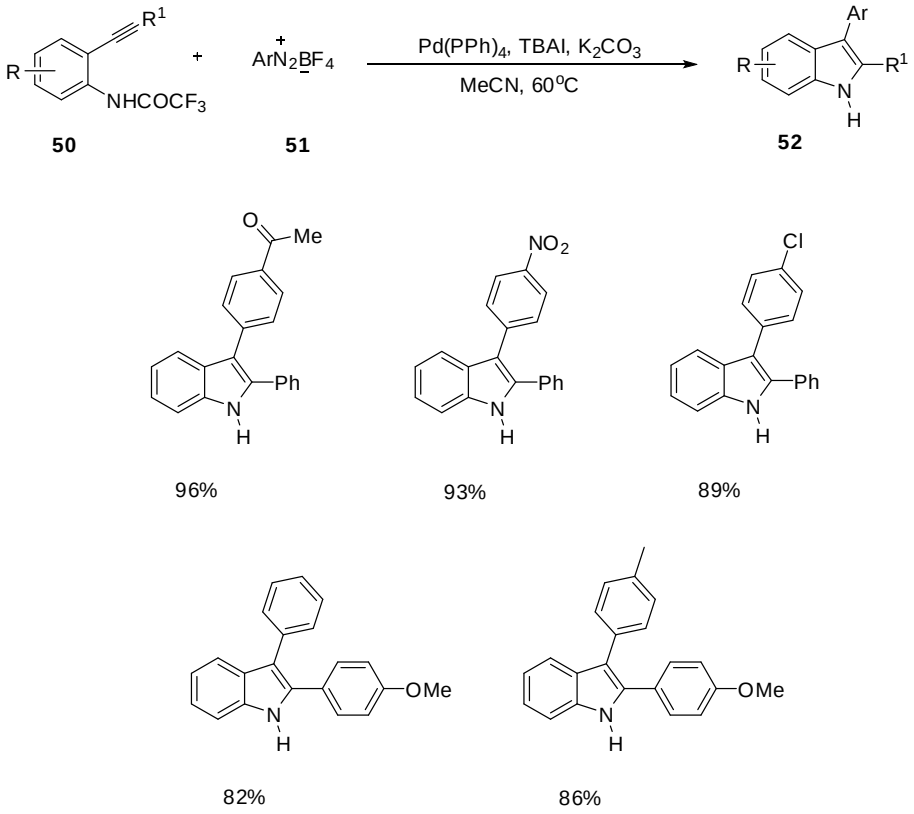


Scheme 16. Synthesis of N-methylated indoles in one-pot reaction under microwave radiation.

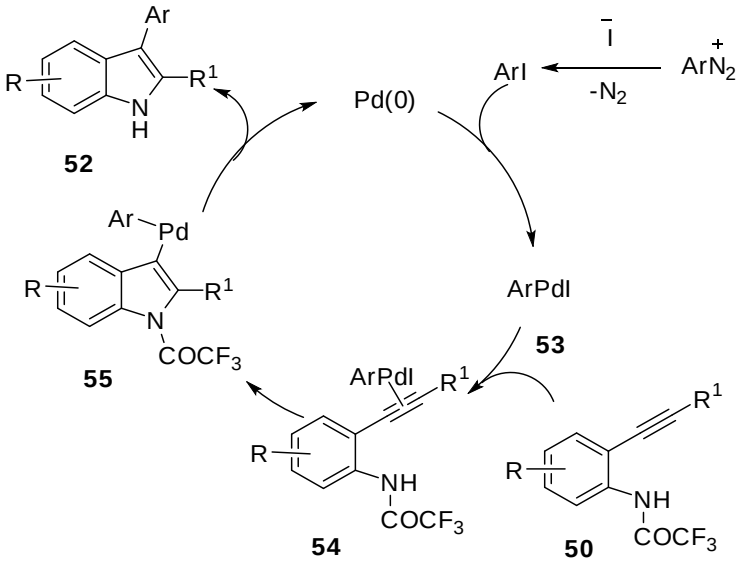


Scheme 17. Possible mechanism for synthesis of N-methylated indoles.

In 2010, Cacchi and co-workers synthesized novel N-H free 2,3-disubstituted indoles (**52**) by reacting 2-alkynyltrifluoro acetanilides (**50**) and arene diazonium tetrafluoroborates (**51**) in the presence of a Pd-catalyst (Scheme 18). The reaction followed the domino process that was started by reacting iodo-dediazoniation with TBAI to form aryl iodide in situ. The aryl iodide was added oxidatively to the $Pd^{(0)}$, affording a sigma-arylpalladium iodide (**53**) which coordinated with the carbon–carbon triple bond to form a π-alkyne-sigma-arylpalladium complex (**54**). This step was followed by intramolecular amino-palladation that yielded a sigma-indolylpalladium intermediate (**55**), which later afforded the desired N-H free indole (**52**) by reductive elimination and hydrolysis (Scheme 19). It was found that the reaction tolerated a variety of the substituents in arene diazonium salt as well as an alkyne, such as halo and cyano, ether, keto, $–NO_2$, –Me, and –OMe substituents as well as other ortho substituents [161].

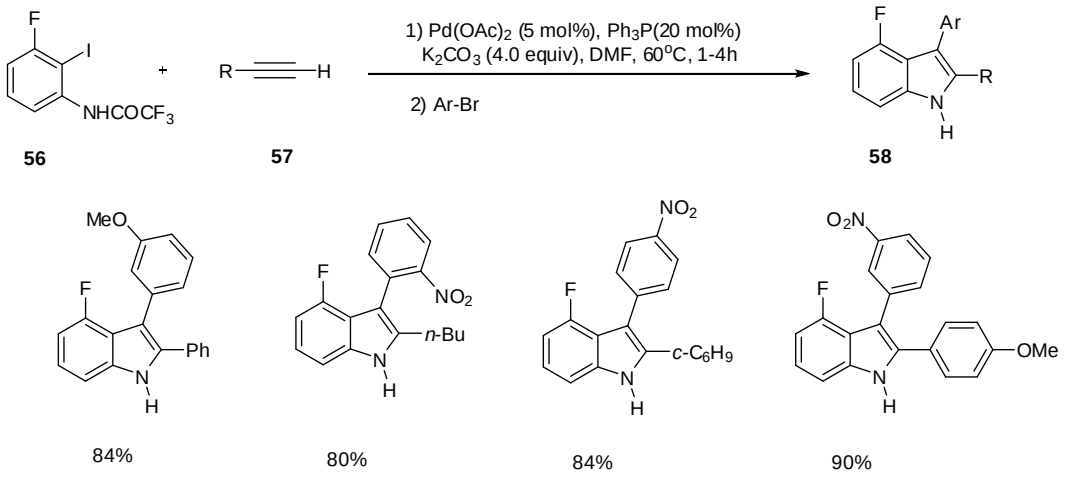


Scheme 18. Synthesis of N-free 2,3-disubstituted indoles using 2-alkynyltrifluoro acetanilides and arene diazonium tetrafluoroborates.



Scheme 19. The domino process for synthesizing N-free 2,3-disubstituted indoles.

Cacchi and colleagues synthesized 3-aryl-4-fluoro-2-substituted-1H-indoles (**58**) regioselectively by using the 3-fluoro-2-iodotrifluoro acetanilide (**56**), terminal alkynes (**57**), and aryl bromide in a single-pot via a cascade Sonogashira-Cacchi reaction (Scheme 20). The results showed that the yields of indole formation were good when using an inorganic base, e.g., Cs_2CO_3 and K_2CO_3. However, the cyclization was better in the presence of a base such as Et_3N in a microwave-irradiated process [162].

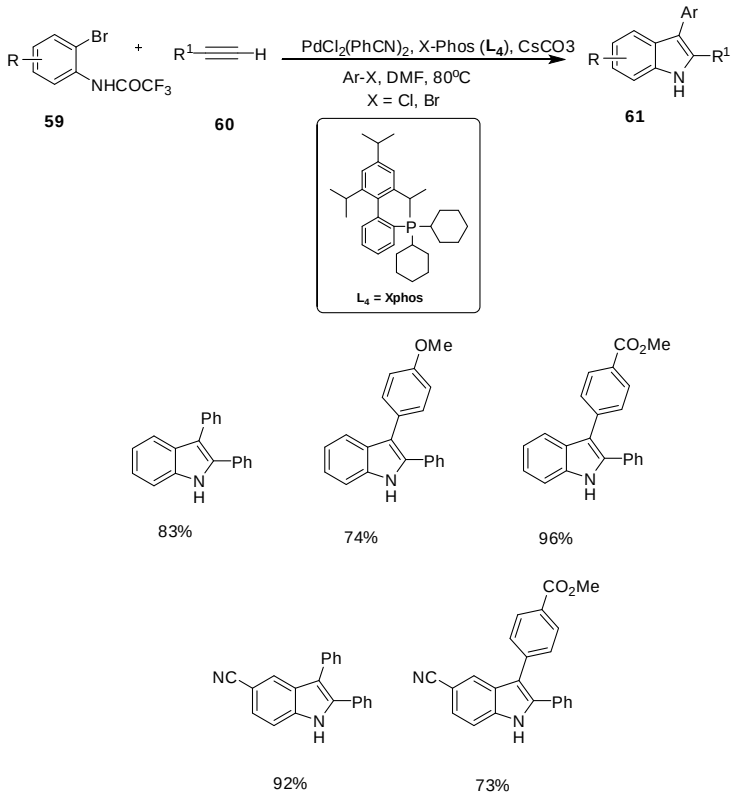


Scheme 20. Synthesis of 3-aryl-4-fluoro-2-substituted-1H-indoles via cascade Sonogashira-Cacchi reaction.

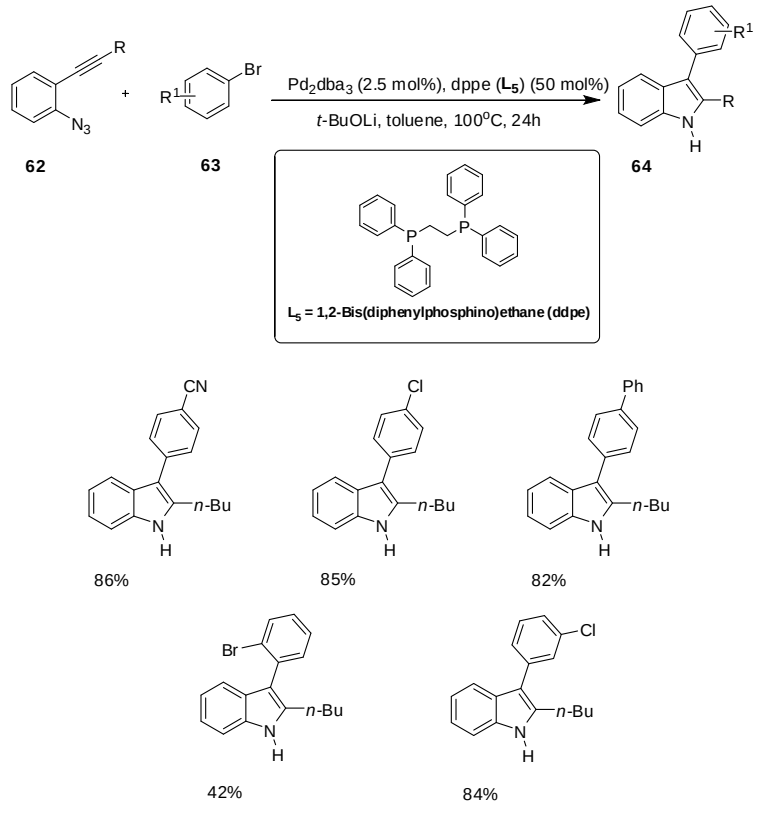
In 2013, Lu and colleagues extended the Cacchi aminopalladation/reductive elimination sequential reaction mechanism by utilizing 2-bromoanilides (**59**) for obtaining 2,3-disubstituted indoles (**61**) instead of corresponding iodides (Scheme 21). They proposed a one-pot reaction involving three components that were found to have one major drawback: the low active and sterically hindered 2-bromo or 2-chloro anilides required harsh reaction conditions for Sonogashira cross-coupling. Thus, the harsh conditions resulted in unwanted intramolecular hydroamidation taking place in the primarily obtained *o*-alkynylanilides without incorporating the aryl group at position-2 of the indole ring. The results suggested that to minimize the formation of hydroamidation in the Sonogashira coupling, the use of a strong base, copper salt as a co-catalyst, and high temperature must be avoided. The Sonogashira cross-coupling reaction proceeded effectively in both NMP and acetonitrile, although the Cacchi cyclization was affected badly in these solvents. The reaction did not proceed in the case of toluene because the base was poorly soluble. It is worth noting that three equivalents of the base Cs_2CO_3 were used during the complete reaction. Moreover, Cacchi cyclization was not completed with the 2.2 equivalent of the base [163].

Zhou and co-workers synthesized various derivatives of 2-aryl indoles (**64**) by reacting aryl bromides (**63**) and 2-alkynyl aryl azides (**62**). They used dppe as a ligand with catalyst Pd_2dba_3 and base t-BuOLi at 100 °C using toluene as a solvent (Scheme 22). For the cyclization, the nucleophilic nitrogen was obtained in situ via the Staudinger reaction from azides [164]. The reaction proceeded via two different pathways. In the first path **A**, aryl bromide (**65**) was added oxidatively to catalyst $Pd^{(0)}$, affording an aryl palladium (II) species (**68**). The 2-alkynyl aryl azide (**62**) imino phosphorane (**69**) were generated in situ by the Staudinger reaction. Then, the intermediate (**70**) was obtained by 5-endo-dig cyclization. Nitrogen acted as a nucleophile and attacked the phosphinimine moiety, present in the aryl palladium (II)-activated triple bond. Later, intermediate (**70**) was converted to intermediate (**75**) by reductive elimination which, after hydrolysis, afforded the product (**66**). The alternative mechanism path **B** involved the carbene species. The Palladium (II) carbene species (**72**) was generated by the palladium intermediate (**70**) via electron's back donation. Then, intermediate (**73**) was formed by subsequent migratory insertion, which afforded intermediate (**74**) by isomerization. The product (**66**) was formed after protonating the intermediate (**74**) and $Pd^{(II)}$ was reduced to $Pd^{(0)}$ by (**71**) (Scheme 23). The yield of the reaction was found to be increased by loading more dppe and Pd_2dba_3. The results concluded that dppe did not solely act as the ligand but also carried out other crucial roles in the transformation. The product yield was sharply reduced by decreased loading of dppe; on the other hand, the decreased loading of Pd_2dba_3 did not affect the yield. Furthermore, the base was found to be necessary for the reaction. The aryl bromides having meta and para substitutions afforded good yields of the required product except in the case of the *p*-CO_2Me substituted bromide. The yield was low in the case of ortho

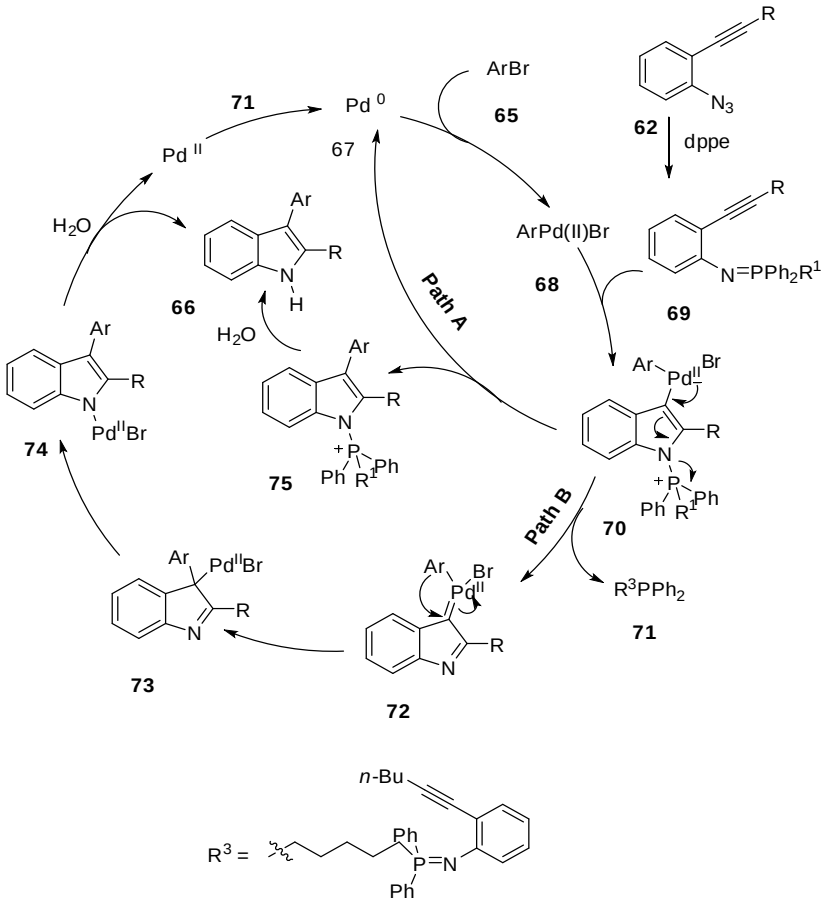
substitution at aryl bromide. Furthermore, the reaction with the azide substrate having an aryl substituent also produced the desired product in a moderate to good yield [165].



Scheme 21. Synthesis of 2,3-disubstituted indoles by Cacchi aminopalladation/reductive elimination.

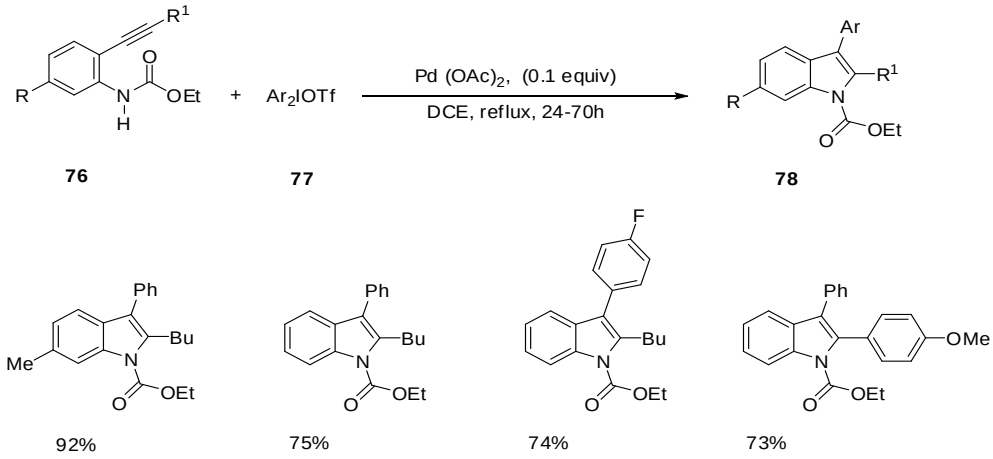


Scheme 22. Synthesis of 2-aryl indoles from aryl bromides and 2-alkynyl aryl azides.



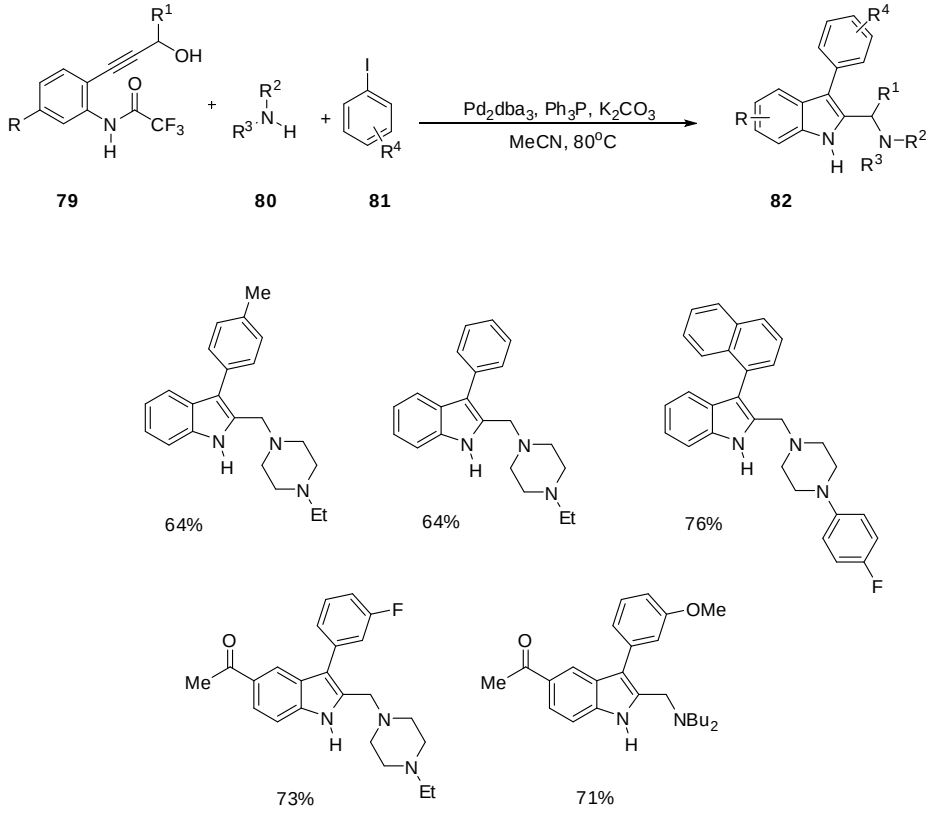
Scheme 23. Plausible annulation paths in the synthesis of 2-aryl indoles.

In 2016, Minami et al. used another sort of amino-palladation/reductive elimination reaction involving the palladium-catalyzed regioselective 5-endo-dig ring-closing reaction between 2-alkynyl phenyl carbamates (**76**) and diaryliodonium salts (**77**), resulting in C-arylated 2,3-disubstituted indoles (**78**) (Scheme 24). This reaction involved the generation of palladium (II) intermediate by the reacting diaryliodonium salts with palladium, which acted as an arylating agent by activating the C≡C. The DCE solvent was found to be the best solvent for this reaction, providing maximum yields [166].



Scheme 24. Synthesis of arylated 2,3-disubstituted indoles by intermolecular cyclization.

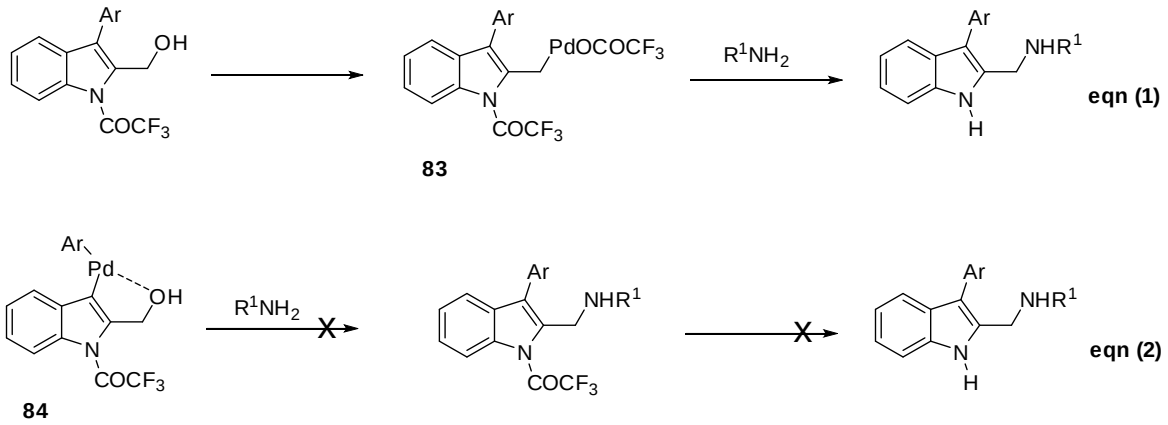
Moreover, Cacchi reported that the three-component synthesis of 2-(aminomethyl)-3-arylindoles (**82**) was catalyzed by palladium. The reaction was carried out between aryl iodides (**81**), amines (**80**) and 3-(ortho-trifluoro acetamide-*o*-aryl)-1-propargyl alcohols (**79**) by a simple a one-pot procedure affording two carbon-nitrogen bonds and one carbon-carbon bond (Scheme 25). The mechanistic studies suggested the formation of trifluoroacetyl ester in the reaction medium. It is also believed that palladium intermediate (**83**) formation is the key step in cyclization. The formation of intermediate was carried by the nucleophilic intramolecular attack of nitrogen on the activated C≡C. The activation of C≡C was performed by $Pd^{(II)}$ moiety generated in situ (Scheme 26, **eqn (1)**). Thus, this assumption rejected the formation of indole by the direct nucleophilic replacement of the -OH by amino group carried out via the palladium coordination to oxygen species (**84**) (Scheme 26, **eqn (2)**). The reaction required mild conditions and both substituted aryl iodide and propargylic alcohols at the propargylic carbon were suitable choices for this reaction. The reaction showed tolerance towards many substituents including chloro, bromo, keto, ether, ester, and cyano groups. Low yields were obtained using other phosphine ligands or Cs_2CO_3 as the base. The primary amines were not a suitable choice for the reaction because they involve inside reactions [167].



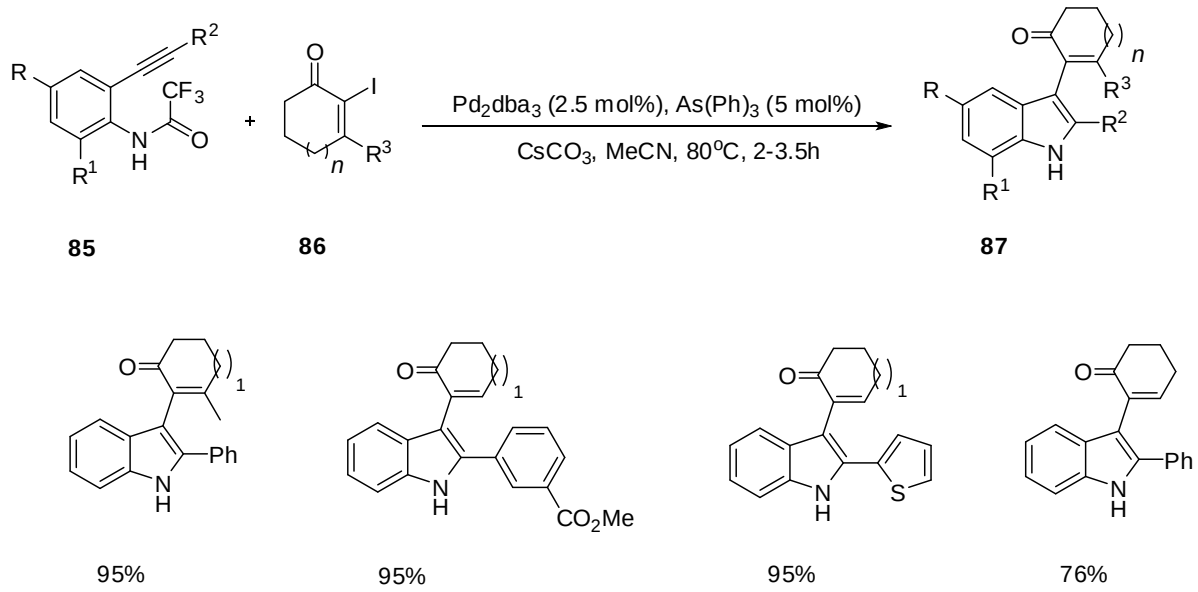
Scheme 25. Synthesis of 2-(aminomethyl)-3-arylindoles by one-pot three component reaction.

Vinyl halides were also used as a suitable electrophile instead of aryl halides for amino-palladation, followed by subsequent reductive elimination of $Pd^{(0)}$ to construct an indole nucleus. In 2010, Arcadi et al. utilized α-iodoenones (**86**) of different ring sizes as organic electrophiles in cyclizing 2-alkynyltrifluoro acetanilides (**85**) in the presence of palladium as a catalyst to obtain 2,3-disubstituted indoles (**87**) (Scheme 27). Among the various conditions tested, weak ligand $As(Ph)_3$ and a catalyst $Pd_2(dba)_3$ provided the best results, whereas $Pd_2(dba)_3$ was much more operative in the absence of a ligand. The K_2CO_3 can also be employed as a base instead of Cs_2CO_3, though slightly better results were obtained in the latter case. The reaction was found to be independent of the ring size

of the alpha-iodoenones. Moreover, various functional groups, e.g., keto, cyano, ester, and nitro, were tolerated under these reaction conditions [168].

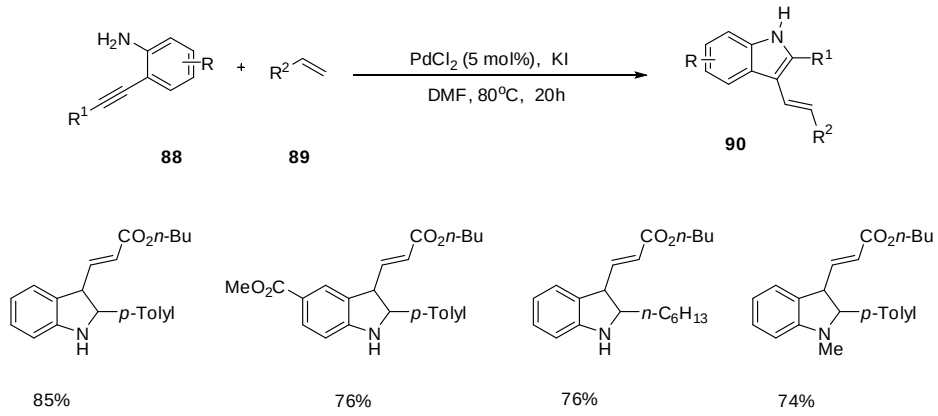


Scheme 26. Annulation of key intermediate in the synthesis of 2-(aminomethyl)-3-arylindoles.



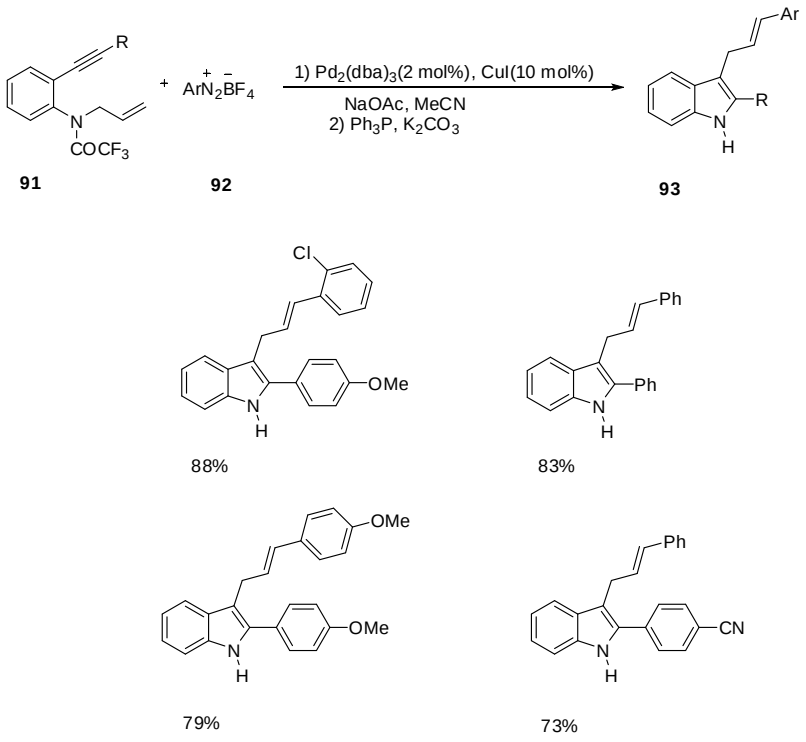
Scheme 27. Synthesis of 2,3-disubstituted indoles from α-iodoenones and 2-alkynyltrifluoro acetanilides.

The cascade intermolecular amino-palladation reactions subsequently followed by oxidative coupling were also carried out with alkenes, contrary to the halide (X) derivatives. In 2010, Alvarez and colleagues reported that structurally diverse C3-alkenylindoles (**90**) were efficiently prepared by using readily available *o*-iodosubstituted aniline, alkynes, and functionalized olefins. In the first step, 2-alkynylanilnes (**88**) were formed by Sonogashira cross-coupling between *o*-iodo substituted aniline and alkynes, then 2-alkynylanilnes (**88**) underwent cascade Pd-catalyzed hetero-cyclization/oxidative Heck cross-couplings with functionalized olefins (**89**), affording the desired C3-alkenylindoles (**90**) (Scheme 28). The 5-endo-dig-cyclization of N-heteronucleophiles occurred regioselectively, and subsequent stereo selectively Heck cross-coupling took place with any mono or disubstituted alkenes, affording mostly (*E*) isomers. Usually, substrates bearing different alkynyl substituents e.g., alkyl (–R) and aryl (–Ar) groups, either electron-rich or electron-poor, produced the desired indole in high yields. Anilines having the trimethylsilyl (TMS) group were not affected during the reaction [169].

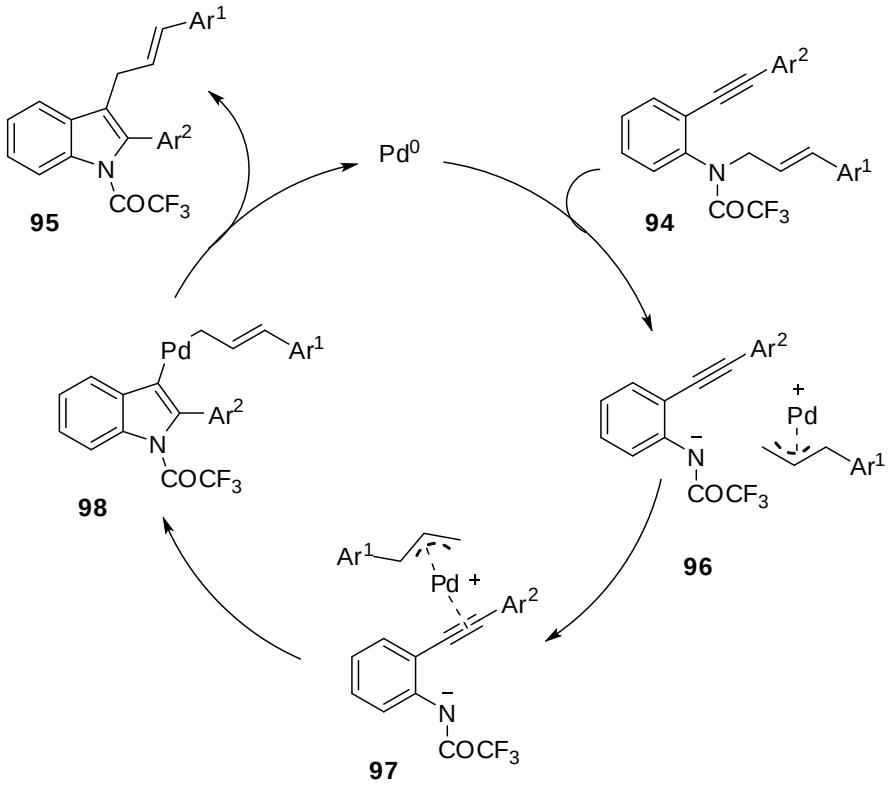


Scheme 28. Synthesis of C3-alkenylindoles by 5-endo-dig-cyclization.

In 2011, Cacchi and co-workers synthesized 2-alkenyl indoles (**93**) by palladium-catalyzed reactions between arene diazonium tetrafluoroborates (**92**) with 2-alkynyl-N-(allyl)trifluoro acetanilides (**91**) (Scheme 29). The reaction involved the following series of subsequent events: (a) Heck reaction, (b) amino-palladation, and (c) reductive elimination to yield the desired product. To carry out this reaction via the single-pot procedure, K_2CO_3 and PPh_3 were added to the crude reaction mixture obtained by the Heck reaction when MeCN was used as a solvent or after evaporating the volatile components from the crude reaction mixture when MeOH was used as a solvent and the temperature was elevated to 100 °C. The reaction mechanism is shown in (Scheme 30), which was involved the reaction of (**94**) with $Pd^{(0)}$ generating π –allylpalladium complex intermediate (**96**), then C≡C coordinated to Palladium and afforded (**97**). After that, a regioselective intermediate (**98**) was formed via intramolecular amino-palladation which, on subsequent reductive elimination, afforded the desired product (**95**) and the active Pd catalyst was regenerated after the cycle. This new methodology tolerated many useful substituents, e.g., –Cl, –Br, and –I, as well as other ortho substituents [170].



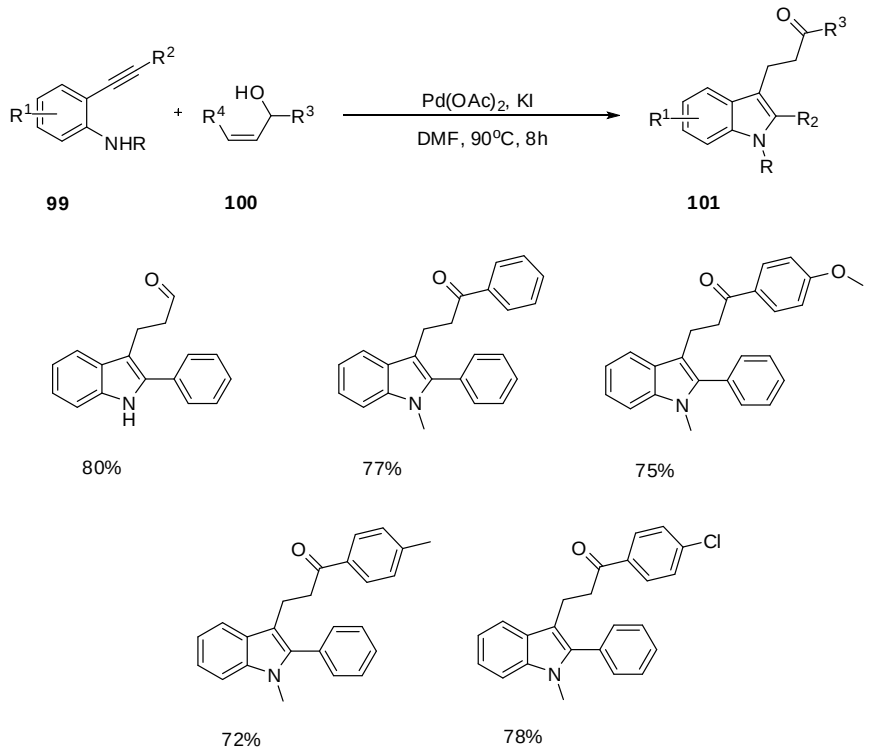
Scheme 29. Synthesis of 2-alkenyl indoles by Heck reaction.



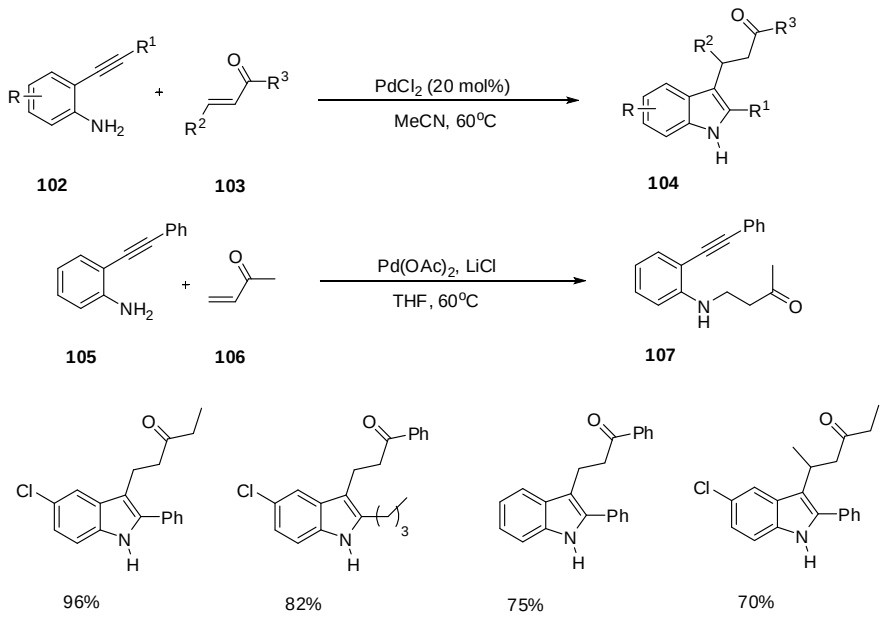
Scheme 30. The single-pot procedure for the synthesis of 2-alkenyl indoles.

In 2013, Wang and co-workers synthesized β-indole ketones (**101**) by coupling 2-alkynyl anilines (**99**) with allylic alcohols (**100**) in the presence of an oxidant using palladium as a catalyst. Contrary to alkenes, allylic alcohols were used in this methodology, with inexpensive dioxygen as the oxidant (Scheme 31). These cross-couplings showed high tolerance towards many useful functional substituents and high reactivity towards electron-deficient allylic alcohols. The cyclization mainly depends on the $(Pd(OAc)_2$ catalyst; additionally, it has a higher reactivity than other palladium catalysts. The presence of oxygen is necessary for regenerating the active $Pd^{(II)}$ species. Polar solvents worked best in this reaction, and studies also concluded that, in the case of DMF, high reactivity was observed in terms of both required reaction time and yield of the product. The obtained β-indole ketones can readily be used to obtain pyrrolo[2,1-a]isoquinolines and β-indole alcohol/amine, which are pharmaceutically significant [171].

In 2013, Janreddy et al. reported a tandem reaction between 2-N-unprotected-2-alkynylanilines (**102, 105**) and different electron-poor alkenes (**103**, **106**) using a Pd-catalyst and affording 2,3-disubstituted indole derivatives (**104**, **107**). The nature of the palladium catalyst was used to affect the formation of the resulting product. The catalyst $PdCl_2$ in MeCN at 60 °C afforded 2,3-disubstituted indole derivatives (**104**), while with $Pd(OAc)_2$/LiCl or LiBr in the THF or MeCN at 60 °C, the same reaction afforded N-alkylated-2-alkynylaniline derivatives (**107**) (Scheme 32). The 2-(phenylethynyl)anilines having electron-donating substituents produced slightly better yields of the desired products than the substrates having electron-withdrawing substituents. Sensitive substituents, e.g., alcohol, ester, and C_3H_5–, were tolerable during the reaction [172].



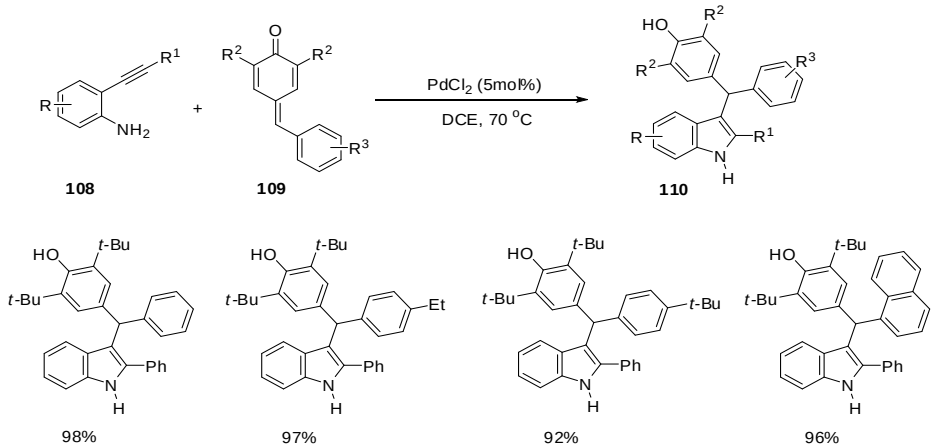
Scheme 31. Synthesis of β-indole ketones by coupling of 2-alkynyl anilines and allylic alcohols.



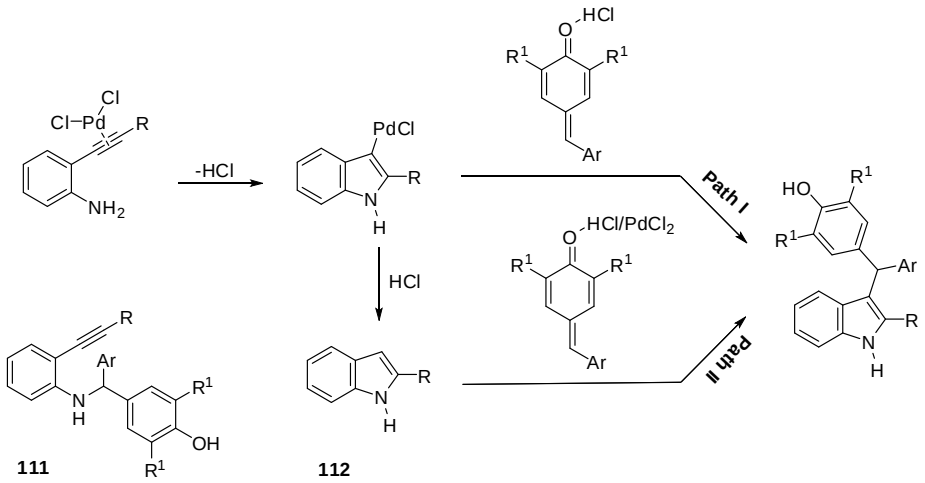
Scheme 32. Synthesis of 2,3-disubstituted indole derivatives by tandem reaction.

In 2015, Reddy and Vijaya Anand reported a domino process catalyzed by palladium to afford unsymmetrical diarylindolyl methane derivatives (**110**) by annulation of *o*-alkynylanilines (**108**) followed by subsequent 1,6-conjugated addition to p-quinone methides (**109**) involving mild reaction conditions (Scheme 33). For this reaction, there was no need to protect the amino group. This reaction proceeded smoothly with p-quinone methides obtained either from the electron-donating, or slightly electron-withdrawing aromatic aldehydes, producing the corresponding diarylindolyl methane yields up to 90%. The o-alkynylanilines obtained either from electron-donating or electron-withdrawing aryl alkynes afforded moderate to excellent yields of the corresponding products. During the

reaction, amine addition product (**111**) was formed by a reversible reaction as its concentration was decreased with increased formation of the indoles (**110**). It was worth noting that the compound (**111**) was not an intermediate of this reaction. The 2-substituted indole (**112**) was regarded as the key intermediate, and it was formed in the rate-determining step during the cyclization process (Scheme 34) [173].



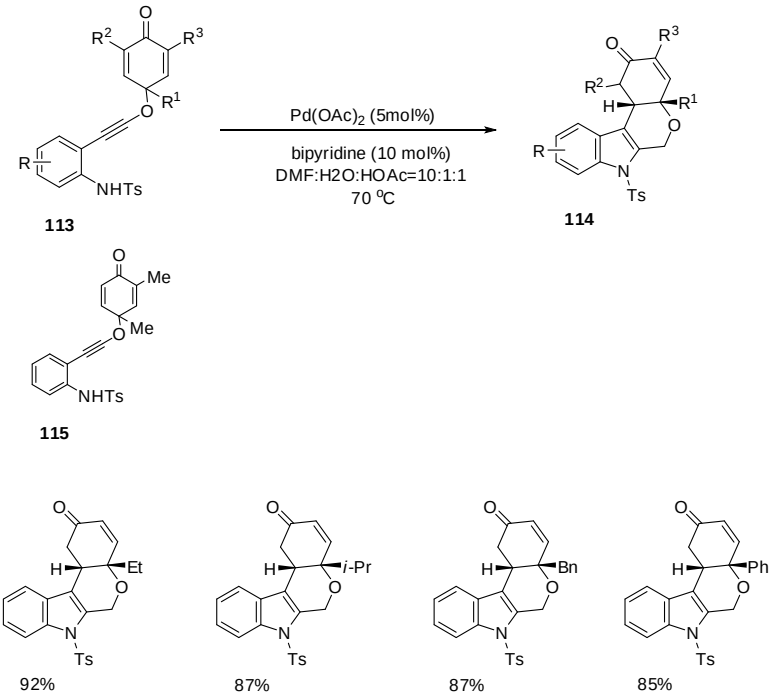
Scheme 33. Synthesis of diarylindolyl methane derivatives by 1,6-conjugated addition.



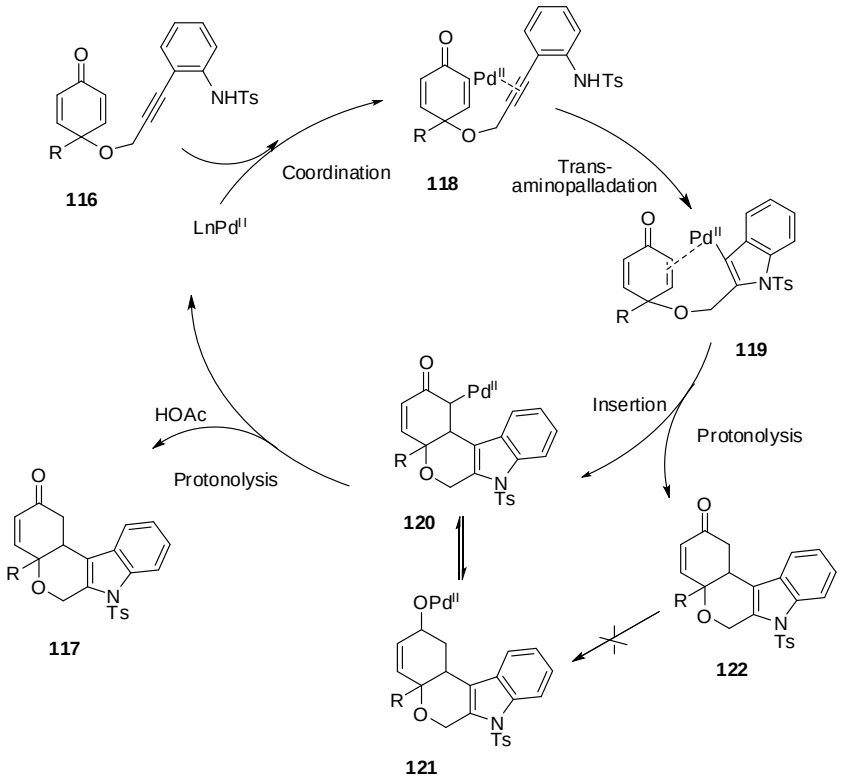
Scheme 34. The key intermediate formation in the synthesis of diarylindolyl methane derivatives.

The cyclohexanone-fused tetrahydropyrano[3,4-b]indoles (**114**) was synthesized by intramolecular $Pd(OAc)_2$-catalyzed cyclization of the aniline-tethered alkynyl cyclohexadienones (**113**) using a ligand and bipyridine in the mixture of solvents of DMF/H_2O/HOAc (Scheme 35). The 1,4 dioxane can also be used instead of DMF, but better results were obtained in the latter case. The mechanistic studies have shown the reaction involved following series of subsequent steps. A vinylpalladium species (**119**) was generated via trans-amino-palladation of the C≡C bond present in (**116**). After this step, conjugate intramolecular C=C was inserted into the Pd-C bond present in (**119**), generating an intermediate (**120**) or an enolate (**121**). The desired product (**117**) was obtained after protonolysis of (**120**) or (**121**). The $Pd^{(II)}$ moiety was regenerated on completion of the cycle. Intermediate (**119**) after protonolysis generated the N-Ts-indole (**122**) as a byproduct. The presence of the tosyl group (Tos) reduced the nucleophilicity at the 3-position in the (**122**), thus it making it unable to produce the desired (**117**) (Scheme 36). In the presence of a chiral ligand such as bipyridines, the asymmetric cascade cyclization produced chirally $(CH_2)_5CO$-fused tetrahydropyrano[3,4-b] indoles (**117**) with remarkable enantioselectivities in a comparatively good yield (Scheme 36). At low temperatures and in the absence of water or HOAc, the reaction did not go well and negative effects on the yields were observed. Except

for substrate (**115**), all other starting substrates afforded the dried product good to excellent yields despite the electronic or steric crowding rendered by the substitutions present in the cyclohexadienone or benzene ring; even trifluoromethyl and bromide substituents were well tolerated in the methodology [174].

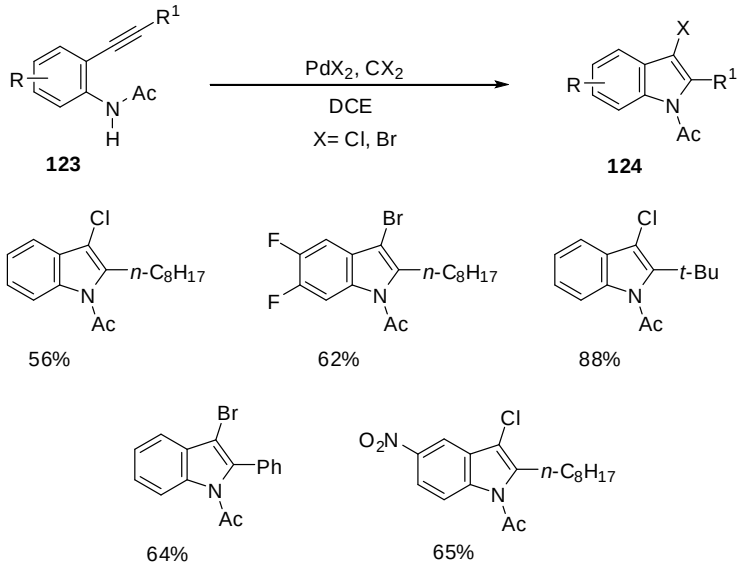


Scheme 35. Synthesis of cyclohexanone-fused tetrahydropyrano[3,4-b]indoles by intermolecular annulation.



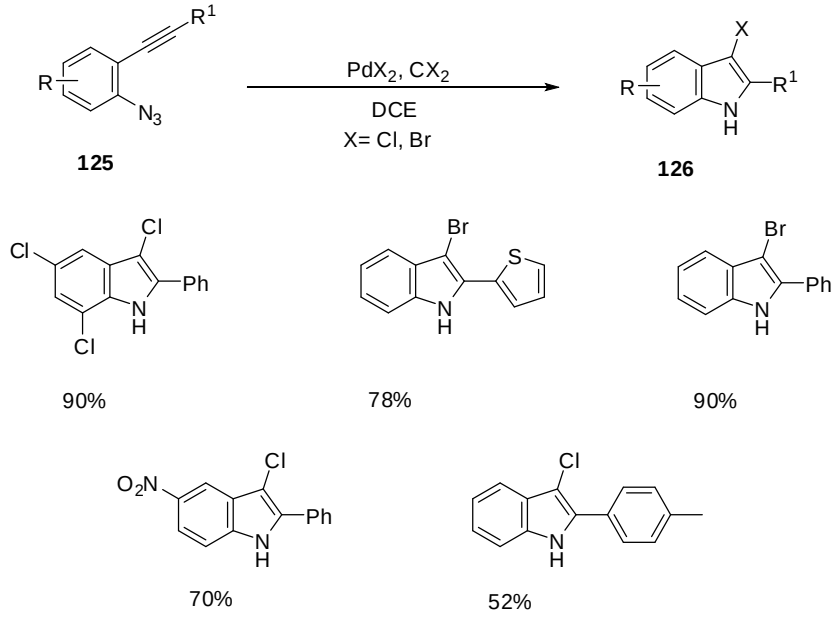
Scheme 36. Annulation process for the synthesis of cyclohexanone-fused tetrahydropyrano[3,4-b]indoles.

In 2007, Tang and co-workers utilized PdX_2 and CuX_2 (X = Chloro, Bromo) in the synthesis of 2-substituted 3-halo-1H-indoles (**124**) via the annulation of 2-ethynyl benzeneamines (**123**) (Scheme 37). The reaction worked successfully only with N-acetyl-protected 2-ethynyl benzeneamines. The substituents on the aromatic rings, e.g., $–NO_2$, halogens (X = F, Cl), were tolerated successfully during the reaction [175].



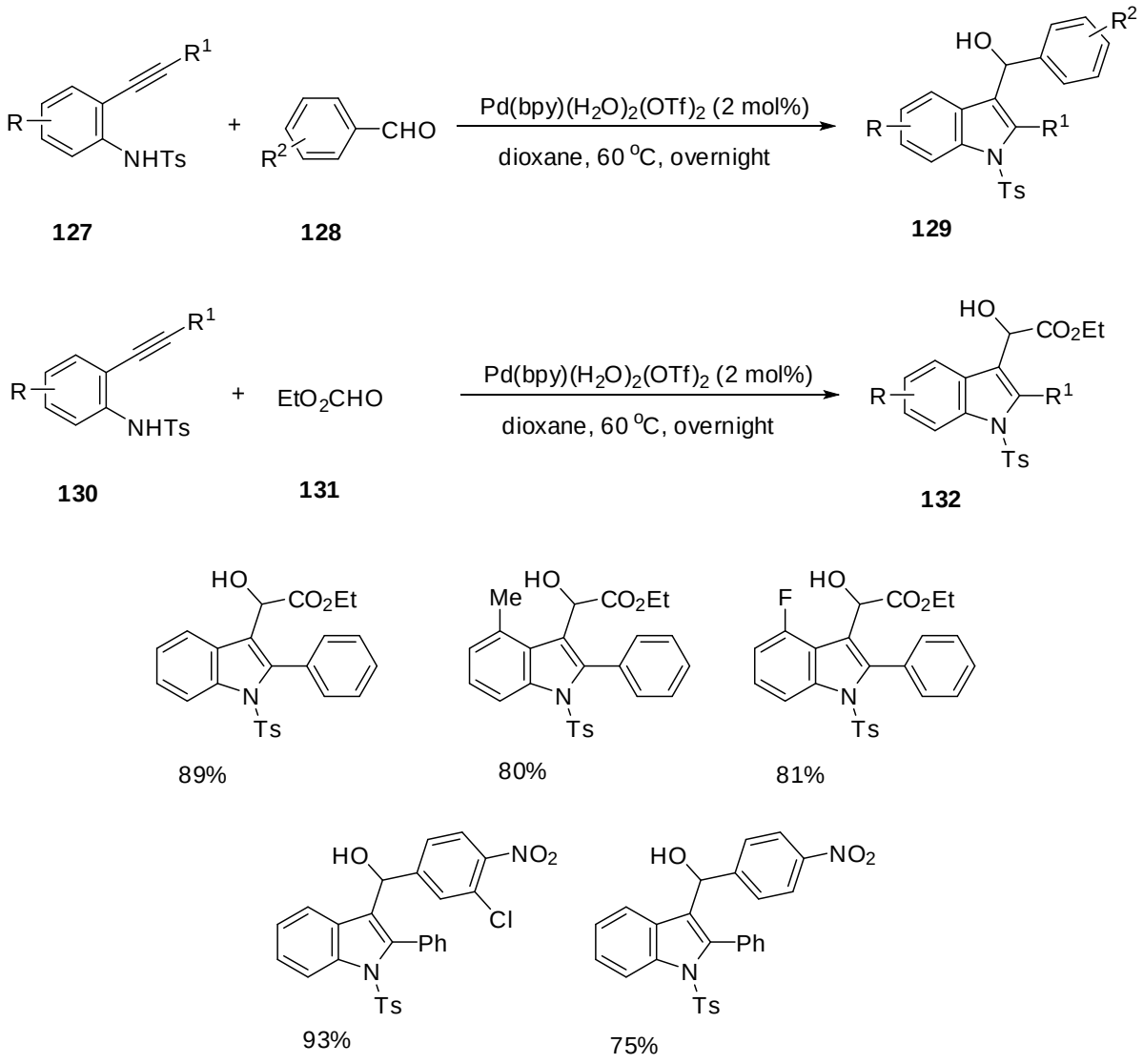
Scheme 37. Synthesis of 2-substituted 3-halo-1H-indoles via the annulation of 2-ethynyl benzeneamines.

In 2011, Zhang et al. reported that for halopalladation cyclization, 2-alkynyl aryl azides (**125**) were suitable substrates. Thus, they synthesized 3-substituted haloindoles (**126**) using $PdBr_2$ or $PdCl_2$ together with halide sources from a variety of 2-alkynyl aryl azides (Scheme 38). Under Cy_2NCl, $PdCl_2$, and $CuCl_2$, alkynes having electron-rich or electron-poor aryl groups produced a moderate yield in the chloro-palladation reaction. The aromatic ring with substituents such as chloro or nitro in the azidobenzene nucleus were successfully tolerated [176].

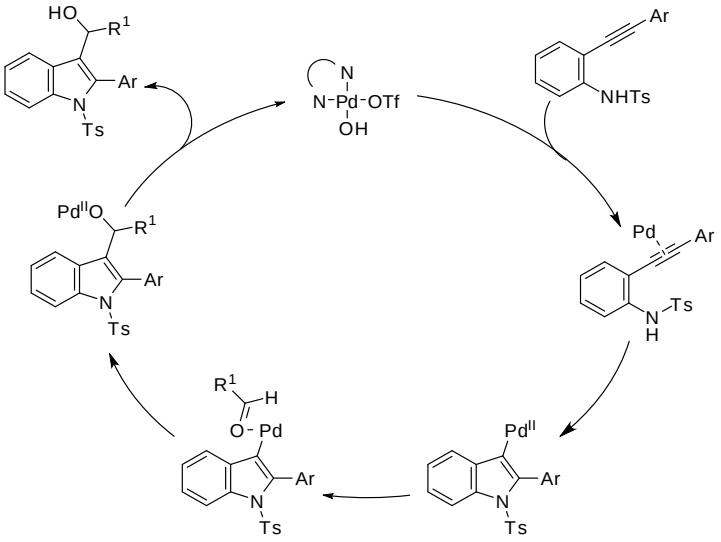


Scheme 38. Synthesis of 3-substituted haloindoles by halopalladation cyclization.

In 2010, Han and Lu synthesized substituted 3-hydroxymethylindoles (**129**) via the intermolecular subsequent formation of C–N and C–C bonds by reacting N-tosyl-2-phenylethynyl anilines (**127**) with aldehydes (**128**) using the cationic catalytic $Pd^{(II)}$ complex in dioxane. The complex $Pd(bpy)(OTf)_2(H_2O)_2$ produced the best yields, although dppp was also used in place of bpy. In solvent screening, different solvents were employed, e.g., CH_3NO_2, toluene, THF, DMSO, and 1,2-dichloro ethane ($ClCH_2CH_2Cl$), but the results were not satisfied with them (Scheme 39). To synthesize, the α-hydroxyindolyl acetate (**132**), the exact conditions were used with ethyl glyoxylate (**131**) to afford good yields. This cascade reaction firstly involved intramolecular aminopalladation of the alkyne substrate. Then, the C–Pd bond was quenched by adding a carbonyl group, and this catalytic cycle was completed and regenerated the $Pd^{(II)}$ species without requiring the redox system (Scheme 40). This reaction only worked successfully only with N-tosyl protected anilines, contrary to those with other protecting groups, e.g., with mesyl or trifluoroacetyl no desired product was obtained. Thus, it is concluded that a strong electron-withdrawing substituent on nitrogen has a vital role for aminopalladation [177].

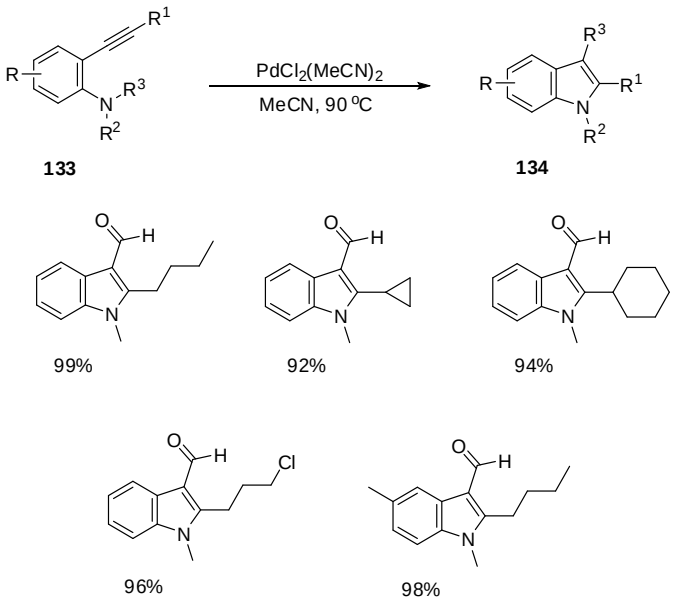


Scheme 39. Synthesis of 3-hydroxymethylindoles and α-hydroxyindolyl acetate indoles by cascade reaction.



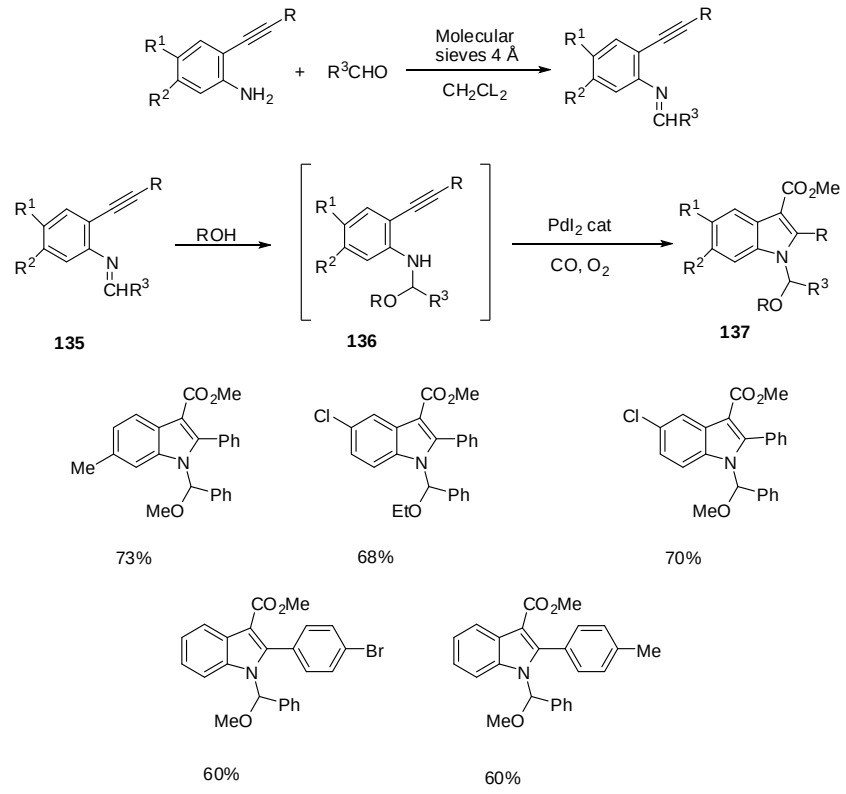
Scheme 40. The plausible mechanism for cascade reaction.

In 2014, Zhao et al. carried out the synthesis of indole nuclei by the intramolecular addition of C−N and S−N bond to alkynes catalyzed by palladium, involving functional group migration to the position-3 of the indole ring. Hence, the reaction of N-acyl-2-alkynylanilines (**133**) in the presence of $PdCl_2(CH_3CN)_2$ in MeCN at 90 °C afforded the 3-acyl-indoles (**134**) involving acyl group migration (Scheme 41). The screening of solvents concluded that the migration of functional groups was highly affected by the solvent used (MeCN was the best solvent) and there was no product observed in the case of $Pd_2(dba)_3$ and $Pd(PPh_3)_4$. This method required low catalyst loading, operated simply, and had a high tolerability towards many functional groups. The substrates with electron-rich substituents, e.g., –Me, or –MeO, halides (X) (X = Br, Cl, F), or electron-poor substituents, e.g., (CF_3) on position R, produced the respective products in remarkably high yields. This method smoothly migrated various functional groups, e.g., sulfonyl, pyruvoyl, acyl, and amide to the 3-position of indoles [178].



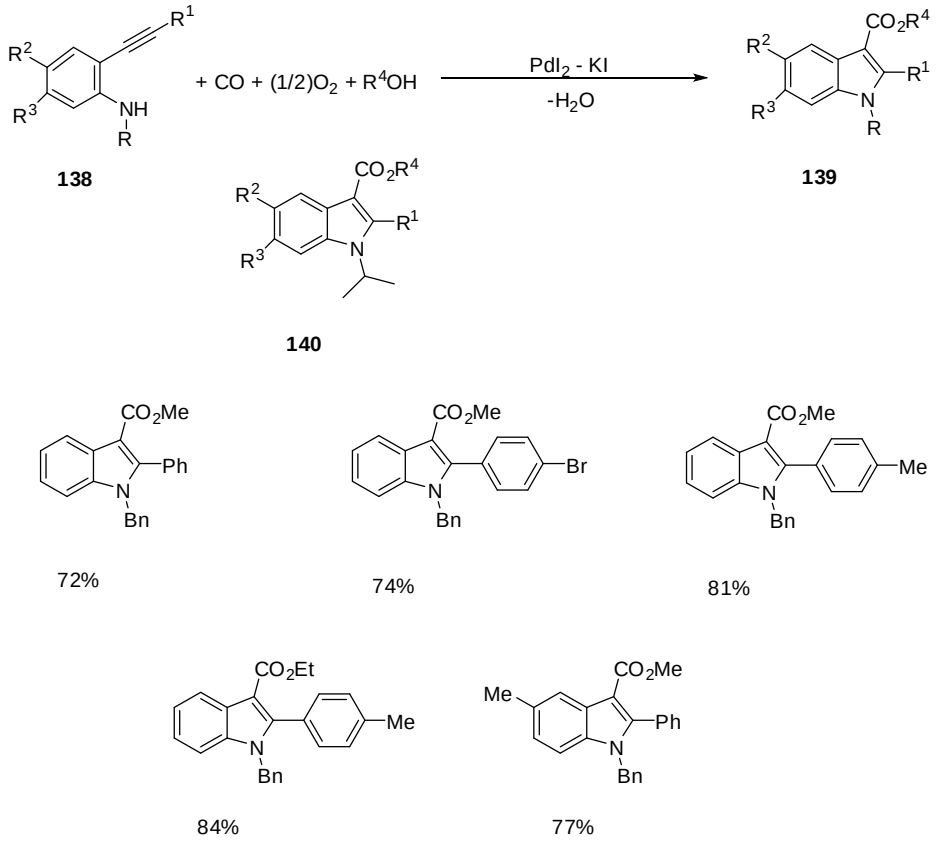
Scheme 41. Synthesis of 3-acyl-indoles by intramolecular cyclization.

Gabriele and colleagues reported a novel multicomponent tandem reaction to synthesize 1-(alkoxyarylmethyl)indole-3-carboxylic ester (**137**) using five basic molecules: 2-alkynylaniline imines, (ROH), (CO), (ROH), and (O_2) in the presence of a Pd-catalyst. The reaction mechanism involved a subsequent series of steps. Firstly, the nucleophilic alcohol (ROH) addition to the imino moiety present in the 2-alkynylaniline imine (**135**) afforded [(alkoxymethyl)(2-alkynylaryl)]amine intermediate (**136**), then the PdI_2-catalyzed reaction with alcohol (ROH), CO (carbon monoxide) and O_2 (oxygen) afforded the desired product 1-(alkoxyarylmethyl)indole-3-carboxylic ester (**137**) via 5-endo-dig cyclization-alkoxycarbonylation (Scheme 42). These five molecules (2-alkynylaniline imines, alcohol (ROH), oxygen (O_2), alcohol (ROH), and carbon monoxide (CO)) were activated sequentially in a two-step tandem process, producing high-functionalized derivative indole. The use of MeC(OMe) as the solvent instead of $HC(OMe)_3$ resulted in a significantly lower yield of the product [179].



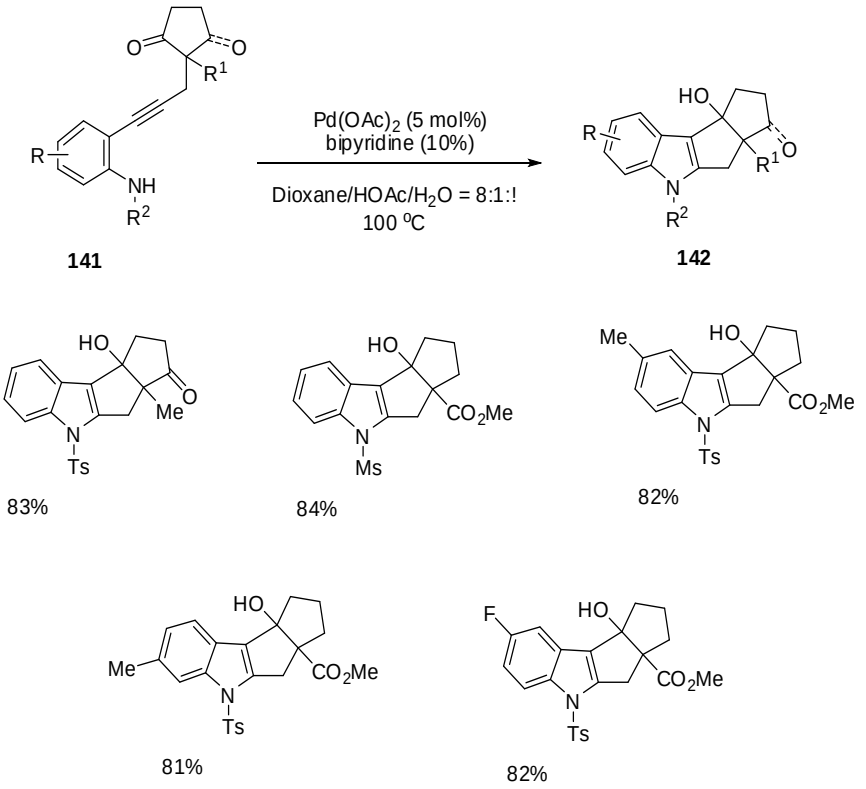
Scheme 42. Synthesis of 1-(alkoxyarylmethyl)indole-3-carboxylic ester by multicomponent tandem reaction.

Furthermore, Gabriele et al. directly obtained indole-3-carboxylic esters (**139**) from 2-alkynylanilines (**138**) having an internal C≡C and 2° amino by reacting them with carbon monoxide (CO), oxygen (O_2), and alcohol (ROH) in the presence of a PdI_2/ KI catalytic system. The reaction conditions used were mild, i.e., a temperature of 100 °C or 25 °C at 20 atm using a 4:1 ratio of the mixture of CO/air (Scheme 43). On switching the alcohol to trimethyl orthoformate, the 2-alkynylanilines afforded intermediate N-(dimethoxymethyl)-2-alkynylaniline derivatives because the 1° amino group in aniline was transformed to 2° in situ and, thus, it further afforded the 1-(dimethoxymethyl) indole-3-carboxylic esters (**140**). Both the electron-withdrawing and electron-donating substituents on the benzene ring worked well. The nitrogen in aniline can have both alkyl and benzyl groups (even the bulkier ones, e.g., isobutyl). The higher concentration of substrate with electron-poor substituents, i.e., (R^3 = CF_3), produced better results. The reaction was also worked smoothly even with higher alcohol, e.g., EtOH [180].

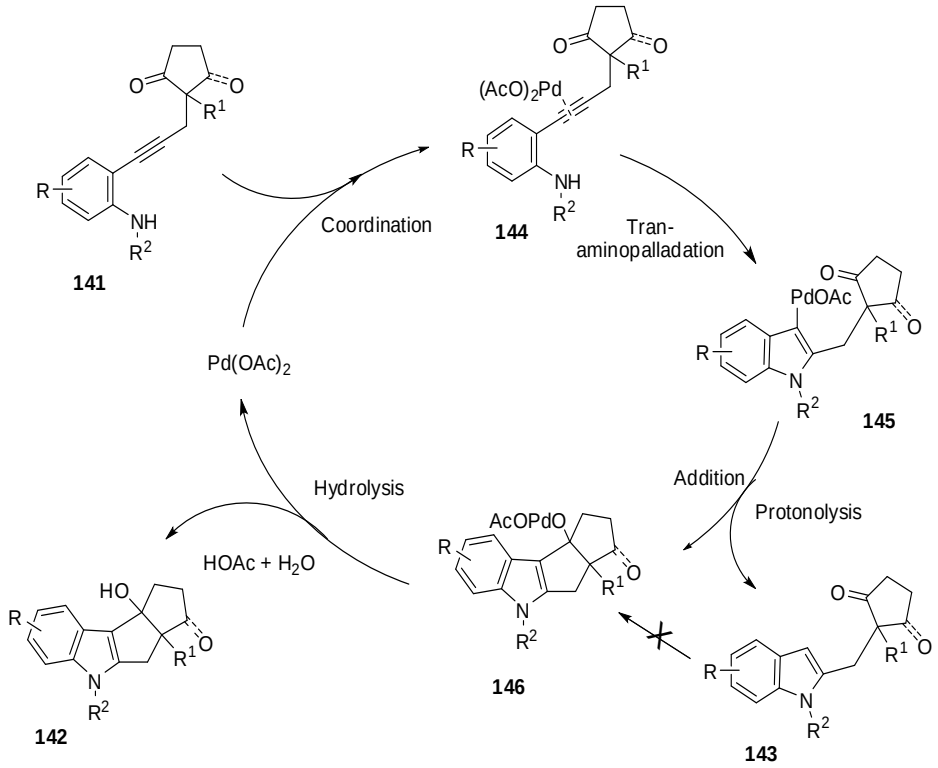


Scheme 43. Synthesis of indole-3-carboxylic esters from 2-alkynylanilines.

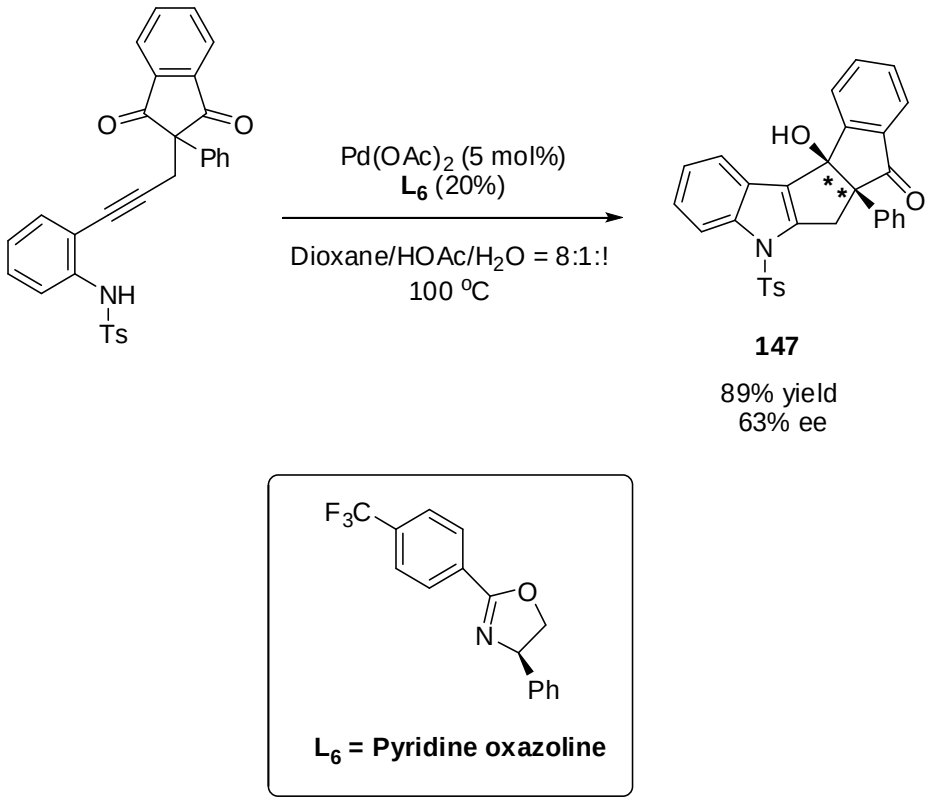
In 2017, Chen and co-workers synthesized pentaleno[2,1-b] indoles (**142**) by Pd $(OAc)_2$-catalyzed cascade aminopalladation followed by the cyclization of 2-alkynylanilines bearing a cyclopentanone (**141**) (Scheme 44). The reaction mechanism was initiated with $Pd^{(II)}$ coordination with C≡C present in alkynes (**141**) followed by trans-aminopalladation, producing intermediate (**145**). Subsequently, the Pd-intermediate was quenched by intramolecular carbonyl addition, affording (**146**). Lastly, the protonolysis of (**146**) yielded the desired product (**142**), while (**145**) on protonolysis gave rise to the byproduct (**143**) (Scheme 45). In the tetracyclic indole structure (**147**), the two adjacent stereocenters (ee) were obtained with higher diastereoselectivity in a single process employing pyridine oxazoline chiral ligand ($\mathbf{L_6}$) in the presence of $Pd(OAc)_2$ at 100 °C (Scheme 46). A benzene ring with electron-donating substituents such as –Me or –OMe afforded the desired products in excellent yields. In the case of the benzene ring substituted with electron-withdrawing substituents, e.g., trifluoromethyl or ester, the reaction went well, although a slight decrease in the yield was observed. In addition, –Cl and –F substituents were tolerated during the transformation. On switching the protecting group from Tosyl to Mesityle, the nitrogen atom was not influenced over the cyclization [181].



Scheme 44. Synthesis of pentaleno[2,1-b] indoles via intermolecular cyclyzation.

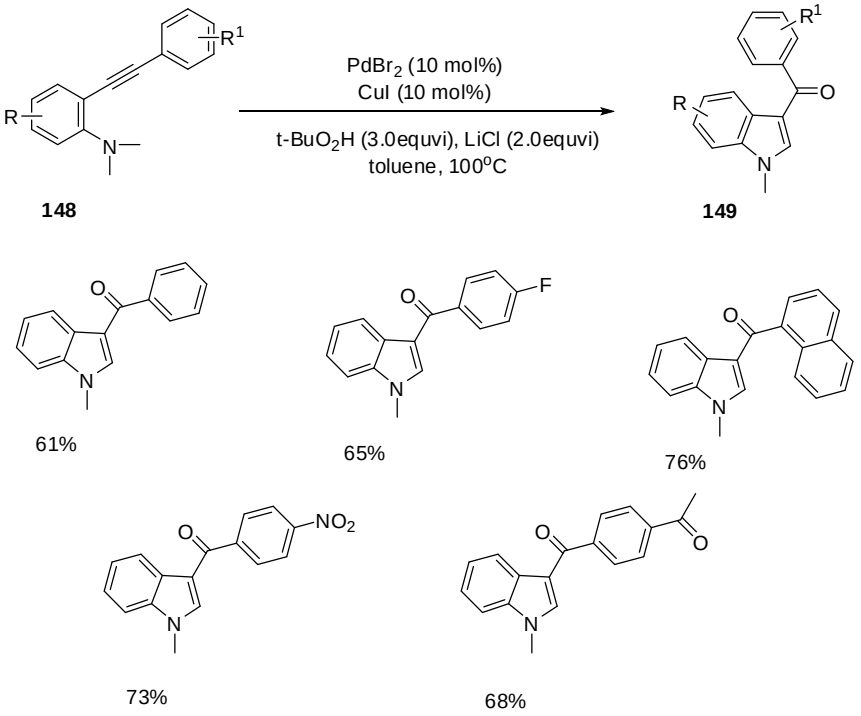


Scheme 45. Annulation process of 2-alkynylanilines having cyclopentanone.

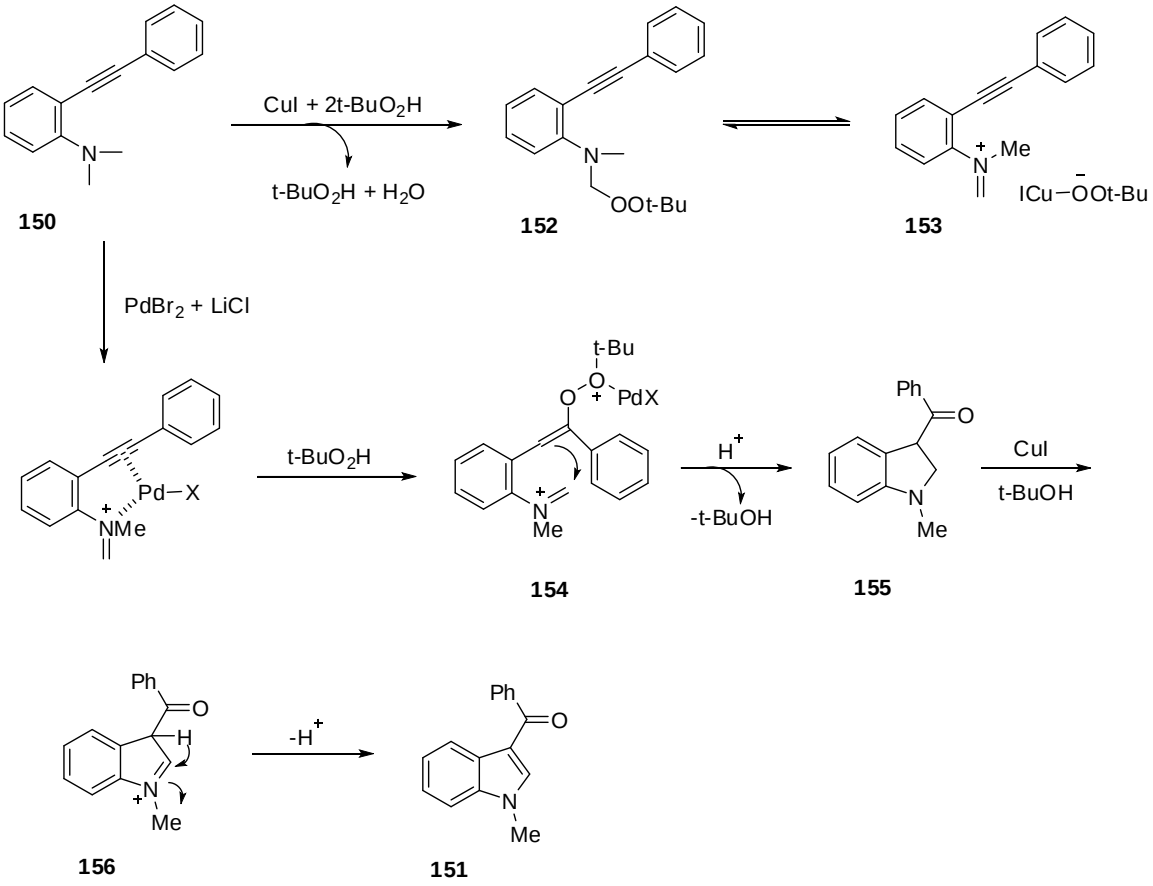


Scheme 46. Synthesis of tetracyclic indole structure by pyridine oxazoline chiral ligand (**L$_6$**).

In 2013, Xia et al. synthesized 3-acylindoles (**149**) via palladium/copper co-catalyzed oxidative cyclization of 2-alkynylaniline (**148**) by utilizing 10 mol% $PdBr_2$ and 10 mol% CuI in the presence of *t*-BuOOH. The 3-acylindoles (**149**) were obtained in a good yield by this reaction (Scheme 47). In this methodology, *t*-BuOOH acted as an oxidant, as well as a source of oxygen to introduce the carbonyl functional group. The results of this controlled experiment indicated that in ketone moiety, and the oxygen atom did not come from the H_2O or O_2 but *t*-BuOOH. These results of the controlled experiments together with ESI/MS analysis encouraged the mechanism for the Pd–Cu co-catalyzed oxidative cyclization shown in (Scheme 48). The reaction was initiated by the reaction of 2-alkynylaniline (**150**) with two molecules of *t*-BuOOH via a radical mechanism in the presence of a copper catalyst, generating a peroxide (**152**) and *t*-BuOH. The iminium intermediate (**153**) was formed spontaneously in equilibrium from (**152**) in small amounts and assisted by Lewis's acid in the presence of a CuI catalyst. Then, the nucleophile was attacked on the alkyne of (**153**) by *t*-BuOOH (TBHP) in the presence of a Pd-catalyst, generating the intermediate (**154**). Subsequently, the intermediate (**154**) was transformed to 3-acylindoline (**155**) by intramolecular cyclization. Then on oxidation, it was converted to intermediate (**156**). The deprotonation of intermediate (**156**) produced the product (**151**) (Scheme 48). The reaction tolerated a broad range of functional groups, e.g., –F, –Cl, NO_2, ether, acetyl, alkyl, and amino alkynes. The electron-withdrawing substituents were more favorable for this reaction than the electron-donating substituents [182].

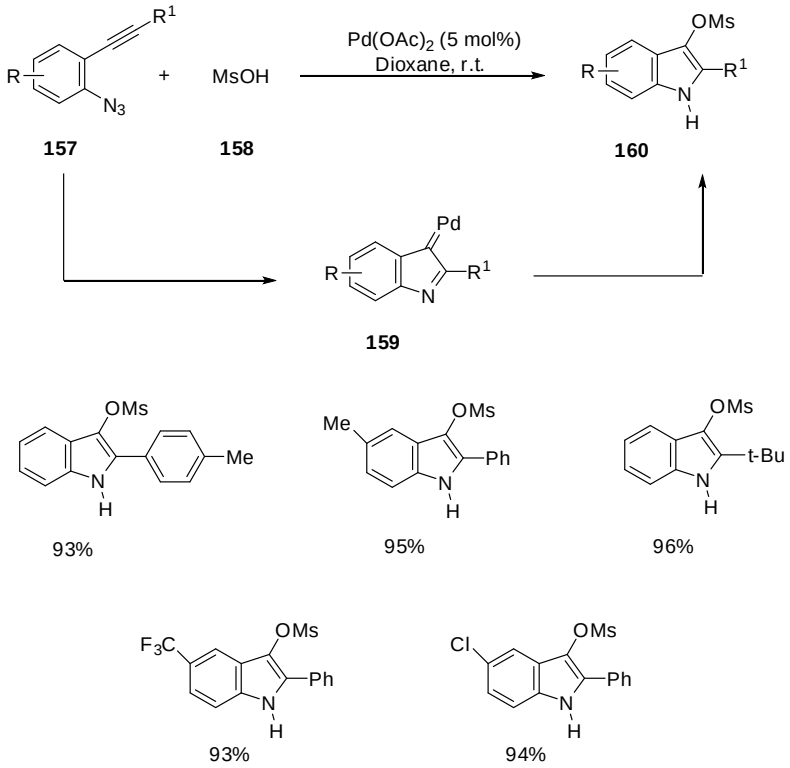


Scheme 47. Synthesis of 3-acylindoles via intramolecular cyclization.



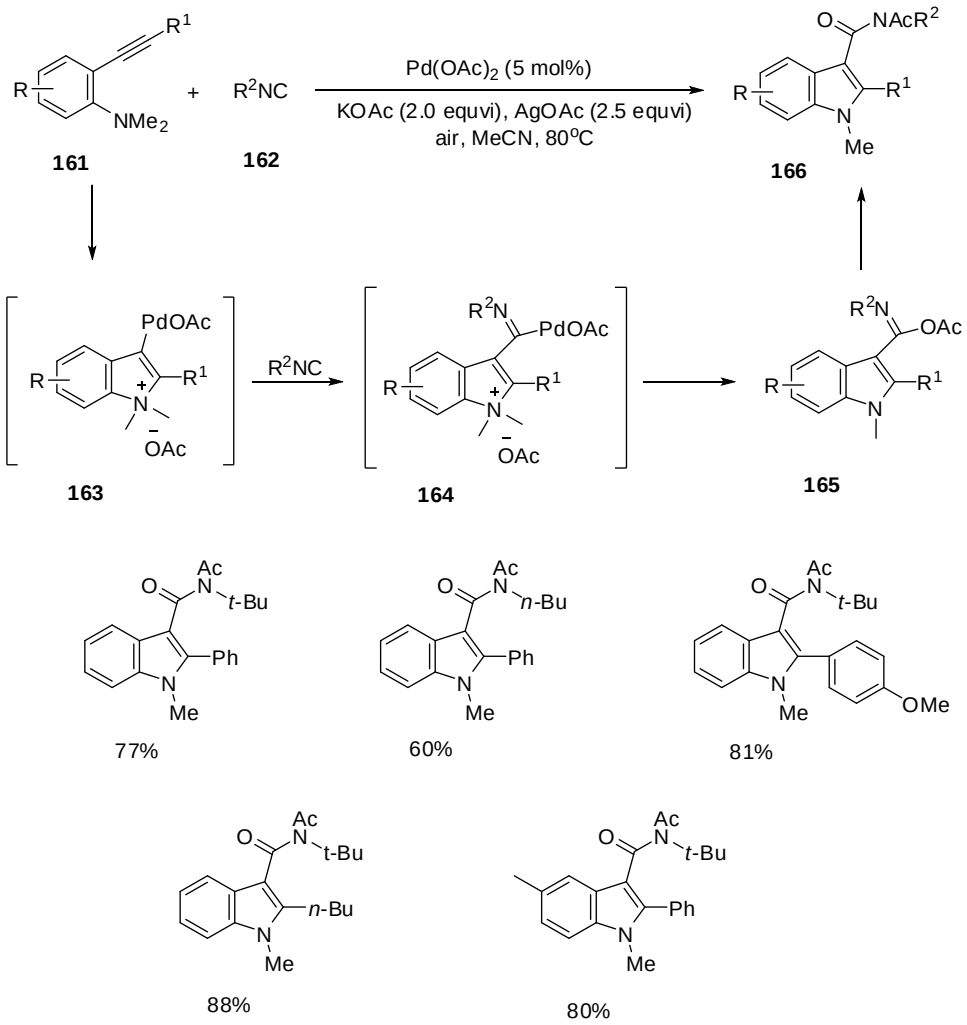
Scheme 48. Mechanism of palladium/copper co-catalyzed oxidative cyclization.

In 2017, Zhang et al. synthesized 1H-indole-3-sulfonates by using 2-alkynyl arylazides and sulphonic acids in the Pd-catalyzed cascade reactions. The reaction afforded the required product, 1H-indole-3-sulfonates (**160**), in higher yields in 10 min by treating 2-alkynyl arylazides (**157**) with sulphonic acids (CH_3SO_3H) (**158**) in the presence of $Pd(OAc)_2$ at room temperature (Scheme 49). The formation of intermediate (**159**) accounted for the progress of the reaction. The reaction provided a high yield of the desired product with 2-alkynyl aryl azides having electron-poorer and electron-rich substituents on the aryl ring as well as with (hetero)aryl group on the C≡C. Moreover, 2-alkynyl aryl azides having different groups on the aromatic ring, e.g., (R = halide (–X), –Me or $–CF_3$), performed smoothly. Under the same reaction condition, 2-Alkynyl aryl azides having aliphatic substituents on the carbon in alkyne underwent the reaction smoothly with a yield 83% to 96% while 2-alkynyl aryl azides bearing terminal alkynes were not a suitable substrate for the reaction [183].



Scheme 49. Synthesis of 1H-indole-3-sulfonates from 2-alkynyl arylazides and sulphonic acids.

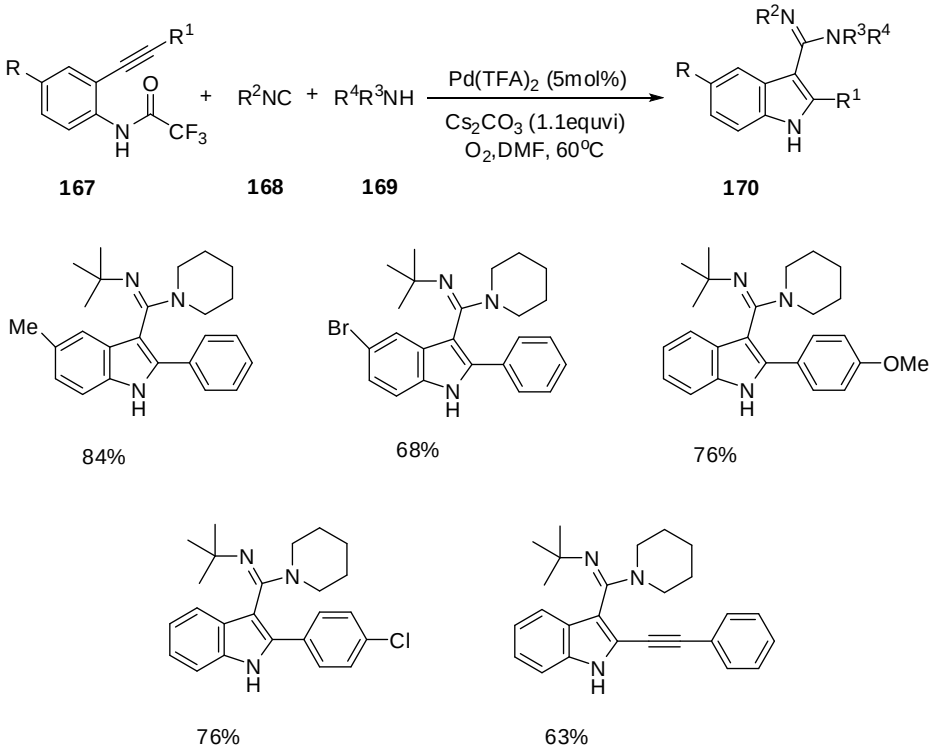
In 2013, Qiu et al. synthesized 3-amidylindoles (**166**) via a Pd-catalyzed reaction of 2-alkynylaniline (**161**), isonitriles (**162**), and CH_3CO_2Ag to afford the yields, which were moderate to good. Five new bonds were constructed during this single-pot procedure with remarkable reaction efficiency. The silver acetate (CH_3CO_2Ag) acted both as a reactant and oxidant. The proposed mechanism in (Scheme 50) suggested that the reaction involved 2-alkynylaniline (**161**) cyclization in the presence of a $Pd^{(II)}$ catalyst to generate intermediate (**163**). In the next step, isonitrile insertion took place to afford intermediate (**164**). Then reductive elimination of intermediate (**164**) generated the compound (**165**), along with the $Pd^{(0)}$ formation. Finally, intramolecular nitrogen attacked the acetyl group and generated the product 3-amidylindole (**166**). Meanwhile, silver acetate oxidized the $Pd^{(0)}$ to $Pd^{(II)}$ for reuse in the catalytic cycle. Different 2-alkynylanilines with an alkyl or aryl substituents at the R^1 were suitable for this reaction. However, N,N-dimethyl-2-(2- trimethylsilylethynyl)aniline failed to produce the reaction. The reaction also went smoothly for the substituents at R, which were fluoro or alkyl groups [184].



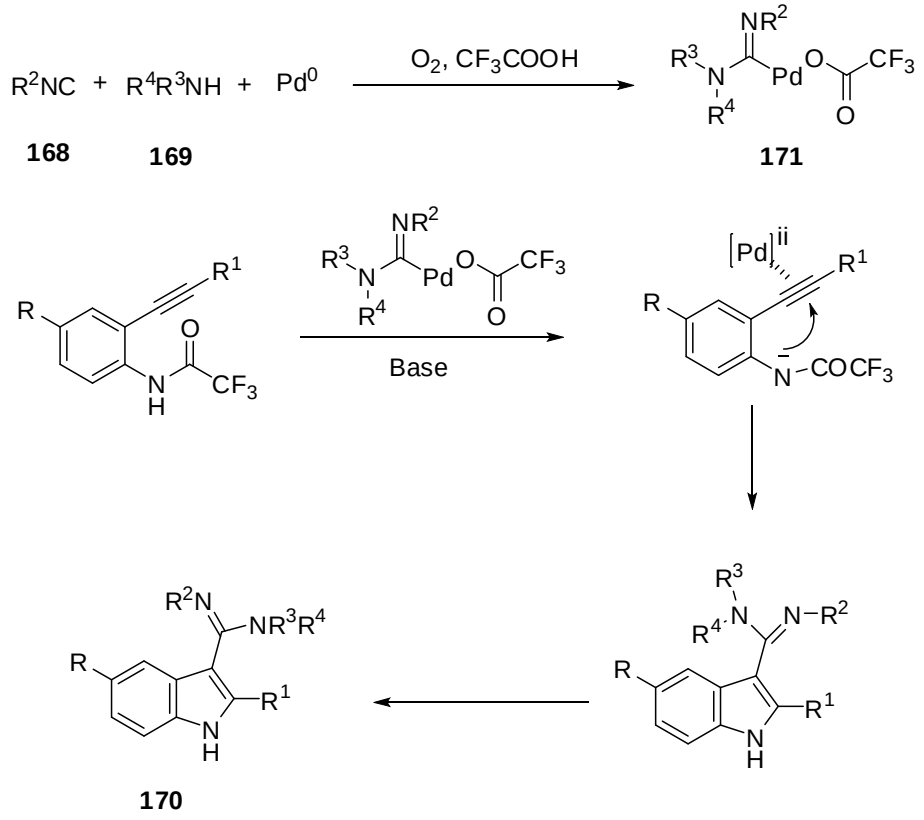
Scheme 50. Synthesis of 3-amidylindoles by single-pot procedure.

Hu and co-workers synthesized 2-substituted 1H-indole-3-carboxamidines (**170**) via a three-component $Pd^{(II)}$ catalyzed reaction using o-alkynyltrifluoro acetanilides (**167**), isonitrile (**168**), and amines (**169**) (Scheme 51). The success of the reaction was the intramolecular amino-palladation of C≡C activated by the isonitrile-ligated $Pd^{(II)}$ species (**171**) (Scheme 52). Dioxygen (O_2) was the only oxidant used for regenerating the palladium (II) species. The reaction tolerated many functional groups. In general, electron-rich substituents provided higher yields in a shorter time than electron-deficient substituents [185].

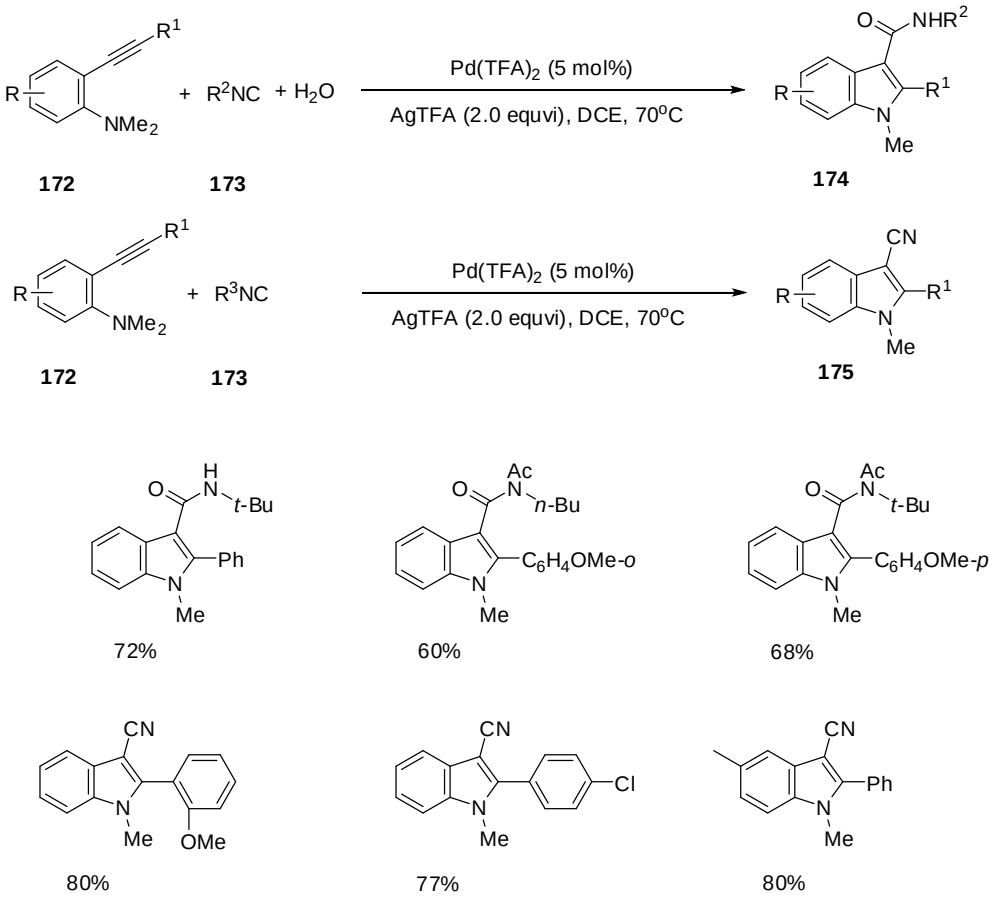
A Pd-catalyzed reaction between isonitriles (**173**) and N,N-dimethyl-2-alkynyl anilines (**172**) afforded 3-amidylindoles (**174**) and 3-cyanoindoles (**175**) (Scheme 53). The success of this reaction was the insertion step of isonitrile. The presence of H_2O is key for the formation of 3-amidylindoles (**174**). Not only R^2CN, but also cyclohexyl isonitriles were tolerated in the reaction and produced 3-cyanated indole [186].



Scheme 51. Synthesis of 2-substituted 1H-indole-3-carboxamidines via the intramolecular cyclization.

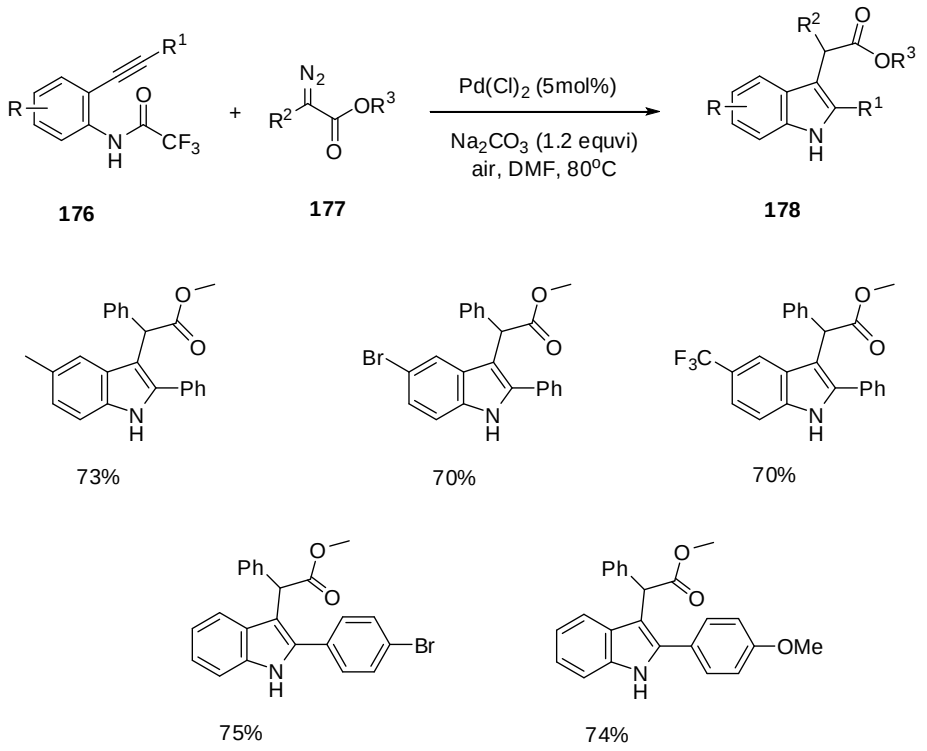


Scheme 52. Mechanism for the 2-substituted 1H-indole-3-carboxamidines synthesis.

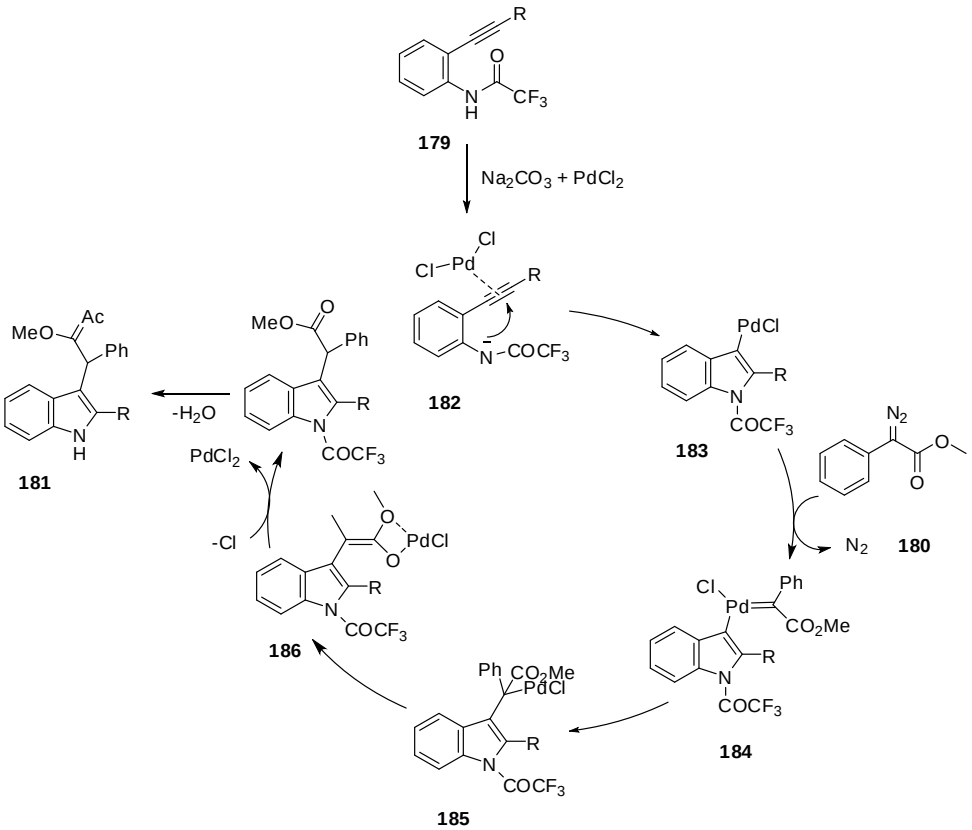


Scheme 53. Synthesis of 3-amidylindoles and 3-cyanoindoles the insertion of isonitrile to N,N-dimethyl-2-alkynyl anilines.

In 2015, Hu and co-workers synthesized C–3 alkylated indole derivatives (**178**) via Pd-catalyzed aminopalladation followed by the insertion of carbene. The reaction took place in the open air with reactants, *o*-alkynyltrifluoro acetanilides (**176**) and α-diazoacetates (**177**), by using a weak base (Scheme 54). The plausible mechanism for the reaction is as follows (Scheme 55). Firstly, a palladium complex (**182**) was generated by deprotonation of the substrate (**179**) via Na_2CO_3. The activation of alkyne moiety took place by $PdCl_2$. Then, the key intermediate indolylpalladium (**183**) was generated by intramolecular aminopalladation of (**182**). The α-phenyldiazoacetate (**180**), on decomposition by (**182**), led to a Pd-carbene species (**184**) and released N_2 gas. The intermediate (**185**) was generated by the insertion of the carbene via migration into the Carbon-Pd bond of sigma-indolylpalladium intermediate (**184**). The intermediate (**185**) tautomerized to a more stable enol from (**186**). Ligand exchange of (**186**) with –Cl followed by protonation and deprotection during workup yielded the desired product (**181**) (Scheme 55). Insertion of carbene species by migration into the sigma-indolyl-Pd intermediate is more favorable than N-H insertion. The reaction had excellent tolerance towards a range of functional groups [187].

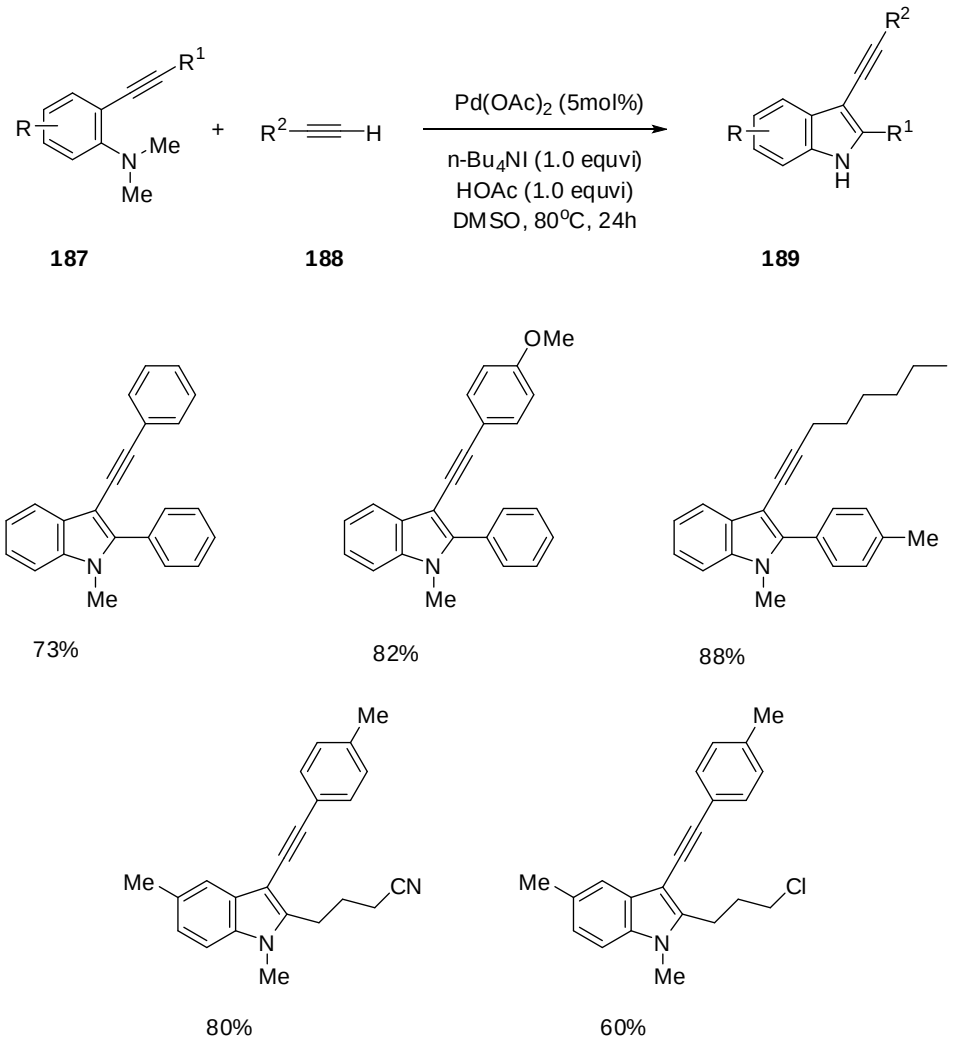


Scheme 54. Synthesis of C–3 alkylated indole by carbene insertion.

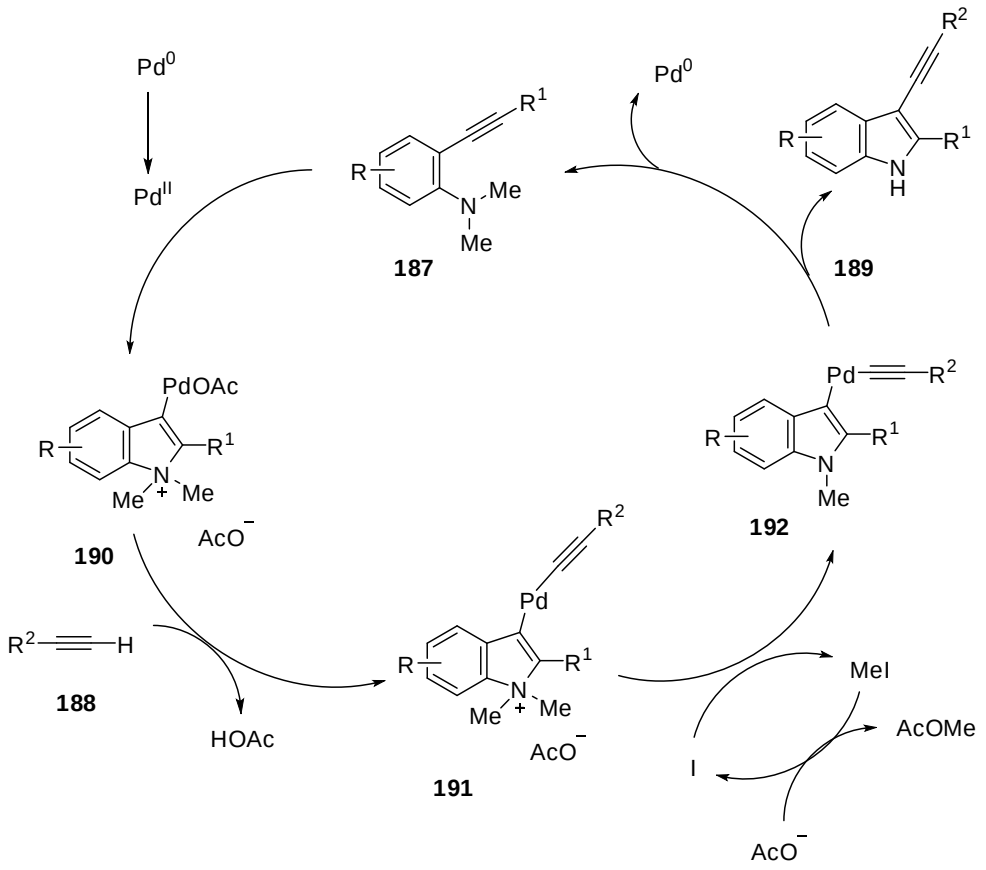


Scheme 55. The Pd-catalyzed aminopalladation involving carbene insertion.

In 2012, Yao and colleagues synthesized 2,3-disubstituted 3-alkynylindoles (**189**) by reacting *o*-alkynylanilines (**187**) and terminal alkynes (**188**) via palladium (II)- catalyzed domino reaction under aerobic oxidative conditions (Scheme 56) [188]. The reaction involved two vital steps for initiating the alkynylation process: (a) sigma-alkynylpalladium (II) complex formation followed by (b) the aminopalladation of *o*-alkynylaniline generating a sigma-indolylpalladium (II) intermediate. Thus, according to the mechanism, the reaction involved the formation of the sigma-indolylpalladium intermediate (**190**) via aminopalladation of *o*-alkynylanilines (**187**). Then, sigma-indolylpalladium was coordinated with terminal C≡C (**188**) followed by the deprotonation step and generated sigma-alkynylpalladium (**191**). Finally, iodide via SN_2 carry out N-demethylation of indolium (**191**) produced the 3-indolylpalladium intermediate (**192**) which, after reductive elimination, yielded the required 3-alkynylindoles (**189**) and $Pd^{(0)}$. In the presence of air, $Pd^{(0)}$ was oxidized to $Pd^{(II)}$, completing the catalytic cycle (Scheme 57). To avoid the retro-aminopalladation of complex (**191**) and spontaneous N-demethylation of (**191**), nBu_4NI was used. It was concluded that the sigma-indolyl-sigma-alkynylpalladium intermediate (**191**) formation occurred before the N-demethylation step (Scheme 57). This reaction had a good tolerance towards many useful functional groups. These oxidative reaction conditions allowed the use of nucleophilic terminal alkynes instead of electrophilic organic halides [188].



Scheme 56. Synthesis of 2,3-disubstituted 3-alkynylindoles by domino reaction.



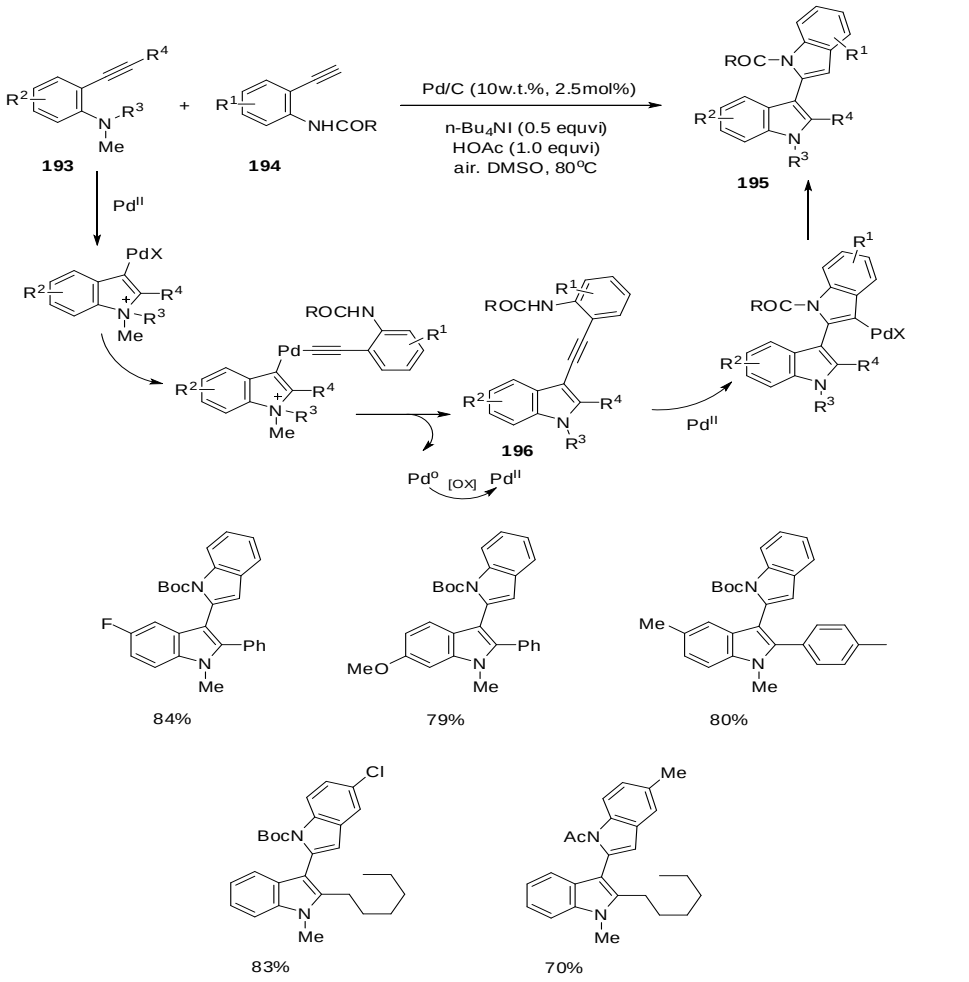
Scheme 57. Mechanism for domino reaction for synthesizing 2,3-disubstituted 3-alkynylindoles.

Similarly, in 2015, Yao et al. used two different *o*-alkynylanilines in a Pd-catalyzed cyclization cross-coupling reaction using aerobic oxidation for synthesizing unsymmetrical 2,3′-bisindoles. The reaction conditions used were Pd/C, CH_3COOH, *n*-Bu_4NBr, and DMSO in presence of air at 80 °C for effective cyclization of *o*-ethynylaniline (**194**) and *o*-alkynylanilines (**193**), affording 2,3′-bisindole derivatives (**195**) (Scheme 58). The proposed mechanism suggested that the reaction involved two catalytic cycles separated temporarily. Firstly, cyclative alkynylation occurred, generating 3-alkynylindoles (**196**); then, a subsequent aminopalladation afforded 2,3′-bisindoles. It is worth noting that the charcoal-supported catalyst was the product of the cyclization of 3-alkynylindoles (**196**) to the desired bisindoles (**195**) (Scheme 58). This methodology was a rare case using Pd/C as pre-catalyst for oxidative Pd^{II}-catalyzed transformations [189].

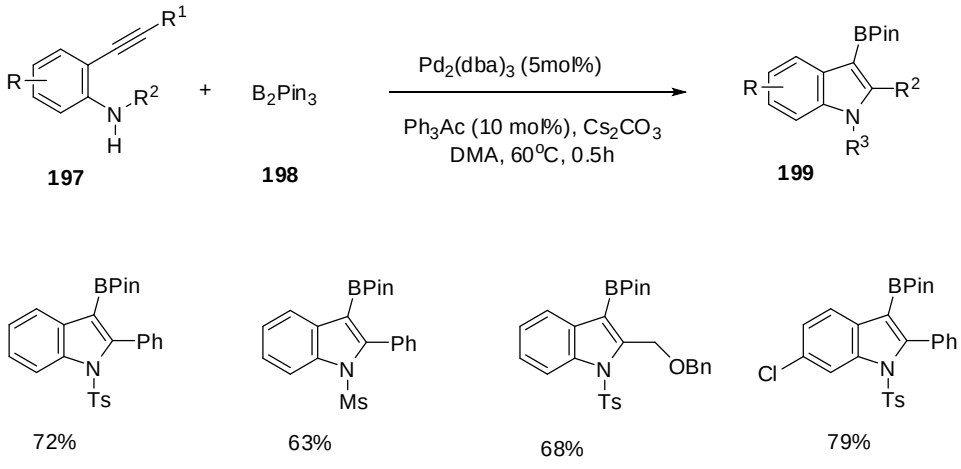
Huang and co-workers carried the direct synthesis of indole 3-boronic esters (**199**) by Pd-catalyzed cyclisation of *o*-alkynylanilines (**197**) merged with a cross-coupling reaction using bis-(pinacolato)diboron(B_2Pin_2) (**198**) in the presence of a catalyst mixture of $Pd_2(dba)_3$ and Ph_3As (Scheme 59). Mechanistic studies under controlled conditions suggested that a borylation reaction occurred during cyclization, rather than after the formation of indole. The reaction worked smoothly only in the presence of a limited sulfonamide-based Ms- and Ts-protected starting substrate and those which were N-Boc or N-Bn protected failed to cyclize [190].

Guo and co-workers developed a one-pot reaction for the synthesis of 3-sulfenylindoles (**202**) via cyclization of 2-(1-alkynyl)benzenamines (**200**) with disulfides (R−**S**−**S**−R′) (**201**) catalyzed by transition metal Pd in aerobic conditions. The presence of air was crucial for the success of the reaction (Scheme 60). The results showed that this annulation methanoyl with $PdCl_2$ in the presence of DMSO as solvent at 80 °C with a ratio of 1:2 among diorganyl disulfides and *o*-alkynylanilines afforded the best results of the desired products. The effectiveness of this reaction was that the two (RS) portions of the organosulfur reagent

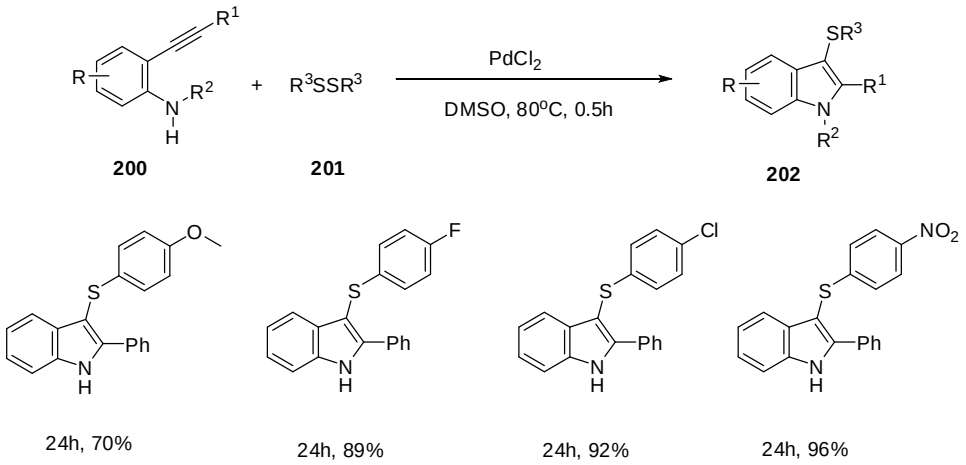
were transferred to the desired product. In amine, replacing hydrogen with Me- worked well, but hydrogen replaced with an acetyl group was a failure and afforded the desired product only in trace quantities. Several useful substituents such as –Me, –OMe, $–NH_2$, $–CF_3$, –CN, $–NO_2$ –Cl, and –F on the aromatic ring in disulfides were tolerable, but better results were obtained with disulfides with electron-deficient aryl substituents [191].



Scheme 58. Synthesis of 2,3′-bisindole derivatives via intermolecular cyclization.



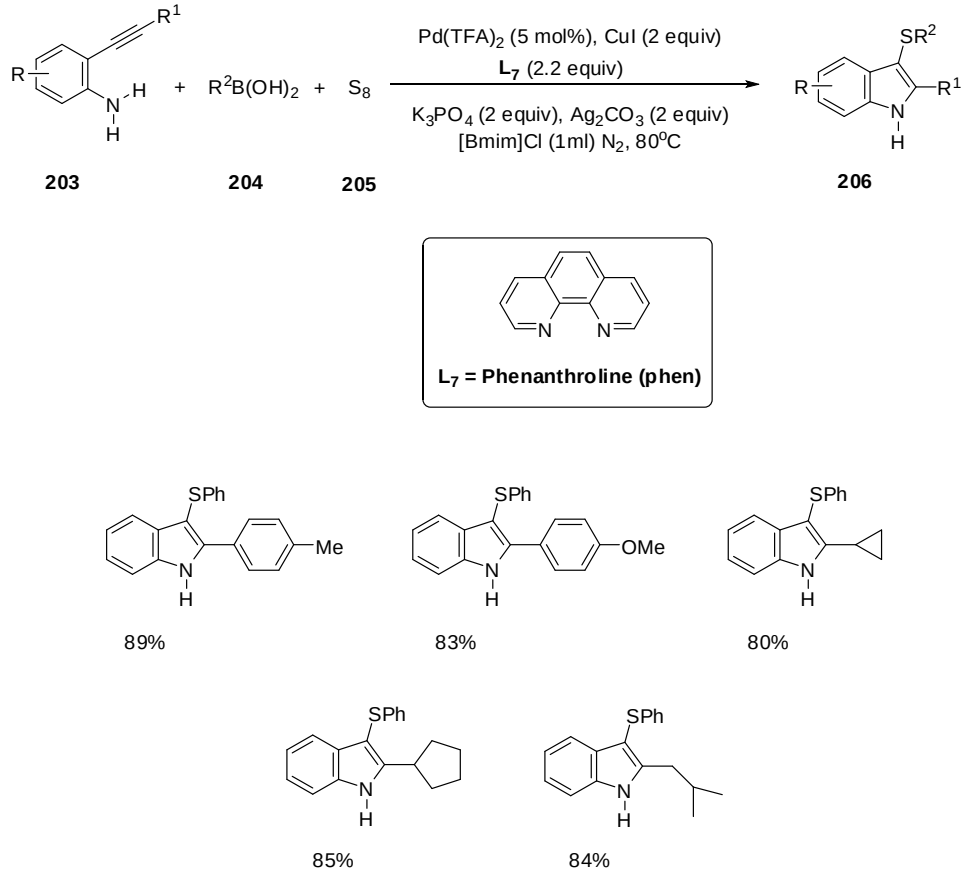
Scheme 59. Synthesis of indole 3-boronic esters via borylation during cyclization.



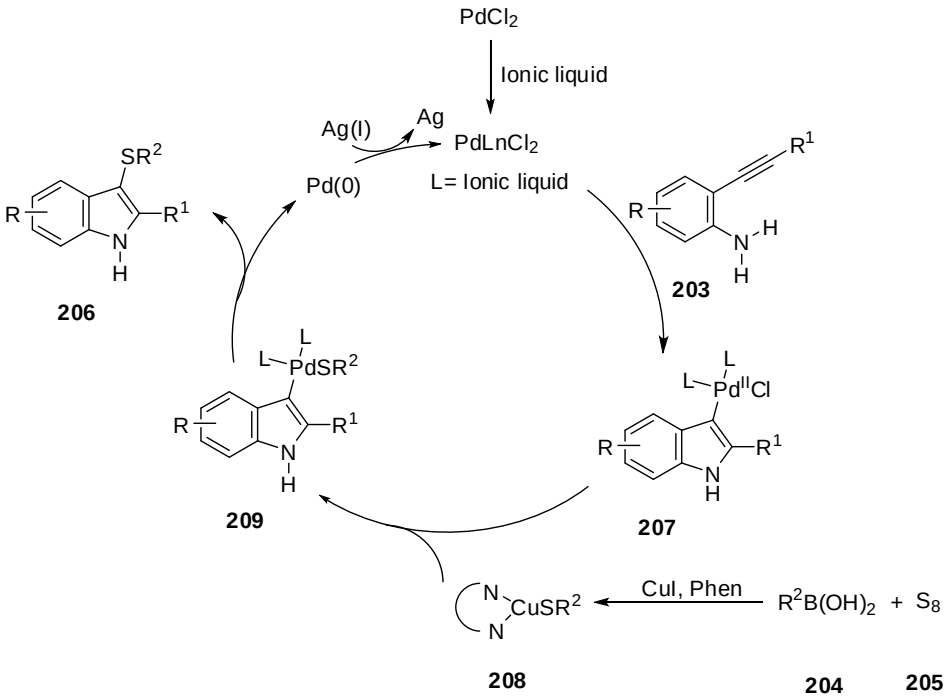
Scheme 60. Synthesis of 3-sulfenylindoles by cyclization of 2-(1-alkynyl)benzenamines and disulfides.

In 2016, Li and colleagues developed a palladium/copper ($Pd(TFA)_2$/CuI)-catalyzed cascade annulation/arylthiolation reaction to afford 3-sulfenylindole derivatives (**206**) by treating *o*-alkynylamines (**203**) with sulphur (S8) (**205**) and aryl boronic acid (**204**) in ionic liquids using phenanthroline (phen) ($\mathbf{L_7}$) as a ligand (Scheme 61). The reaction produced a moderate to a good yield of the desired 3-sulfenylindole derivatives. The 3-sulfenylindoles were obtained in higher yields via a single-pot procedure without the preparation of the diorganyl disulfides. The mechanism is depicted in (Scheme 62). Firstly, the Pd-complex was generated in situ in presence of an ionic solvent [192–199]. Subsequently, nucleopalladation of *o*-alkynylamines (**203**) generated the vinyl-Pd intermediate (**207**) [200,201]. Then, aryl boronic acid (**204**) reacted with elemental sulfur (S8) (**205**), spontaneously generating an in situ organo-copper thiolate complex (**208**) in the presence of the CuI complex [202–206]. Subsequently, intermediate (**209**) was obtained by a trans-metalation process of intermediate (**207**) with an organo-copper thiolate complex (**208**). Finally, after reductive elimination, the desired product (**206**) was obtained. The $Pd^{(0)}$ oxidized to $Pd^{(II)}$ and the catalytic cycle was completed (Scheme 62). It was suggested from the mechanism that the palladium complex (**209**) was the key intermediate for this successful cyclization. This reaction possessed remarkable tolerance towards a number of functional groups used [207].

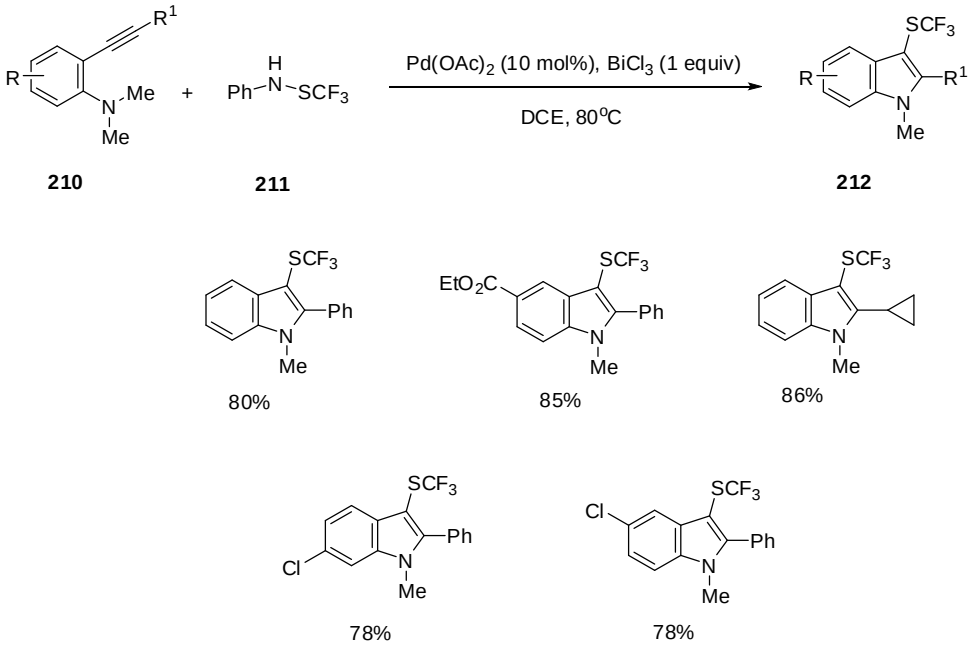
In 2014, Sheng et al. carried out a reaction between trifluoro methane sulfanilamide (**211**) and 2-alkynylaniline (**210**) for obtaining 3-((trifluoromethyl)thio)indoles (**212**) using $Pd^{(II)}$ acetate [$Pd(OAc)_2$] and bismuth(III) chloride ($BiCl_3$) (Scheme 63). The $BiCl_3$ played a key role as it participated in the electrophilic addition of trifluoromethane sulfanilamide (**211**) to the iodolium (**213**). The proposed mechanism is depicted in (Scheme 64). It was suggested that intermediate (**213**) was generated by the intramolecular annulation of N,N-dimethyl-2-alkynylaniline (**210**). Subsequently, chloride of bismuth(III) chloride attacked the intermediate (**213**) and removed the –Me group present at the intermediate (**213**). Meanwhile, the $BiCl_3$ activated the trifluoromethane sulfanylamide (**211**), generating trifluoromethanesulfanyl cation (CF_3S+), which then reacted with the iodolium generated in situ, affording the 3-(trifluoromethyl)thio)indole (**212**). Many functional groups including halogens (X) (X = Cl, F), and ester were tolerated in this reaction. Moreover, N,N-dimethyl-2-alkynylanilines underwent the reaction smoothly with different substituents present at C≡C [208].



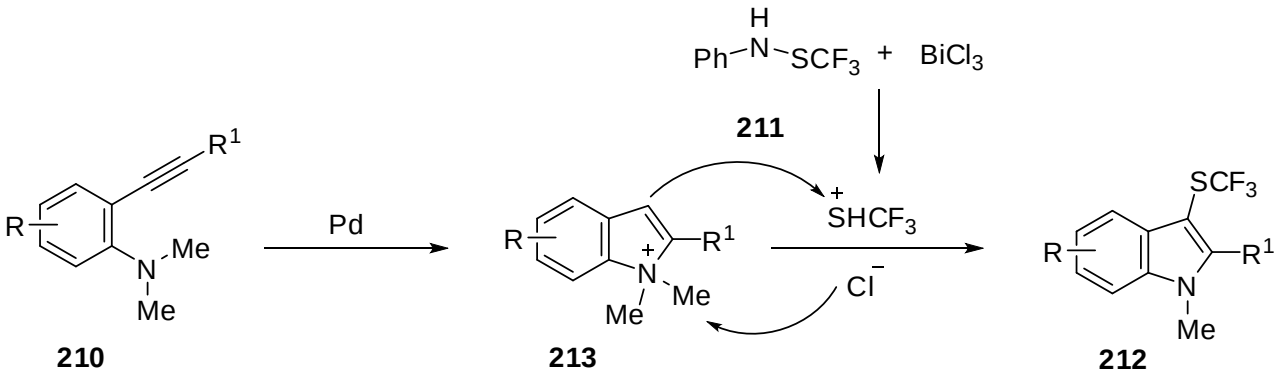
Scheme 61. Synthesis of 3-sulfenylindole derivatives via cascade annulation/arylthiolation reaction.



Scheme 62. The mechanism of cascade annulation/arylthiolation reaction.

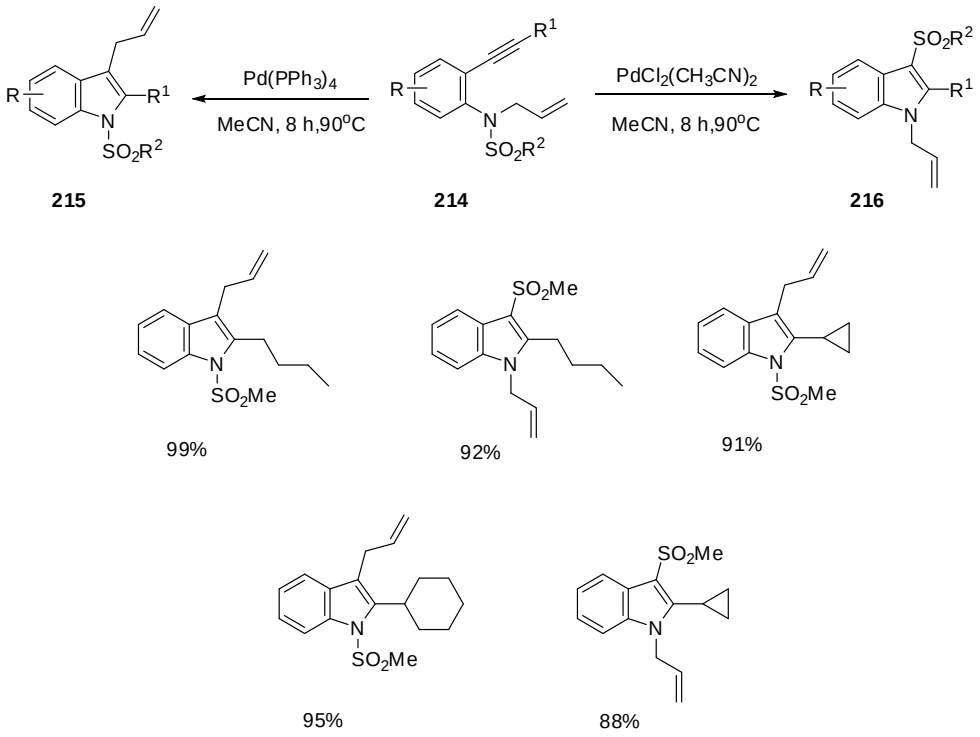


Scheme 63. Synthesis of 3-((trifluoromethyl)thio)indoles via intramolecular annulation.



Scheme 64. The plausible mechanism for intramolecular annulation of N,N-dimethyl-2-alkynylaniline.

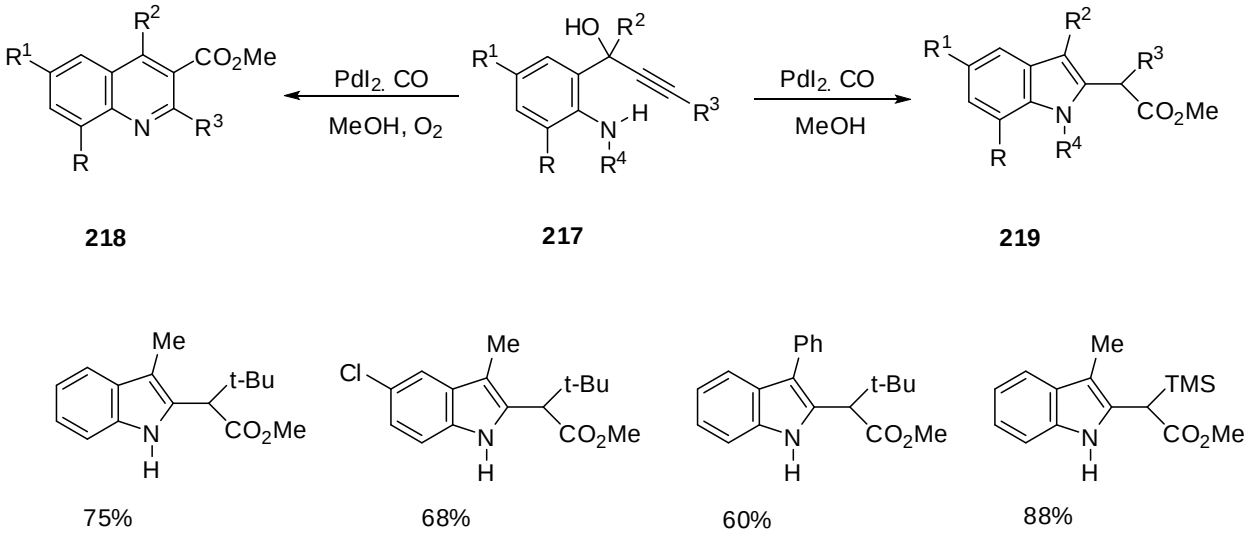
The 3-sulfonyl indoles were prepared by another simple and effective method. The migratory group in intramolecular migration was the sulfonyl group instead of the allyl group. In 2016, Wu et al. developed intramolecular selective addition of S–N and C–N bonds to C≡C in the presence of a Pd-catalyst, forming two distinct indoles. During the reaction difference in oxidation states of palladium, salts were the significant feature in the migration of groups. The allyl group migrated while employing $Pd^{(0)}$, and the sulfonyl group migrated while employing $Pd^{(II)}$. Herein, the N-allyl-N-sulfonyl-o-alkynylanilines (**214**) reacted with the $Pd(PPh_3)_4$ and afforded 3-allylindoles (**215**) by exclusively transferring the allyl group. In the presence of $PdCl_2(CH_3CN)_2$, however, the selective transfer of the sulfonyl group took place and yielded the 3-sulfonylindoles (**216**) (Scheme 65). Thus, using the same set of substrates, simply switching the palladium catalyst afforded two distinct functional indoles. The yields were quite good in the case of both electrons in the donating as well as withdrawing groups [209].



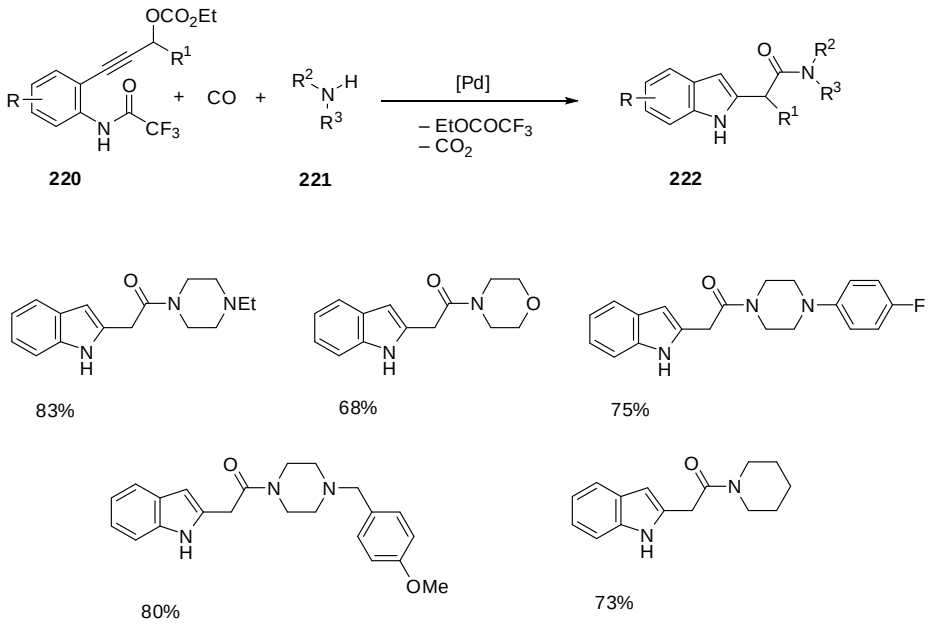
Scheme 65. Synthesis of 3-sulfonyl indoles by cyclization involving allyl group migration.

In 2008, Gabriele and coworkers utilized 1-(2-Aminoaryl)-2-yn-1-ols (**217**) for the carbonylation under a PdI_2-KI catalytic system, in oxidative as well as non-oxidative conditions, to obtain quinoline 3-carboxylic esters (**218**) and indol-2-acetic esters (**219**) respectively (Scheme 66). By carrying out 5-exo-dig annulations and subsequently dehydrating methoxy-carbonylation of 1-(2-aminoaryl)-2-yn-1-ols with either 1° or 2°-NH_2 groups, and C≡C with bulkier substituents, indol-2-acetic esters (**219**) were produced in a moderate to good yield, in the absence of oxidative conditions (2 mol% PdI_2, 20 mol% KI and 90 atm of carbon monoxide in methanol at 100 °C). On the other hand, in oxidative conditions (2 mol% PdI_2 and 20 mol% KI, 80 atm of carbon monoxide-air mixture in a 4:1 ratio in methanol at 100 °C), the same substrate 1-(2-aminoaryl)-2-yn-1-ols having the 1°-NH_2 group was transformed into quinoline 3-carboxylic esters (**218**) selectively via 6-endo-dig annulation and subsequent dehydration and oxidative methoxy-carbonylation. It was concluded that the starting substrate with bulky substituents on the C≡C preferentially underwent 6-endo-dig annulation instead of 5-exo-dig annulation [210].

Cacchi and colleagues synthesized free-NH indole 2-acetamides (**222**) by treating ethyl 3-(o-trifluoroacetamidoaryl)-1-propargylic carbonates (**220**) either with 1° or 2° amines (**221**) in the catalytic system composing of $Pd_2(dba)_3$, carbon monoxide (CO) and dppf using solvent THF at 80 °C (Scheme 67). Furthermore, the free-NH indole 2-acetic acid methyl esters were synthesized. This reaction had certain limitations while using 1° amines, e.g., aniline or benzylamine, as they obtained only a trace amount of indole yielding deacylated propargylic esters and urea [211,212] derivatives as the side products. Thus, more hindered primary amines should be used to limit these side reactions. Out of other bidentate phosphines employed, the dppf ligand was the effective one for this methodology [213].

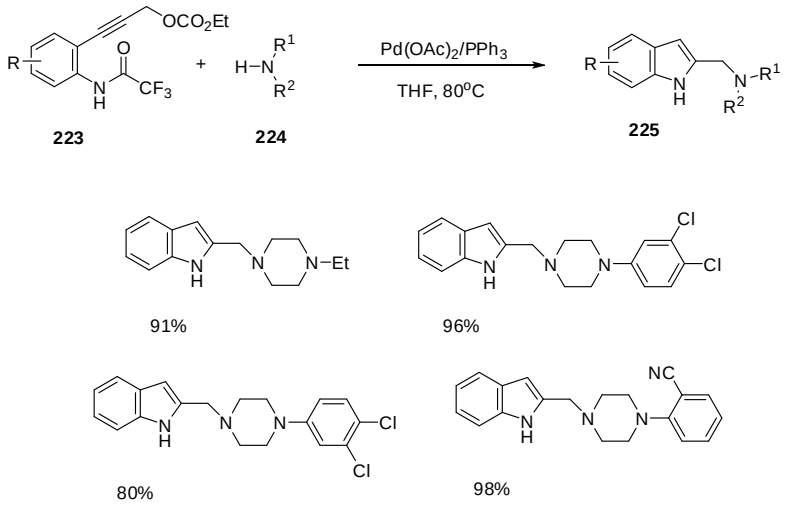


Scheme 66. Synthesis of indol-2-acetic esters by carbonylation of 1-(2-Aminoaryl)-2-yn-1-ols.

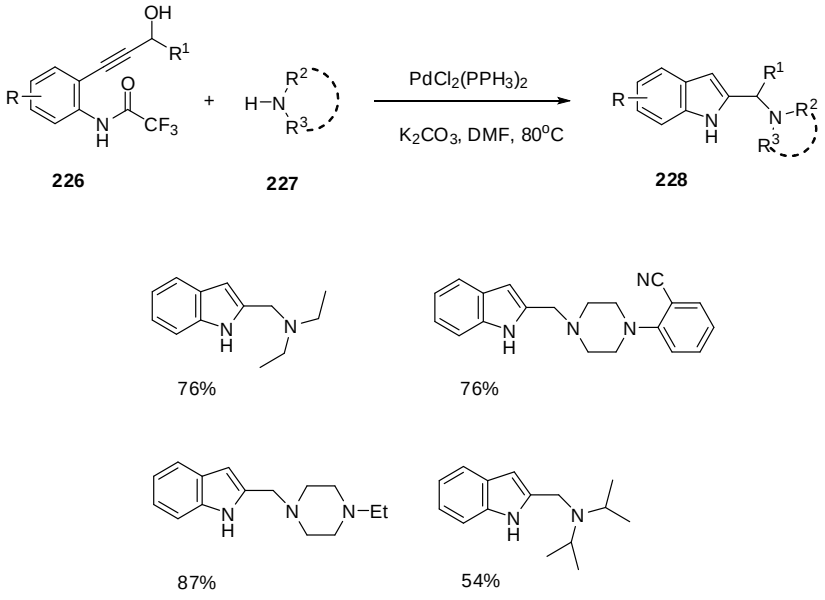


Scheme 67. Synthesis of free-NH indole 2-acetamides from ethyl 3-(o-trifluoroacetamidoaryl)-1-propargylic carbonates.

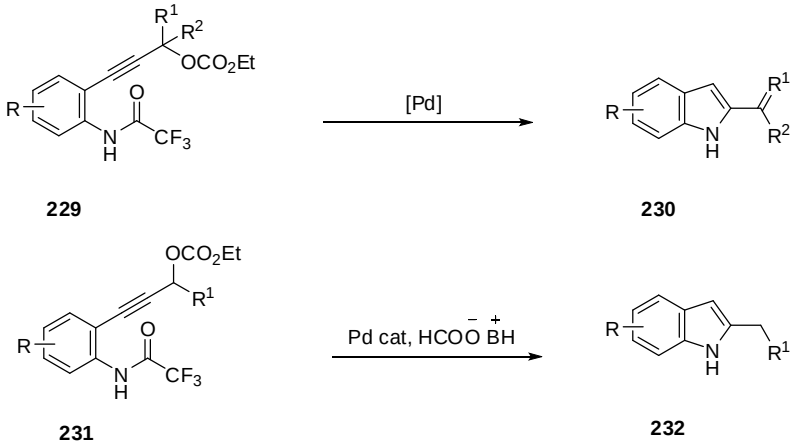
Moreover, Cacchi et al. cyclized 3-(o-Trifluoroacetamidoaryl)-1-propargylic esters (**223**) with amines (**224**) to synthesize the corresponding 3-unsubstituted 2-substituted indole derivatives (**225**). The annulation was catalyzed by $PdCl_2(PPh_3)_2$ (Scheme 68) [214]. Additionally, 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols (**226**) with amines (**227**) using $Pd(PPh_3)_4$ as a catalyst and 2-(aminomethyl)indoles (**228**) were obtained (Scheme 69). This reaction was worked well with both 1° as well as 2° amine, although with 2° amine the yields were better. The reactions went smoothly and provided better yields with 3-(o-trifluoroacetamidoaryl)-1-propargylic alcohols than with the respective carbonate esters [215]. The ethyl 3-(o-trifluoroacetamidoaryl)-1-propargyl carbonates (**229**) with the alkyl group on the propargyl carbon showed an elimination reaction, forming 2-vinylic indoles (**230**) and 2-vinylic indoles stereo-selectively. Ethyl-3-(o-trifluoroacetamidoaryl)-1-propargylic carbonates (**231**) also afforded 2-alkylindoles (**232**) in the presence of HCOOH, with base Et_3N, and catalyst $Pd(PPh_3)_4$ in solvent CH_3CN 80 °C (Scheme 70) [214].



Scheme 68. Synthesis of 3-unsubstituted 2-substituted indoles from 3-(o-Trifluoroacetamidoaryl)-1-propargylic esters.

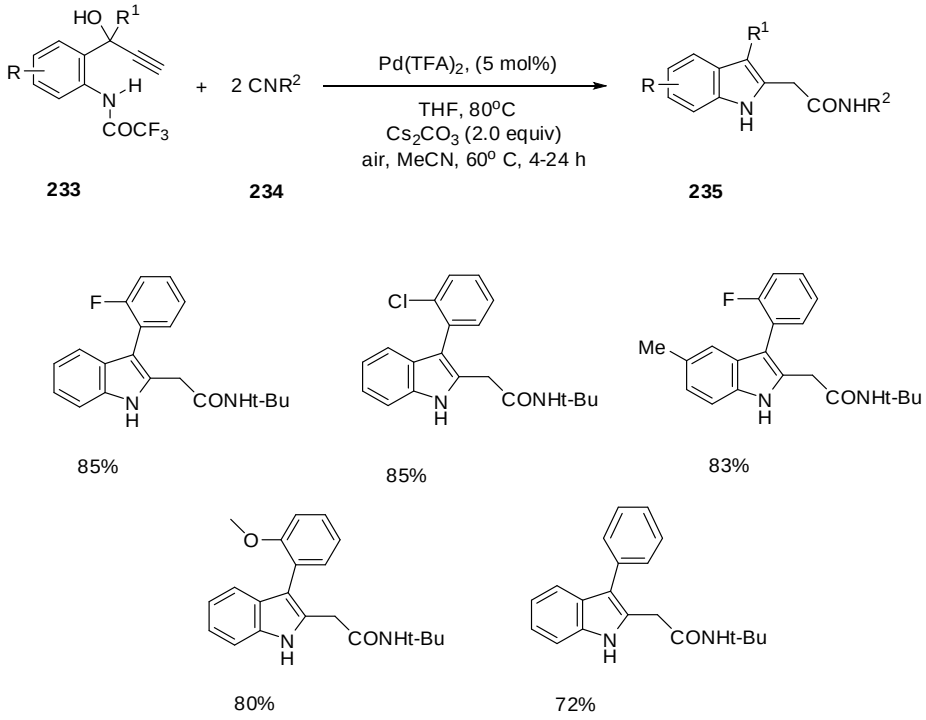


Scheme 69. Synthesis of 2-(aminomethyl)indoles from 3-(*o*-trifluoroacetamidoaryl)-1-propargylic alcohols.



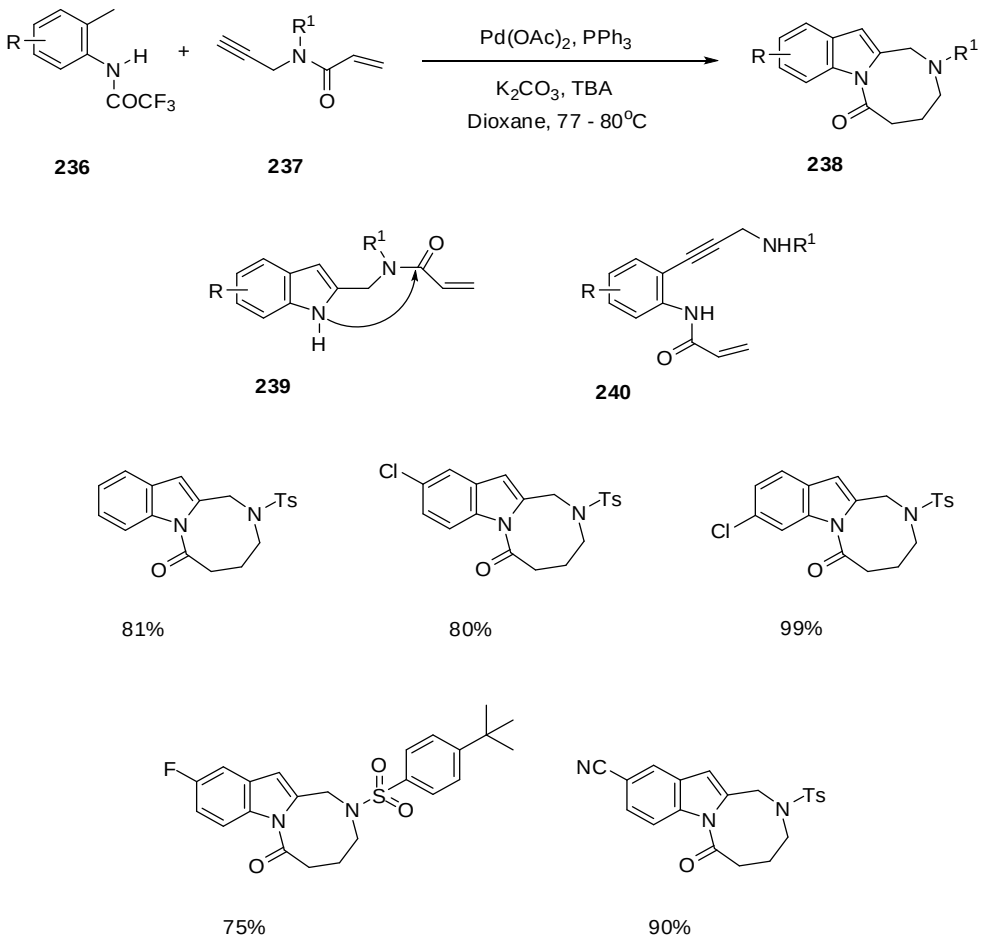
Scheme 70. Stereoselective formation of 2-vinylic indoles and synthesis of 2-alkylindoles.

In 2014, Thirupathi and colleagues developed 2-indolylacetamides (**235**) by a Pd-catalyzed tandem annulation of (amino aryl)propargyl alcohols (**233**) and isonitriles (**234**) in excellent yields. The transformation was carried out in the presence of a $Pd(TFA)_2$ catalyst, Cs_2CO_3 base, and CH_3CN solvent in the open air at 60 °C (Scheme 71). It was found that electron-deficient substrates as well as less hindered isopropyl isonitriles and phenyl isonitriles remained intact in this transformation. Additionally, the internal alkynes yielded this reaction even on increasing the reaction time at high temperatures. Halogens were well tolerated during this reaction. The plausible mechanism suggested that the reaction was a tandem process that involved trans-aminopalladation and 5-exo-dig cyclization. Then isonitrile insertion followed the migration of the 1,4-OH group. For this reaction, palladium in its two oxidation states $Pd^{(0)}$ and $Pd^{(II)}$ activated the reactants and carried out the annulation process without additional oxidants [216].



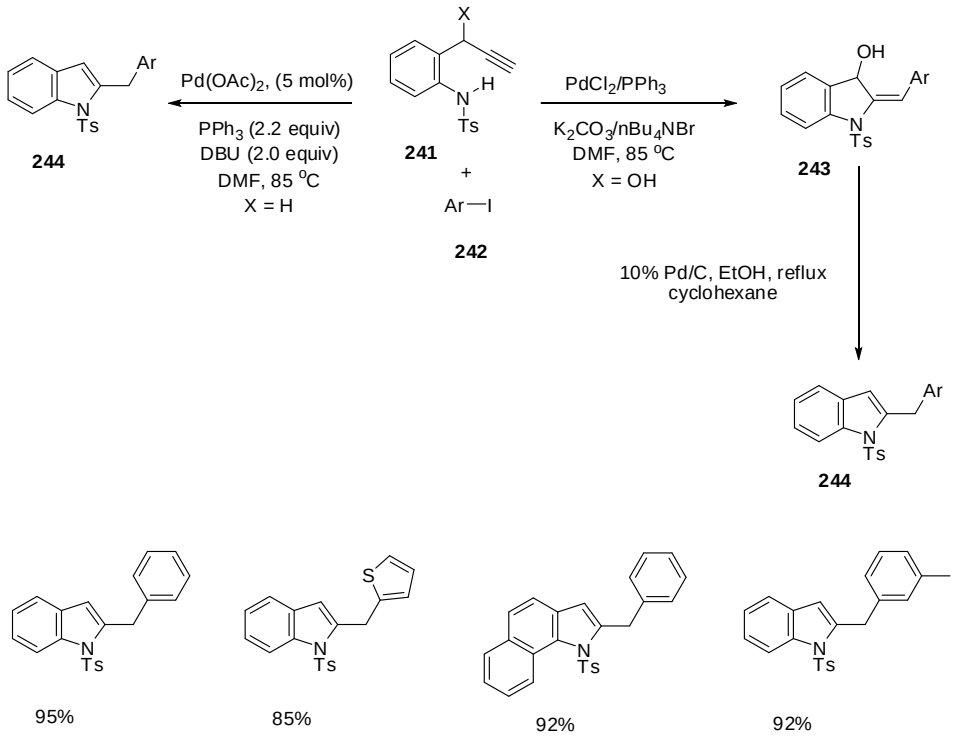
Scheme 71. Synthesis of 2-indolylacetamides by tandem annulation.

In 2015, Liu and co-workers used a Pd-catalyzed cascade process for the synthesis of tetrahydro[1,4]diazepino[1,2-a]indoles (**238**) by treating 2,2,2-trifluoro-N-(2-iodophenyl)acet amides (**236**) with N-protected (prop-2-yn-1-yl)acrylamides (**237**) (Scheme 72). By this method, 1,2-fused tricyclic indoles were obtained. The mechanistic studies suggested a plausible mechanism involving Sonogashira cross-coupling or annulation of indole by regioselective as well as chemoselective N-1 acylation and subsequent 1,4-Michael addition. It is worth noting that the formation of (**239**) was the consequence of this cyclization. The assumption thus rejected the participation of intermediate (**240**) obtained through trans-intermolecular amidation. The benzene ring with electron-donating substituents, e.g., –Me and –OMe, afforded the products in lower yields; on the contrary, excellent yields were obtained with electron-withdrawing substituents such as –F, –Cl, –Br, and –CN. However, the reaction yield was observed in the cases of powerful electron-withdrawing substituents, like carbonyl and trifluoromethyl, being introduced. While investigating the influence of the protecting group on the tandem reaction, it was found that the substrates bearing a sulfonyl protecting group with substituted benzene worked perfectly. Moreover, the benzene ring with electron-donating substituents afforded better yields for an electron-withdrawing substitute [217].

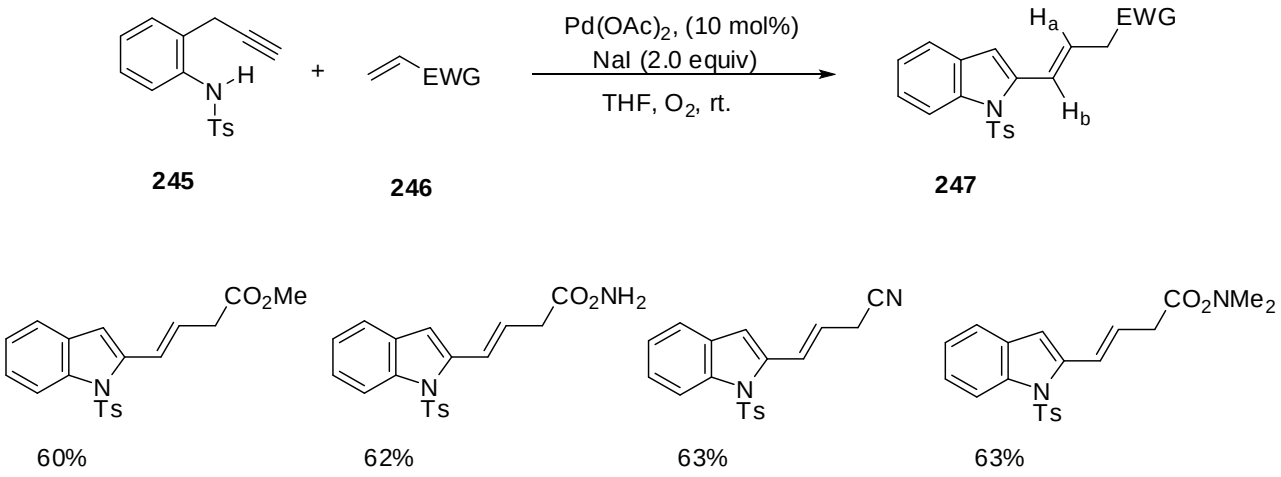


Scheme 72. Synthesis of tetrahydro[1,4]diazepino[1,2-a]indoles by Pd-catalyzed cascade process.

The Pd-catalyzed tandem annulation has been used as an effective alternative for the synthesis of C-2 functionalized indoles. Das and co-workers synthesized 2-arylmethylindoles (**244**) by reacting 2-(2-propynyl)aniline or 2-(2-propynyl)tosylanilide (**241**) and aryl iodides (Ar–I) (**242**) in the presence of $Pd(OAc)_2$, Ph_3P, and DBU (Scheme 73). Aryl iodides with electron-withdrawing substituents, e.g., –F, –Br, $–CF_3$, or $–NO_2$, produced the C-2 functionalized indole in better yields. The 2-(2-Propynyl)tosylanilides (**245**) were more reactive towards the electron-poor olefines (**246**) in the presence of catalyst $Pd(OAc)_2$ and NaI in air, yielding 2-vinylic indoles (**247**) with remarkable (*E*)-stereochemistry around the side chain C=C (Scheme 74) [218]. Furthermore, Chowdhury et al. synthesized (*E*)-2-arylmethylidene-N-tosylindolines (**243**) and their respective quinoline derivatives by reacting 1-(2-tosylaminophenyl)prop-2-yn-1-ols (**241**) and aryl iodides (Ar-I) (**242**) under Pd catalyzed conditions, i.e., $PdCl_2/Ph_3P$ as a catalyst, n-Bu_4NBr as a phase transfer catalyst, and K_2CO_3 as a base in solvent DMF. The proposed mechanism of this reaction has been involved the trans-aminopalladation during 5-exo-dig annulations ensuring high (*E*)-stereochemistry in end products [219].



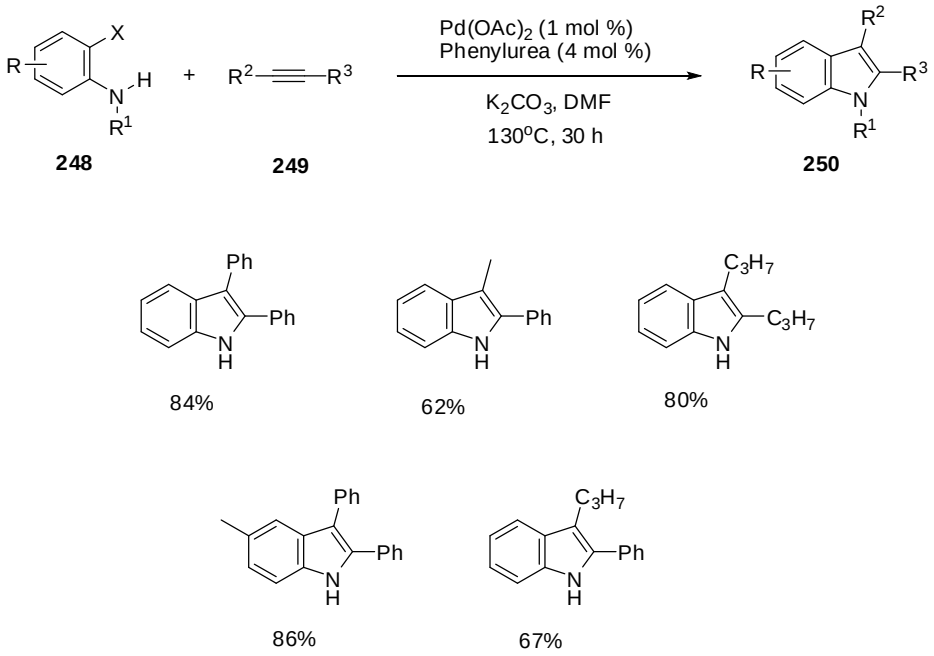
Scheme 73. Synthesis of 2-arylmethylindoles by 5-exo-dig annulation.



Scheme 74. Synthesis of 2-vinylic indoles from electron-poor olefines.

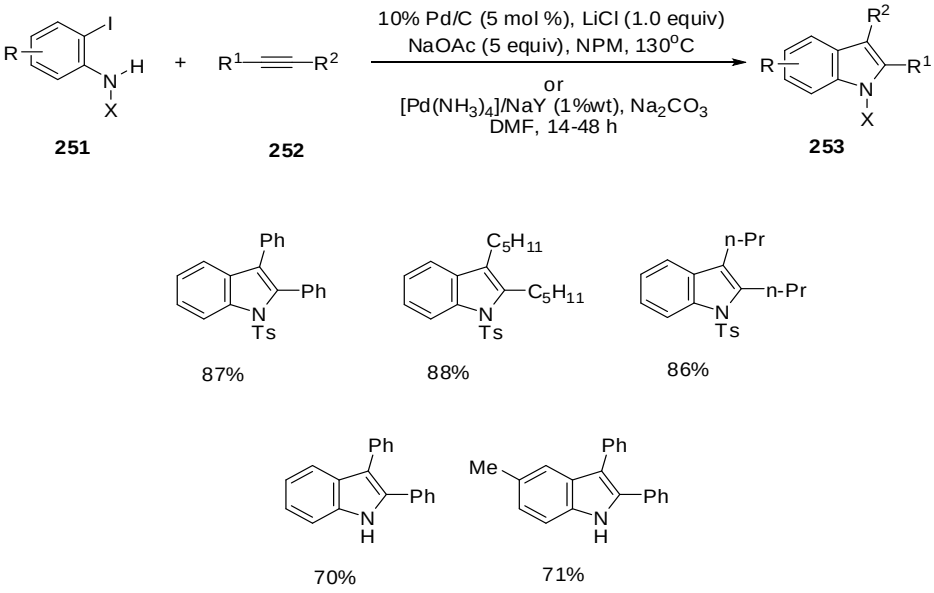
2.3. Indole Synthesis via Annulations of Non-Terminal Alkynes

In 2009, Cui and colleagues developed a methodology utilizing a phosphine-free ligand to accelerate Pd-catalyzed indole synthesis using 2-bromoanilines (**248**) and internal alkynes (**249**) [220]. Phenylurea acted as the optimal ligand promoting indolization by affording 2,3-disubstituted indoles (**250**). The yields of this reaction were quite good. The catalyst $Pd(OAc)_2$ was used to achieve excellent regioselectivity (Scheme 75). It is worth noting that the electron-poor alkynoic acid and ester were not suitable substrates for this reaction [220].



Scheme 75. Synthesis of 2,3-disubstituted indoles from internal alkynes.

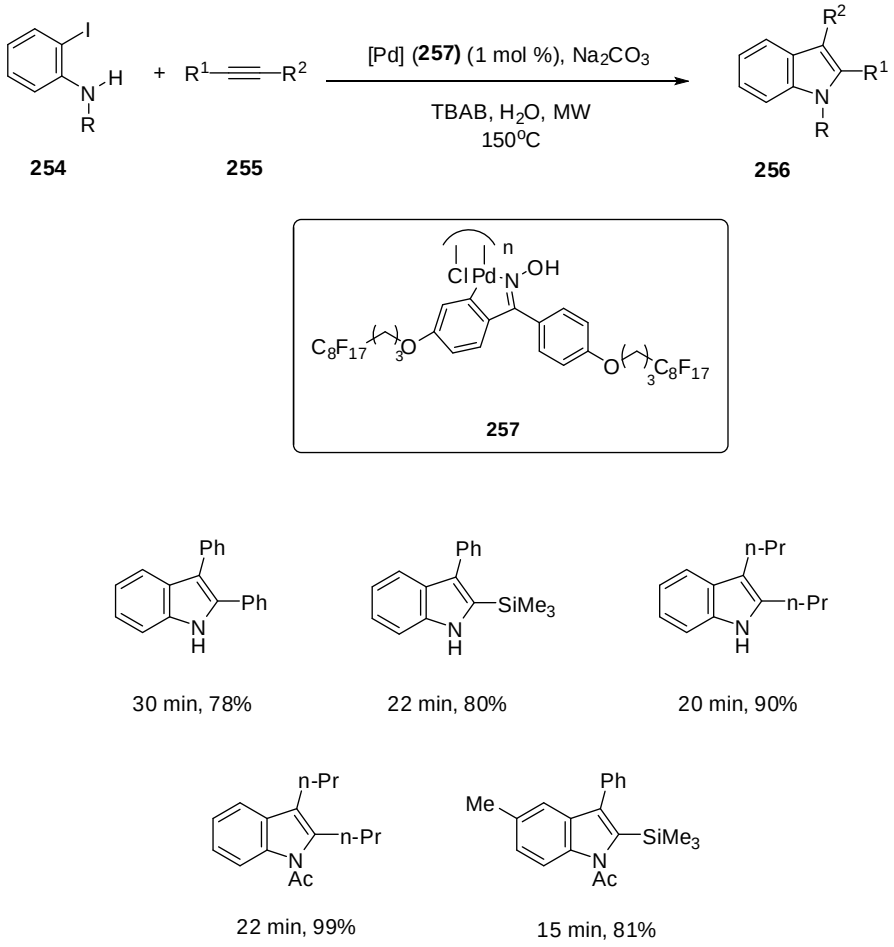
Furthermore, Batail and co-workes developed a methodology using heterogeneous ligands in the absence of salt for obtaining indoles. For this heteroannulation, *o*-haloanilines (**251**) and internal alkynes (**252**) were used in the presence of a Pd/C catalytic system by using Na_2CO_3 as a base in DMF solvent at 120 °C, affording indole derivatives (**253**) (Scheme 76) [221–223]. This catalytic system worked perfectly in the presence of air and was reutilized up to four times. This reaction was independent of the nature of the substrate used [222].



Scheme 76. Synthesis of indole derivatives via heteroannulation.

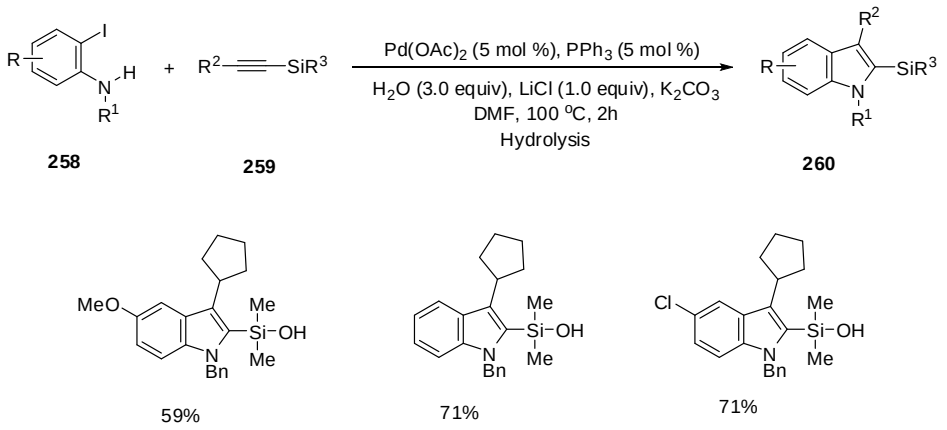
In 2014, Ang et al. synthesized indole derivatives (**256**) by an alternative method using palladacycle (**257**) as a pre-catalyst during annulations of functionalized aryl halides (**254**) with either symmetrical or asymmetrical internal alkynes (**255**) in the presence of H_2O using microwave irradiation (Scheme 77). Internal alkynes, either symmetrical or asymmetrical,

with alkyl (–R), aryl (–Ar), or silyl substituents underwent annulation smoothly. This cyclization reaction afforded the products with high regioselectivity. Usually, solely one product or the major product is formed. The catalytic system could be recycled and reused for up to five cycles. Moreover, the reduction in Pd-catalyst activity was quite slow [224].

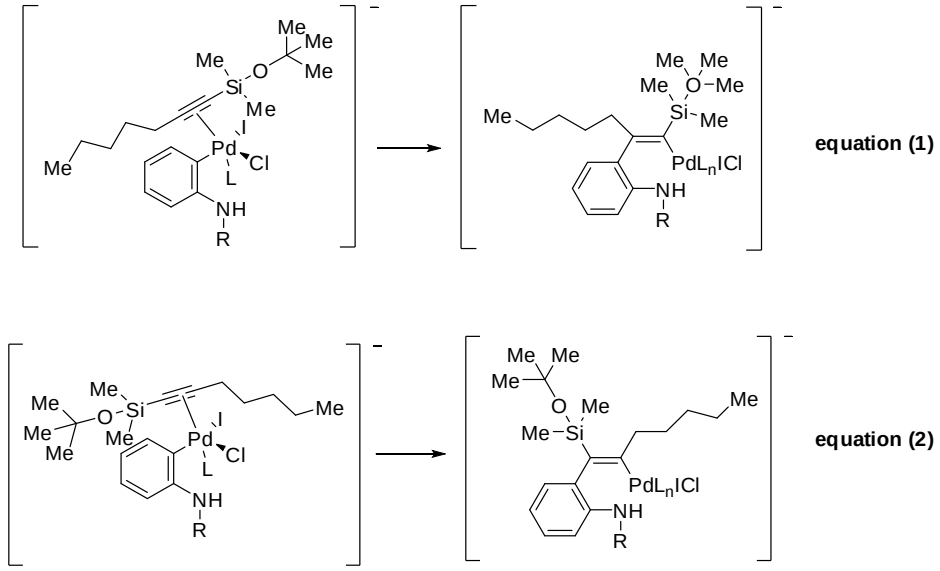


Scheme 77. Synthesis of indole derivatives by using palladacycle.

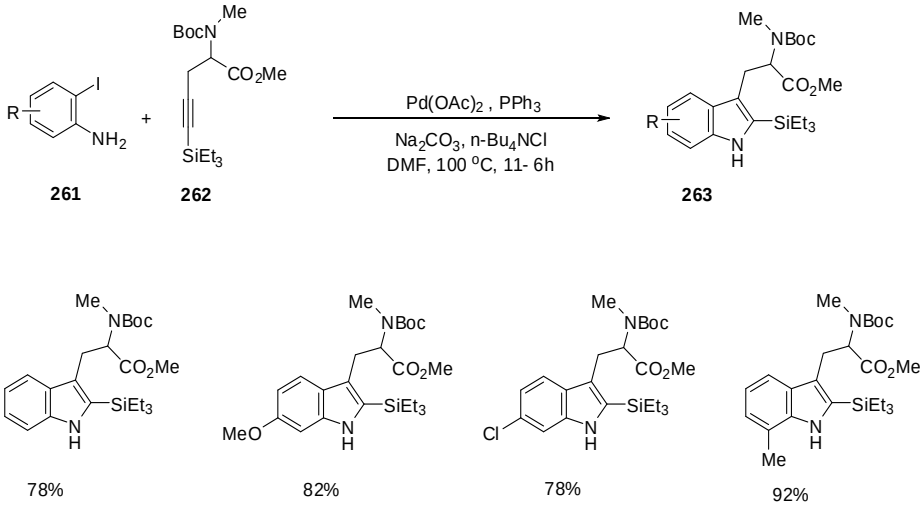
Moreover, Denmark et al. synthesized 2,3-disubstituted indoles (**260**) by sequential Larock hetero cyclization and a cross-coupling reaction directed by silicon. In this reaction, *o*-iodoanilines (**258**) and alkynyldimethyl silyltert-butyl ether (**259**) were used as reactants affording indole-2-silanols by Larock heterocyclization and subsequent hydrolysis. Then, the corresponding sodium 2-indolylsilanolate salts were effectively engaged in a coupling reaction with aryl bromides (Ar–Br) or chlorides (Ar–Cl) to afford poly-substituted indoles (**260**) with excellent regioselectivity (Scheme 78) [225]. For this indolization reaction to occur effectively, only slight changes such as the addition of H_2O and a t-butoxysilyl ether were performed in the original Larock's indole-synthesis conditions. The vital feature for regioselectivity was the steric hindrance of the *t*-butoxysilyl ether present on the alkynes pointing away from it (Scheme 79 (Equation (1))). The migratory insertion, however, occurred and minimized the steric crowding at the shortest carbon-carbon bond (Scheme 79 (Equation (2))), Furthermore, the Pd-catalyzed cross-coupling of derivatives of triethyl silyl propargyl glycine (**262**) with *o*-iodoanilines (**261**) by using Larock's conditions afforded N-ethyl-D-tryptophans (**263**) (Scheme 80) [226].



Scheme 78. Synthesis of 2,3-disubstituted indoles by Larock heterocyclization.

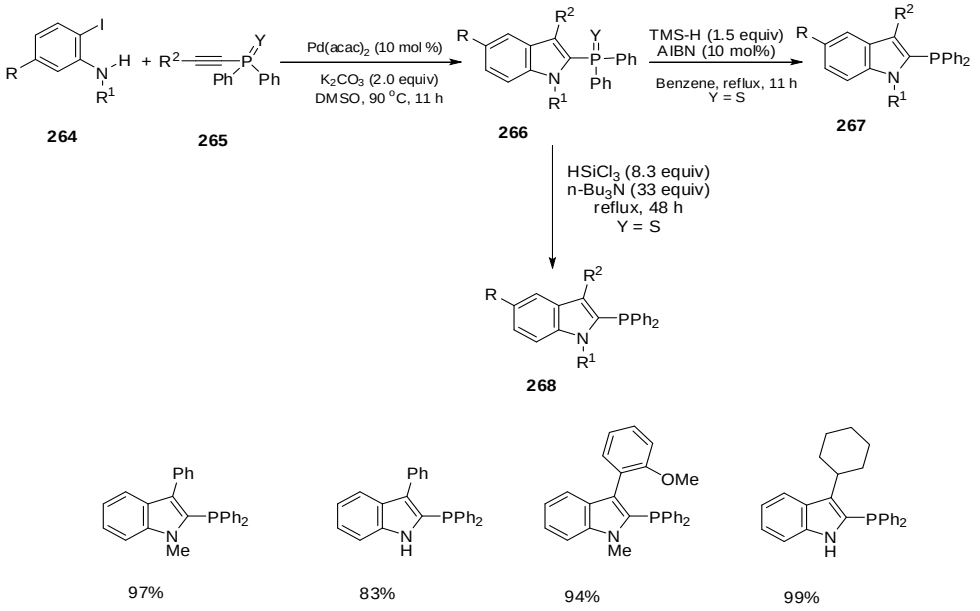


Scheme 79. Effect of steric hindrance on the regioselectivity.



Scheme 80. Synthesis of N-ethyl-D-tryptophans under Larock's conditions.

In 2010, Kondoh and co-workers carried out Pd-catalyzed cyclization of 1-alkynylphos phine sulfides (**265**) with *o*-iodoanilines (**264**) and subsequent desulfidation to afford 3-substituted 2-indolylphosphines (**266**). The plausible mechanism for this reaction involved the Pd-catalyzed cyclization of 1-alkynylphosphine sulfides and 2-iodoanilines, affording 2-indolylphosphine sulfides with a substituent directly derived from the 1-alkynylphosphine sulfides present in proximity to the thiophosphinyl group. Thus, this created steric crowding around the phosphorus and the substituent present on the nitrogen atom. Then, they were reduced to the respective trivalent phosphines (**267**) using tris-(trimethylsilyl) silane [$(Me_3Si)_3SiH$] and AIBN[$(CH_3)_2C(CN)]_2N_2$ in a catalytic amount. (Scheme 81). Moreover, Pd-catalyzed annulation of 1-alkynylphosphine oxides afforded 2-indolylphosphine oxide derivatives and these derivatives further afforded the trivalent phosphine (**268**) on reduction in the presence of trichlorosilane (HCl_3Si) and TBA [$(C_4H_9)_3N$]. This reaction was worked well in aprotic solvents, like DMS, which was considered to be the best choice. On switching the base to Cs_2CO_3 or Na_2CO_3, the results were not satisfactory, although K_3PO_4 provided good results, similarly to K_2CO_3 [227].

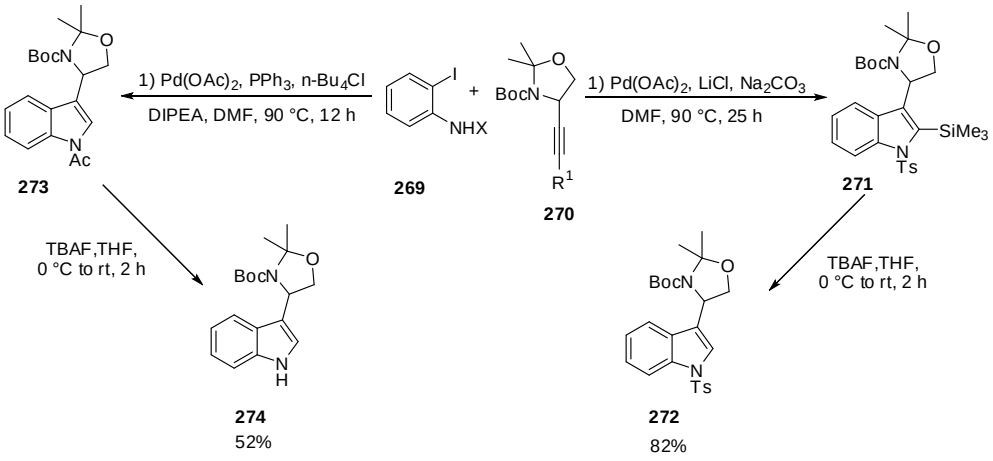


Scheme 81. Synthesis of 3-substituted 2-indolylphosphines.

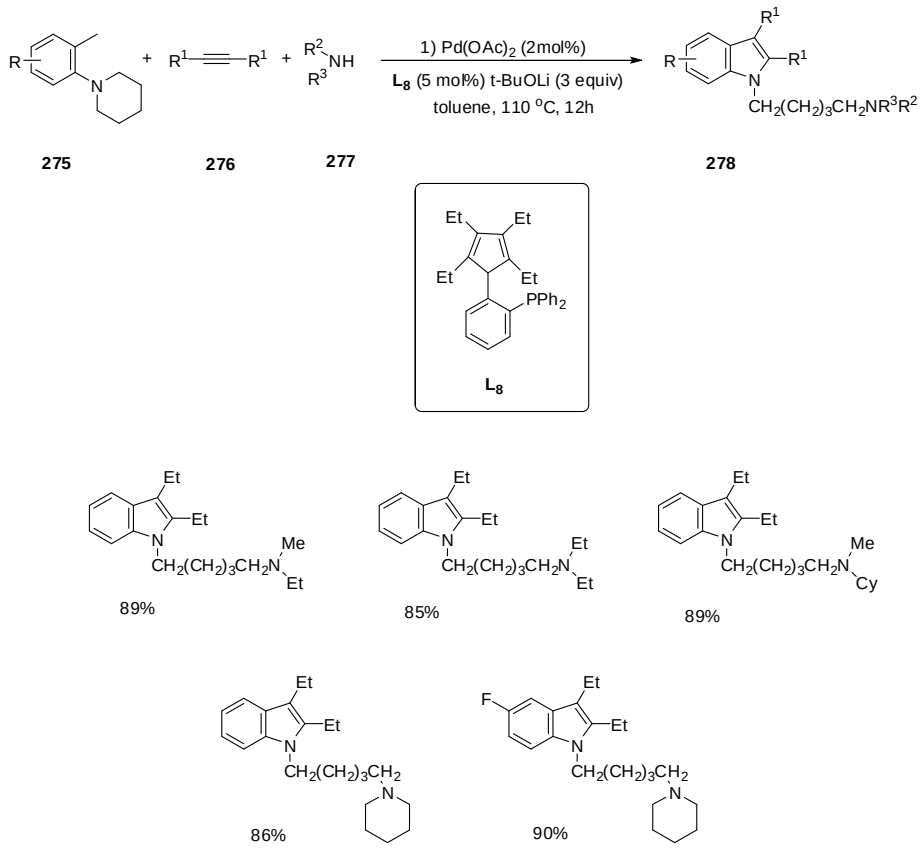
In 2012, Goswami and colleagues synthesized 3-indolylglycine derivatives by reacting 2-iodoaniline (**269**) with ethynyl oxazolidinones (silylated internal alkyne) (**270**) under Larock'sindole synthesis conditions, which afforded 2-silyl-3-indolylglycine derivatives (**271**). The optically active compound (**271**), after desilylation, afforded 3-indolylglycine (**272**). On the other hand, ethynyl oxazolidinones with *o*-iodo-N-Ts-anilines cyclized at 90 °C to yield (**271**) using $Pd(OAc)_2$, LiCl, and Na_2CO_3 in DMF. Rather, the reaction using $Pd(OAc)_2$, Ph_3P, DIPEA, and n-Bu_4Cl in a DMF solvent at 90 °C yielded (**273**) which, on desilylation, afforded 3-indolylglycine (**274**) (Scheme 82) [228].

Furthermore, indoles were synthesized by Pd-catalyzed coupling involving three to four components, i.e., alkynes, aryl iodides (Ar-I), and amines. In 2014, Hao et al. synthesized N-substituted indoles (**278**) via a one-pot reaction between N-substituted-2-iodoanilines (**275**), amines (**277**), and alkynes (**276**) by using $Pd(OAc)_2$ as a catalyst, cyclopentadiene–phosphine as a ligand ($\mathbf{L_8}$), and *t*-BuOLi as a base in the presence of toluene as the solvent at 110 °C. A variety of aryl iodides reacted with both cyclic as well as acyclic amines, and symmetric as well as asymmetric alkynes underwent the reaction smoothly, affording good to excellent yields (Scheme 83). The cyclopentadiene phosphine ligand ($\mathbf{L_8}$) was highly effective [229]. The mechanism suggested that the C(sp^3)–N bond cleavage in the intermediate (**279**) was the product of this reaction. Later on, the reaction

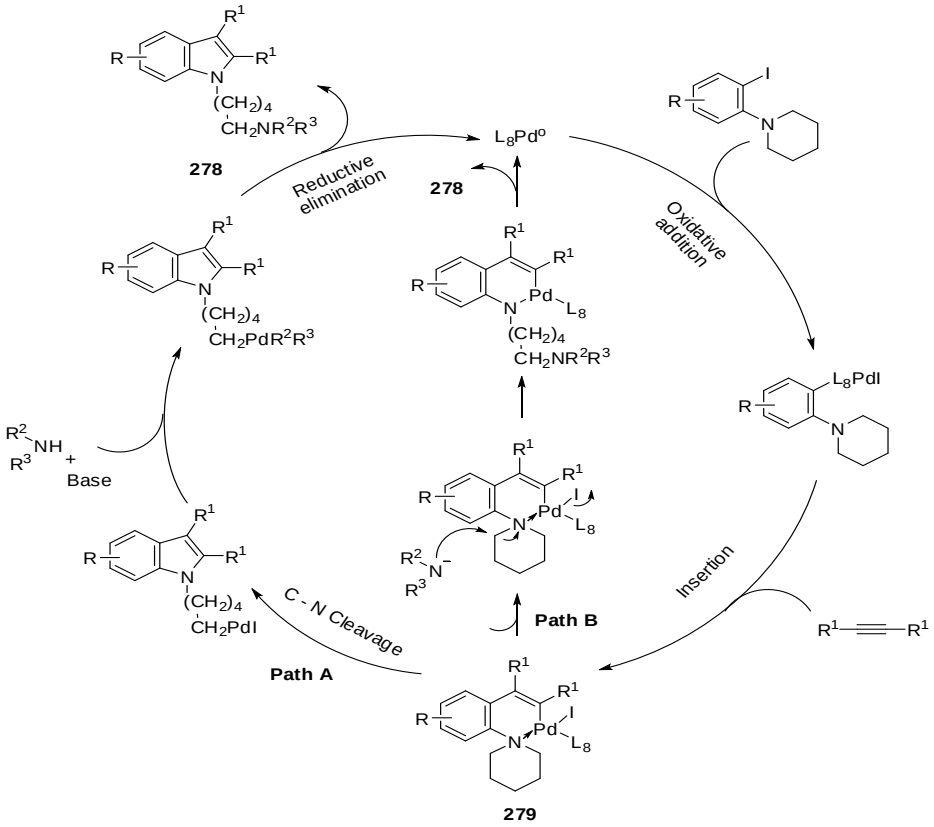
took place by any of the paths, as shown in (Scheme 84). The same research group also reported that the indole N-substituted with alkyl iodides (**280**) were afforded without using amines by Pd-catalyzed C(sp^3)–I bond development through reductive elimination, despite the elimination of sny-β-hydride (Scheme 85) [230]. Furthermore, the Pd(pie-allyl)Cp rather than $Pd(OAc)_2$ promoted the formation of the C(sp^3)–I bond by reductive elimination. Herein, pre-catalyst Pd(pie-allyl)Cp, without the base assistance, generated a highly active species PdL_6 in the presence of phosphine (L_6 = phosphine ligand). Additionally, Pd(pie-allyl)Cp worked well with Ph_3P for this reaction in the presence of base LiO*t*Bu [231].



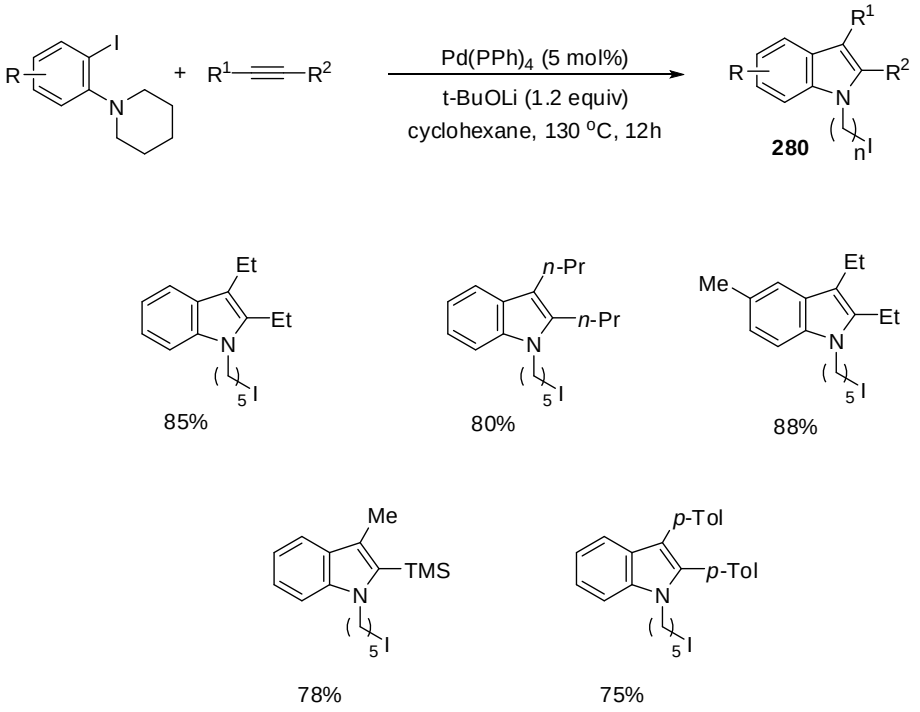
Scheme 82. Synthesis of 3-indolylglycine derivatives by Larock's indole synthesis.



Scheme 83. Synthesis of N-substituted indoles via one-pot reaction.

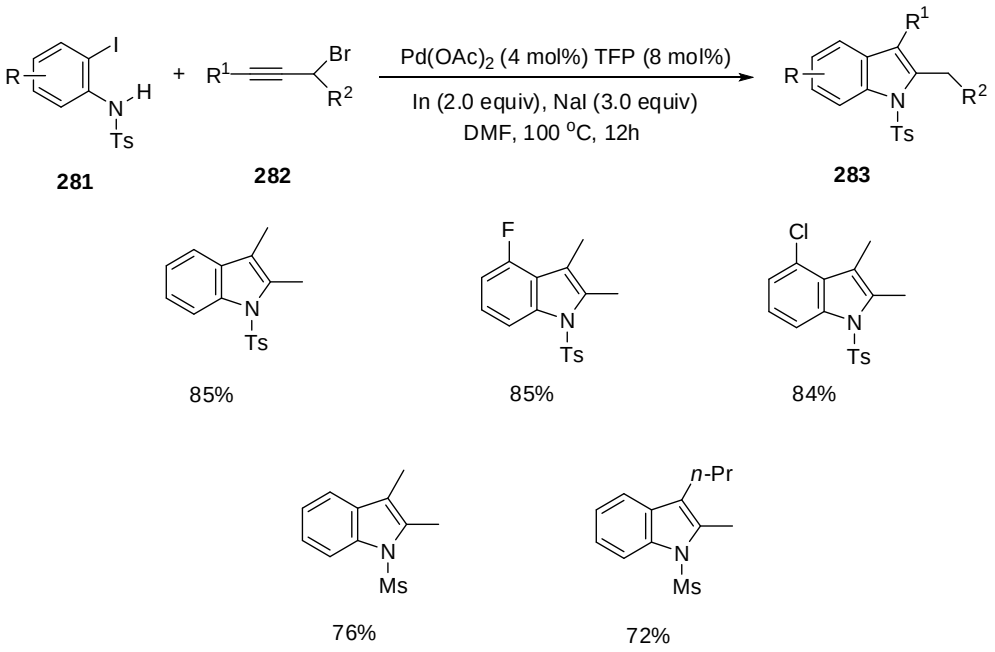


Scheme 84. The plausible mechanism for the one-pot synthesis of N-substituted indoles.



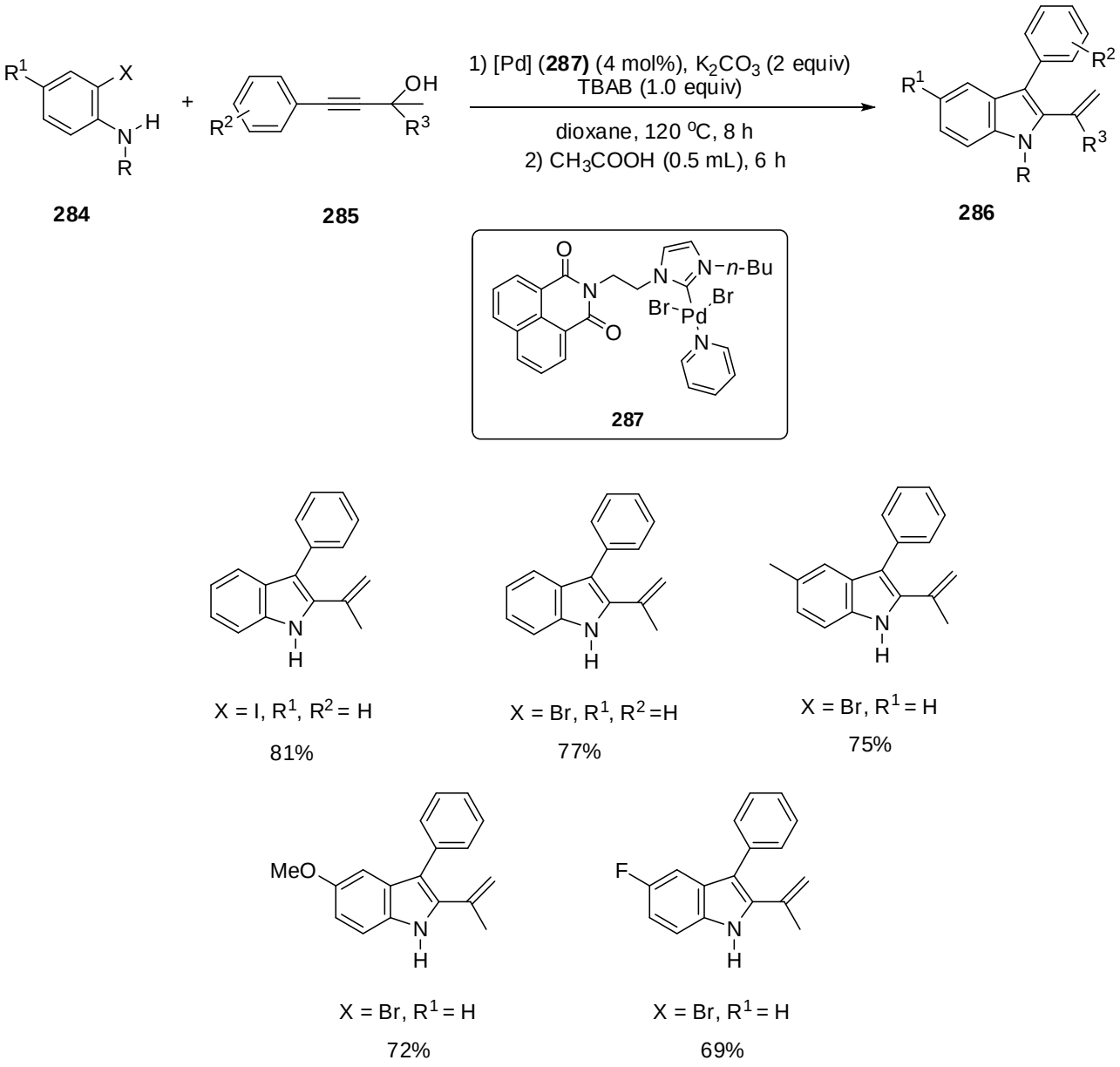
Scheme 85. Synthesis of N-substituted indole through reductive elimination.

In 2013, Zhu and colleagues extended Larock's heteroannulation by employing propargyl bromides instead of simple alkynes. They reported a single-pot reaction between N-protected *o*-iodoanilines (**281**) and propargylic bromides (**282**) to obtain the desired poly-substituted indoles derivative (**283**) (Scheme 86). The cascade reaction took place by C–C bond formation catalyzed by $Pd^{(0)}$ involving in situ-produced organindium and subsequent cyclic isomerization. The effectiveness of this reaction was owing to allenes formation and azapalladation. The choice of protecting groups highly affected the reaction. The N–Ms or N–Tos protected *o*-iodoanilines worked smoothly, producing the desired indole in good yields; on the contrary, N-*p*-Ns-protected *o*-iodoaniline (p-Ns = 4-NO_2-benzenesulfonyl) produced the required indole solely in trace quantities [232].



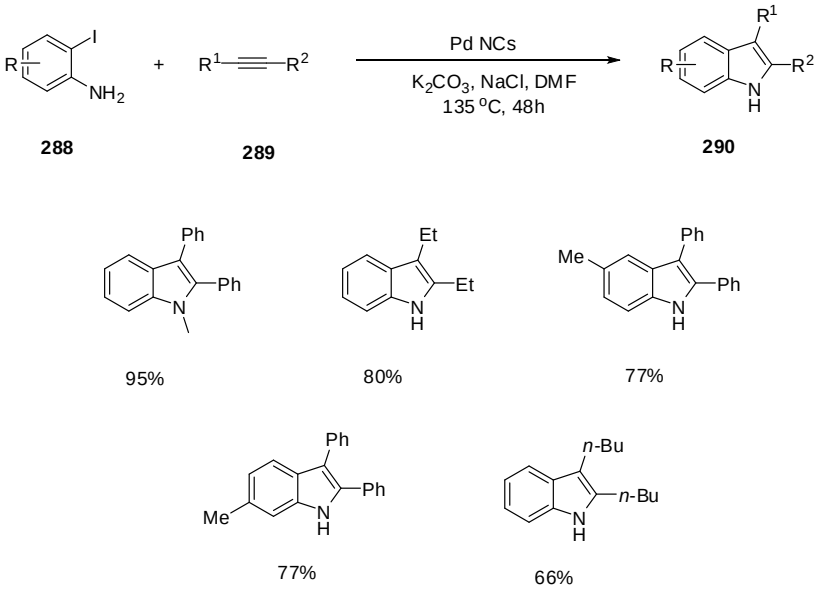
Scheme 86. Synthesis of N-protected indoles by Larock's heteroannulation.

Panyam and Gandhi further expanded the scope of alkynes in Larock's heteroannulation; monometallic and bimetallic Pd(II)/N-heterocyclic carbene complexes appended with bisnaphthalimide or naphthalimide moieties brought about the heteroannulation regioselectivity of tert-propargyl alcohols (**285**) with *o*-haloanilines (**284**), affording 2-alkenylindoles derivatives (**286**) (Scheme 87). A single asymmetrical regioisomer was generated, and the success of this remarkable regioselectivity depended on the directing effect and coordination of the propargylic –OH group to the Pd-catalyst in the Pd-insertion. In addition, experimental studies concluded that in situ HBr generation was responsible for the formation of terminal C=C by a dehydration reaction. Furthermore, the bisnaphthalimide and naphthalimide moieties of the Pd-NHC were critical for the catalytic process. The [Pd] complex (**287**) formed with naphthalimide worked best for this methodology. The reaction only worked perfectly with CH_3COOH, rather than other acids. Deprotection of haloanilines took place during the cyclization. The substrates having –F, –OMe, –MeCO, –EtOOC, –Me, and –CN substituents at position-4 were readily tolerable [233].



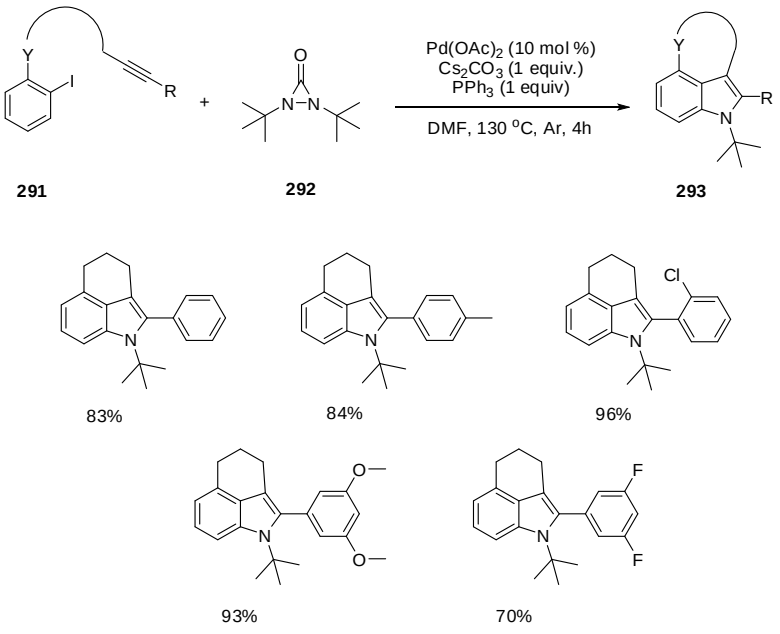
Scheme 87. Synthesis of 2-alkenylindoles derivatives by Larock's heteroannulation.

In 2018, Onishi and co-workers synthesized 2,3-disubstituted indole derivatives (**290**) by reacting *o*-iodoanilines (**288**) and alkynes (**289**) via Larock indole synthesis using Pd nanoclusters (NCs) stabilized by N,N-dimethylformamide (DMF) (Scheme 88). Low catalyst loading was required for this reaction to proceed without needing phosphine ligands. Pd NCs is recyclable and was used for up to three cycles. No product formation was observed in the absence of Pd NCs. The haloanilines with electron-donating substituents, e.g., –Me at 4 and 5 positions with diphenylacetylene, afforded the respective indole derivatives in moderate to excellent yields. However, when the substrates with electron-withdrawing substituents, e.g., 5-Cl and 4-CF_3, were used, the reaction was sluggish [234].

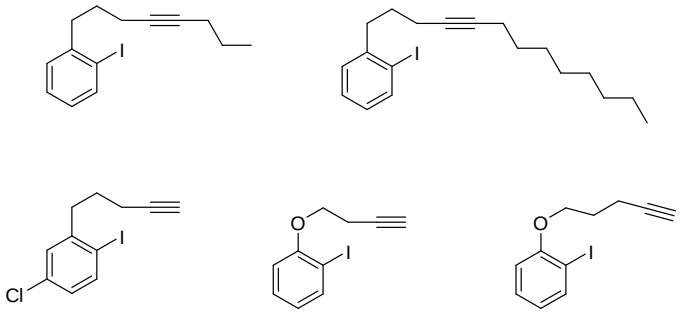


Scheme 88. Synthesis of 2,3-disubstituted indole derivatives by Larock indole synthesis.

In 2020, Zhang et al. reported the synthesis of 3,4-fused tricyclic-indole (**293**) derivatives via Pd-catalyzed cascade [2 + 2 + 1] cyclization of alkyne-tethered aryl iodides (**291**) and diaziridinone (**292**) (Scheme 89). The C,C-palladacycles formed by intramolecular reaction between aryl halides (Ar–X) and alkynes severed as the key intermediates during this annulations. The controlled experimental studies concluded that less loading of PPh_3 and lowering of the temperature decreased the yield of the product. The aryl ring attached to the internal alkyne with electron-donating and electron-withdrawing substituents in ortho, meta, and para underwent the reaction smoothly, affording the desired indoles in 71−96% yields. However, in the case of alkenyl substituents on the internal alkyne, no product was afforded under optimized reaction conditions. The aryl iodide ring and electron-donating as well as electron-withdrawing substituents, worked well. However, alkyl-unsubstituted as well as a substituted alkyne failed to produce this reaction (Scheme 90) [235].



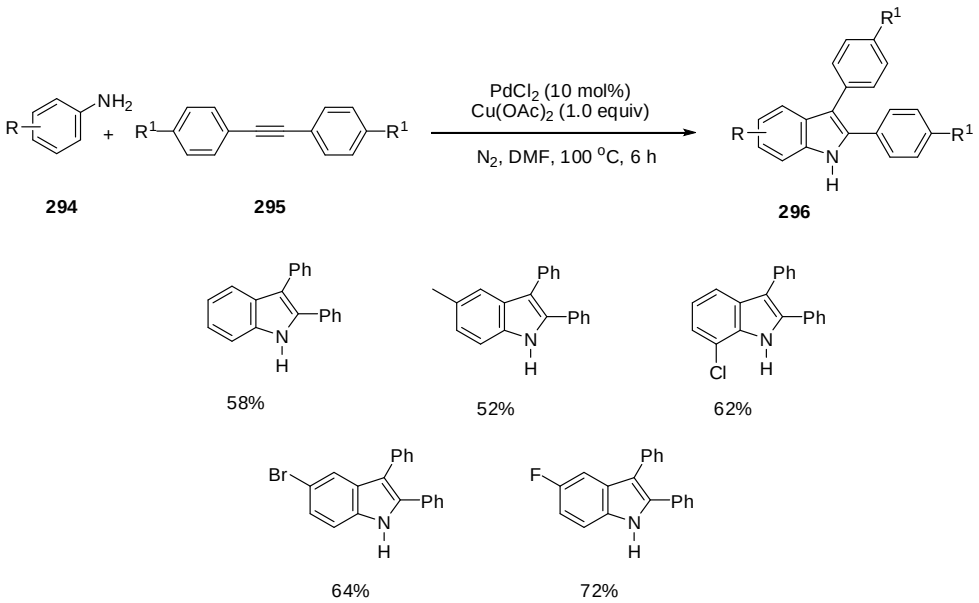
Scheme 89. Synthesis of 3,4-fused tricyclic-indole by cascade [2 + 2 + 1] cyclization.



Scheme 90. Unsuccessful substrates for cascade [2 + 2 + 1] cyclization.

2.4. Indole Synthesis via C-H Activation

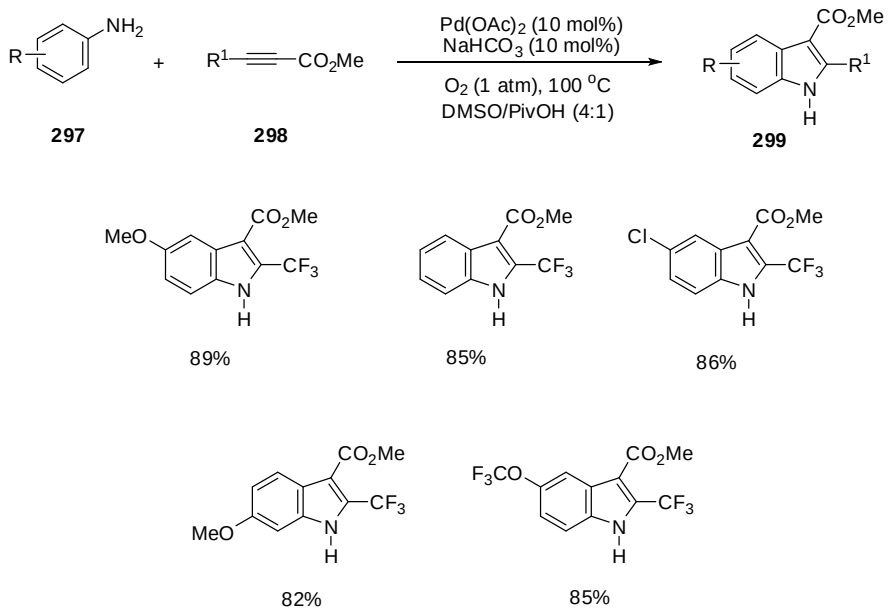
C-H bond activation catalyzed by Pd has an effective synthetic methodology to obtain an indole nucleus [236]. In 2012, Chen and co-workers developed another alternative to the Larcokc's heteroannulation to prepare indoles nuclei. They used Pd-catalyzed intermolecular annulation of symmetrical diarylalkynes (**295**) and anilines (**294**) to afford 2,3-diarylindoles (**296**) or pyrrole derivatives (Scheme 91) in the absence of a phosphine ligand. On using asymmetrical diaryl alkynes, the yield was compromised and a mixture of three indole isomers with zero regioselectivity was obtained. The solvent highly influenced the product formation in this reaction. This was an alternative to Larock's, involving direct activation of the C–H bond and coordination of solvent DMF with the centre of Pd. On using the 1,4-dioxane as a solvent, the end product was penta arylpyrroles. With electron-withdrawing substituents on the alkyne, high product yields were afforded, whereas electron-donating substituents afforded decreased yields [237].



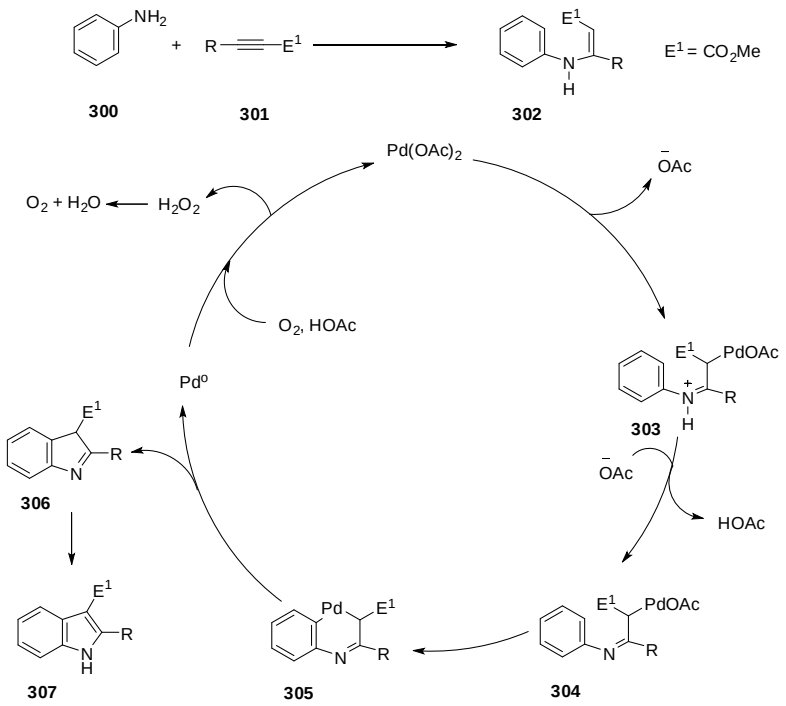
Scheme 91. Synthesis of 2,3-diarylindoles by C-H bond activation.

Shen and colleagues synthesized 2-Perfluoroalkylated indoles (**299**) from anilines (**297**) and alkyl perfluoroalk-2-ynoates (**298**) by a single-pot tandem Michael-addition type reaction/Pd-catalyzed intramolecular CDC (cross-dehydrogenative coupling) in the presence of oxygen (O_2) as an oxidant and DMSO as a solvent at 100 °C (Scheme 92) [238]. Asymmetrical electron-poor alkynes, i.e., methyl perfluoroalk-2-ynoates, were employed for excellent regioselectivity in the desired indole. This reaction was tolerated a wide range of useful electron-donating and electron-withdrawing substituents present at the para position of the aniline. Anilines having powerful electron-withdrawing groups,

however, e.g., $-NO_2$, produced no reaction. The proposed mechanism involved the Michael-type reaction between aniline (**300**) and alkyne (**301**), generating nucleophilic enamine (**302**). Subsequently, electrophilic palladation of (**302**) afforded Pd-intermediate (**303**). The intermediate (**303**) after deprotonation afforded palladium complex (**304**) which underwent aromatic electrophilic palladation via a concerted metalation-deprotonation process (CMD), generating (**305**). Finally, reductive elimination (**305**) afforded the 3H-indole product (**306**) which, on spontaneous tautomerization, produced the desired indole (**307**) and Pd^0 complex which, oxidized in acid again by O_2, regenerated the active Pd-species to carry out the next cyclization (Scheme 93) [238].

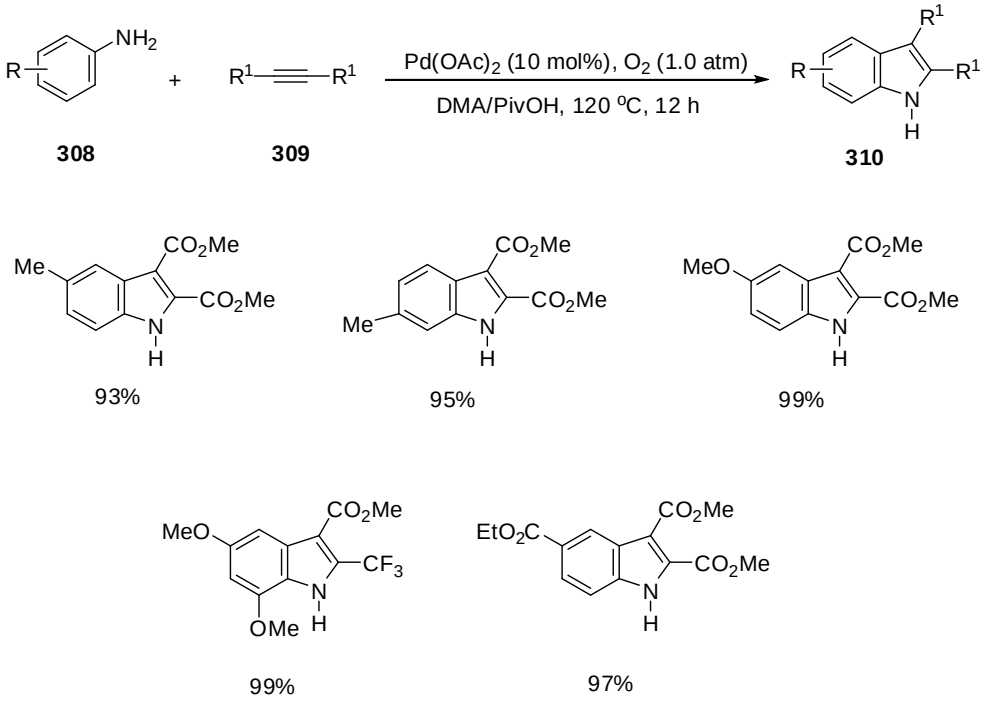


Scheme 92. Synthesis of 2-Perfluoroalkylated indoles by tandem Michael-addition type reaction.



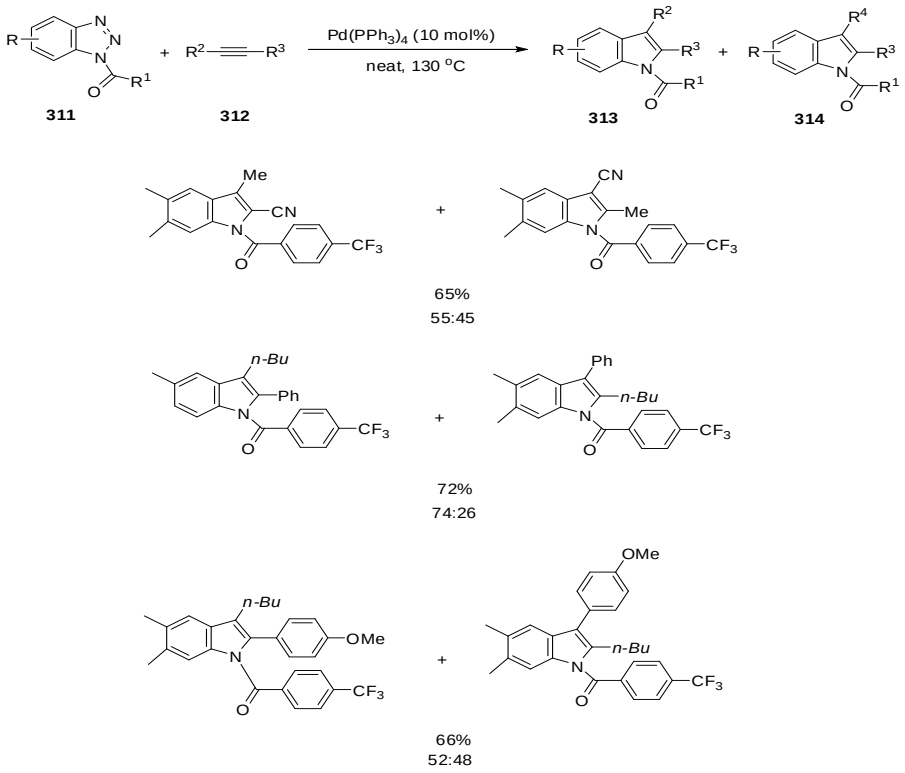
Scheme 93. The plausible mechanism for the synthesis of 2-Perfluoroalkylated indoles.

In 2009, Shi and co-workers constructed indole derivatives (**310**) by direct activation of the C-H bond in the presence of a catalyst and O_2 (1 atm) in the regioselective reaction between anilines (**308**) and alkynes (**309**) (Scheme 94). The role of the oxidant was crucial in the catalytic annulations in the activation of the C-H bond. The studies showed that oxygen (O_2) was the ideal oxidant for this reaction and BQ, $Cu(OAc)_2$, $PhI(OAc)_2$, and AgOAc also worked perfectly in this methodology. The N-unsubstituted and N-alkyl mono-substituted anilines underwent the reaction smoothly, affording the desired indoles. Due to milder reaction conditions, an additional ligand or base was not required. The reaction proceeded well with electron-deficient alkynes- and anilines bearing either electron-withdrawing or electron-donating substituents, producing moderate to excellent yields. Steric crowding was not influenced by reactivity. Thus, all ortho, para, and meta-substituted anilines underwent this reaction smoothly, producing the corresponding products. It is worth noting that the activation of the C-H bond was not a reversible step, and hydroamination took place before the reductive elimination [239].

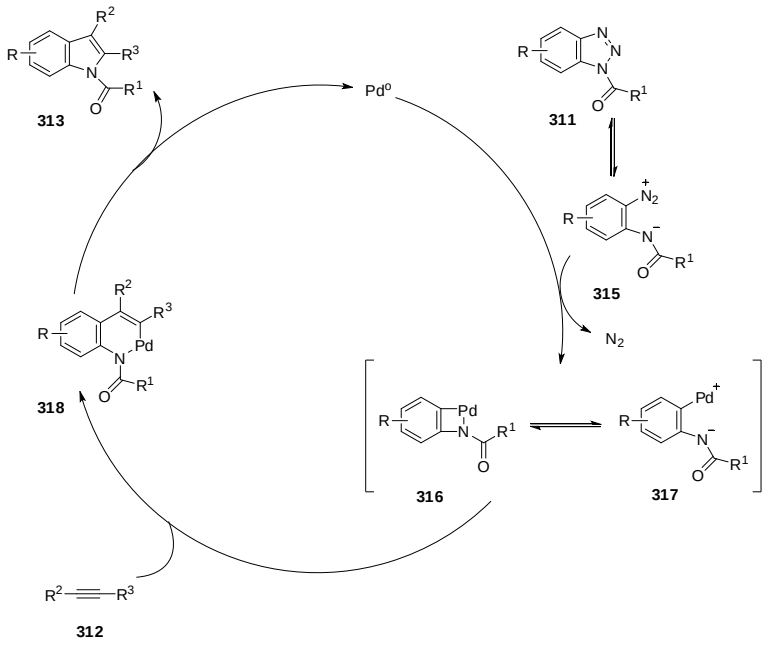


Scheme 94. Synthesis of indoles by direct activation of C-H bond.

Nakamura et al. reported the Pd-catalyzed annulation of N-aroylbenzotriazoles (**311**) in the presence of internal alkynes (**312**) to afford corresponding poly-substituted indoles (**313**, **314**) by using $Pd(PPh_3)_4$ as a catalyst at 130 °C in the absence of a solvent (Scheme 95) [240]. The yields of the corresponding indoles were good. This reaction was also one of the alternatives of Larock's seteroanulation and the aroylbenzotriazole was used instead of *o*-haloanilide. During the reaction with asymmetric alkynes, a mixture of regioisomers was obtained with the major product bearing the bulkier group at C–2 of the indole ring. The plausible mechanism for the reaction involved oxidative $Pd^{(0)}$ insertion to the C-N bond of diazonium species present in the 2-imino benzenediazonium (**315**), releasing N_2 and affording the intermediates (**316**) or (**317**). The (**315**) was generated thermally from benzotriazole (**311**) [241–244]. The Palladacycle species (**318**) was obtained after internal alkyne (**312**) insertion into the C–Pd formed bond present on the intermediates (**316**) or (**317**). Finally, reductive elimination afforded the product (**313**) (Scheme 96) [240].



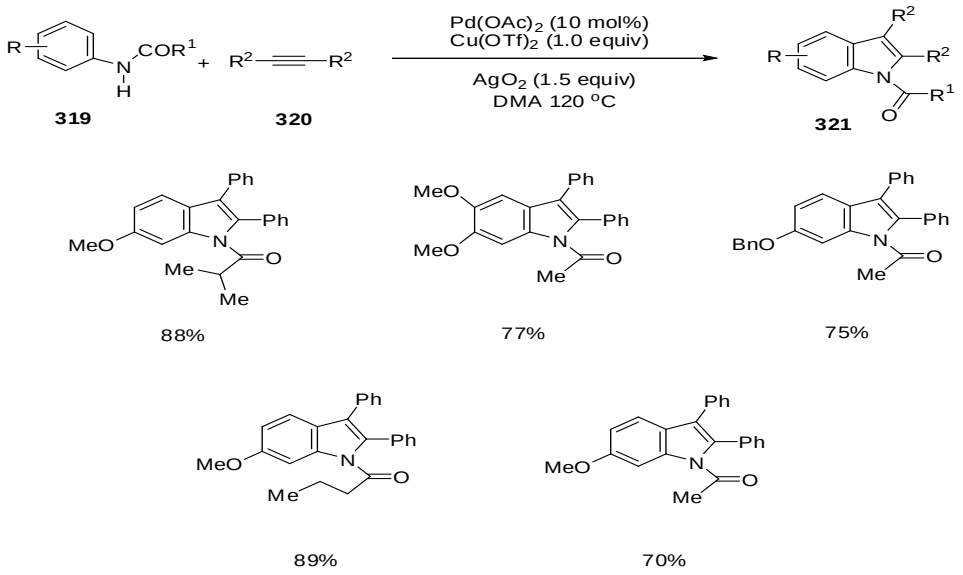
Scheme 95. Synthesis of poly-substituted indoles from N-aroylbenzotriazoles and internal alkynes.



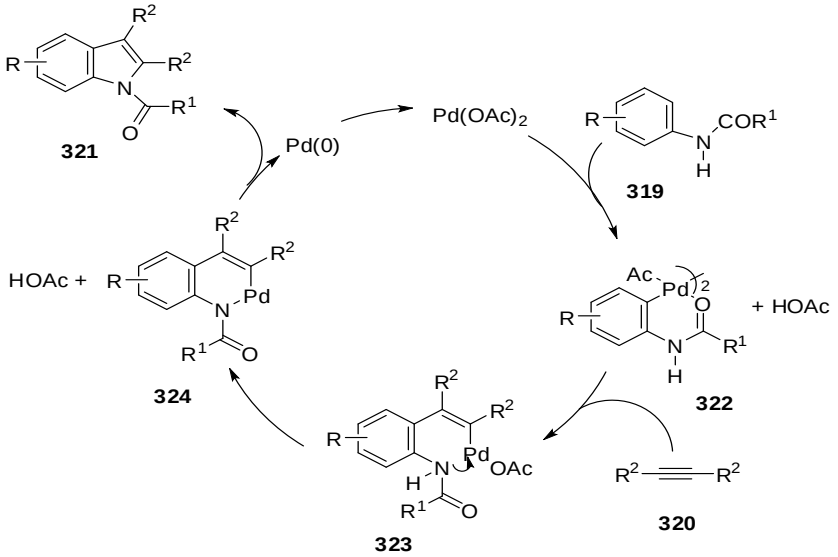
Scheme 96. The alternative mechanism of Larock's heteroanulation.

In the Pd-catalyzed activation of the C–H bond, the N-acetyl anilines were effective substrates for constructing an indole nucleus. In 2011, Zhou and colleagues reported a strategy involving activation of C–H bond present in N-aryl amides (**319**) in the cross-coupling reaction with alkynes (**320**) using a catalytic system comprised of catalyst $Pd(OAc)_2$, oxidants Ag_2O and $Cu(OTf)_2$ in the presence of solvent DMAc to obtain the corresponding indole derivatives (**321**) (Scheme 97). Herein, the presence of acetamino performed two tasks: one as the directing group and the second as a source of N-atom for the indole

nucleus (Scheme 97). A plausible mechanism showed that the reaction involved a six-membered palladacycle (**322**) generated by ortho electrophilic palladation of aromatic moiety with the coordination of the acetamino substituent [245,246]. The (**322**) after alkyne (**320**) insertion afforded the vinylic $Pd^{(II)}$ intermediate (**323**), then intramolecular attacking of the amide group followed by deprotonation step afforded the respective palladium amide intermediate (**324**). Finally, intermediate (**324**), on reductive elimination, produced the respective indole derivatives (**321**), releasing a $Pd^{(0)}$ complex. The $Pd^{(0)}$ was oxidized back to the $Pd^{(II)}$ by Ag_2O and $Cu(OTf)_2$. It is worth noting that when $CuCl_2$ was replaced by $Cu(OTf)_2$, there was no formation of diketone as a byproduct. It was found that the formation step of the cyclopalladated complex (**322**) was the product of this annulation reaction. To carry out a stoichiometric reaction, the best results were obtained by using bipyridine in dimethylformamide at 120 °C, which resulted in the formation of the required indole in moderate quantities (Scheme 98). The substrate N-aryl amides with electron-rich substituents at the meta position were most suitable for this reaction [247].

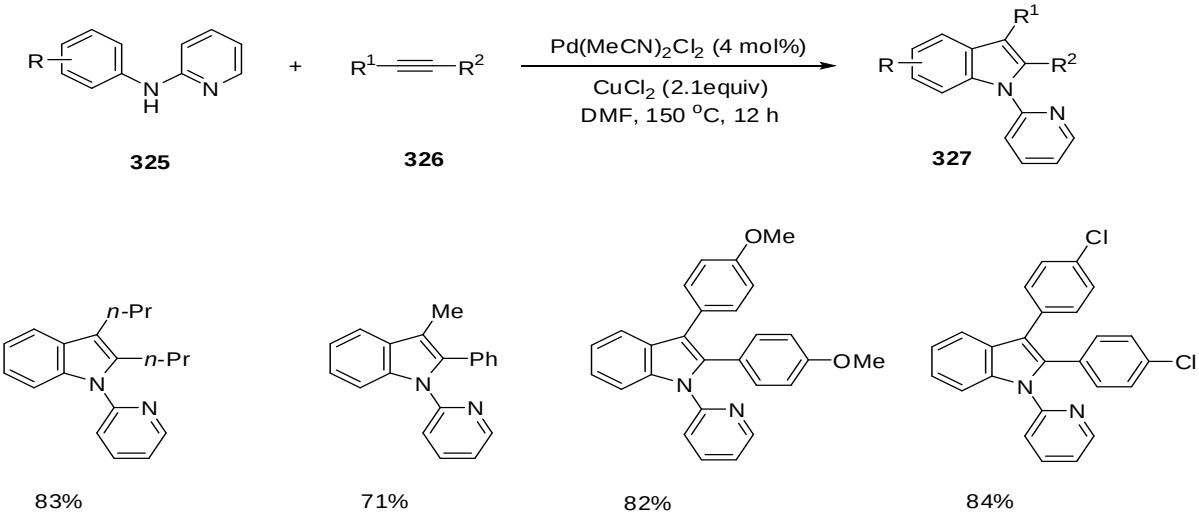


Scheme 97. Synthesis of indoles from N-aryl amides and alkynes.



Scheme 98. Mechanism for the synthesis of indole involving six-membered palladacycle.

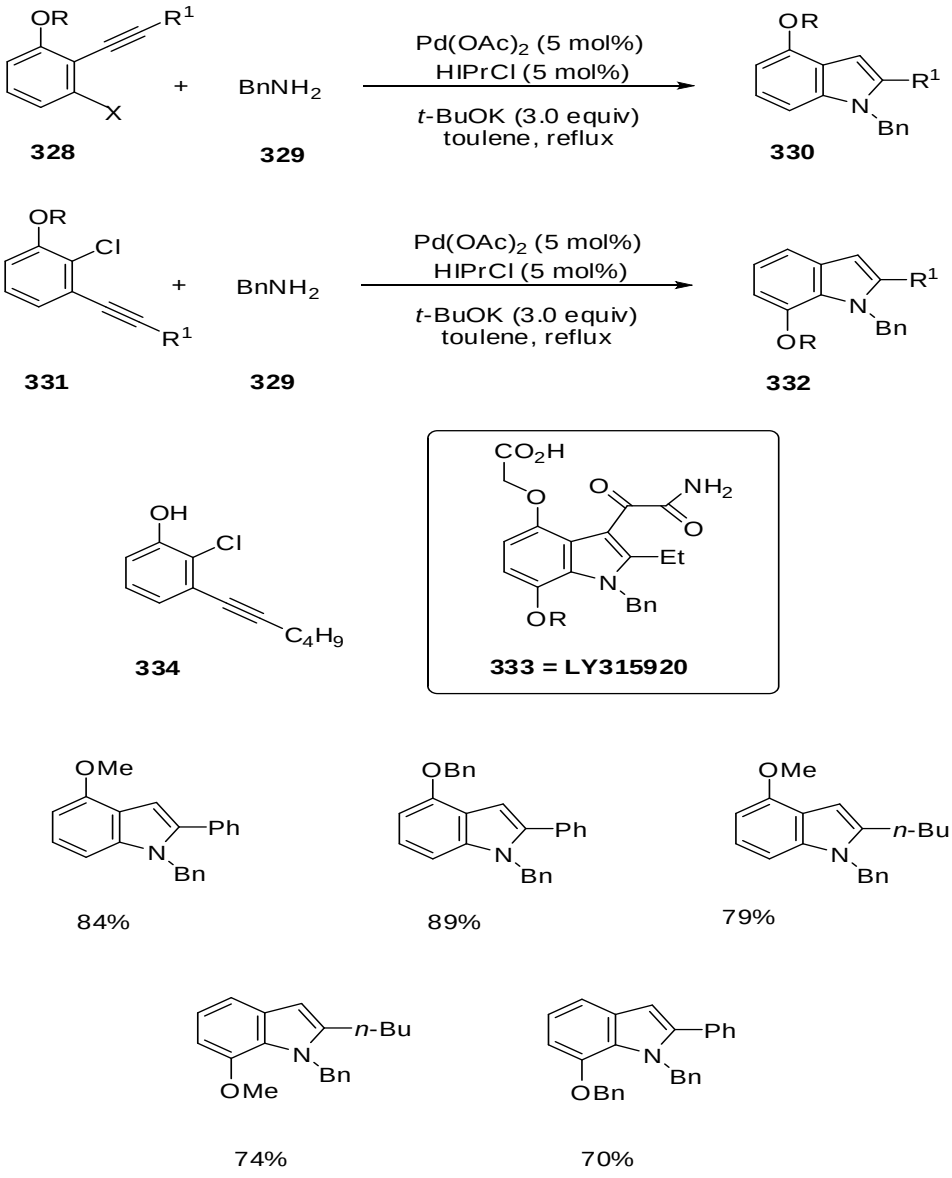
In 2011, Chen et al. synthesized N-(2-pyridyl)indole derivatives (**327**) by an oxidative Pd-catalyzed cross-coupling reaction between N-aryl-2-aminopyridines (**325**) and internal alkynes (**326**). The reaction was performed in the presence of catalyst $Pd(CH_3CN)_2Cl_2$, oxidant CuCl2. Herein, O_2 could also be employed as a terminal oxidant with co-oxidant $CuCl_2$. Moreover, this reaction involved the regioselective ortho activation of the C–H bond of N-aryl-2-aminopyridines (Scheme 99). This methodology with internal alkynes having an alkyl chain attached directly at C≡C and formed a mixture containing two regioisomers of indoles. On the contrary, asymmetrical alkyl (–R) and heteroaryl-substituted alkynes afforded solely one isomer in the product. The results of the reaction further concluded that the steric crowding at the nitrogen in pyridine and the N-aryl moiety was sensitive towards this methodology. Additionally, the N-aryl moiety having electron-withdrawing substituents present on the ring promoted the coupling [248]. In 2014, they extended this work by the synthesis of N-(2-pyridyl)indoles via coupling asymmetrical internal alkynes substituted with an aryl (–Ar) and alkyl (–R) with N-phenylpyridin-2-amines in the presence of catalyst Pd/CeO_2, oxidant Cu(II), salt, and free air co-oxidant. The desired products in a moderate to high yield were afforded via the activation of the C-H bond, with similar results for regioselectivity. However, an indole with an alkyl substituent at the C-3 was the major product [249].



Scheme 99. Synthesis of N-(2-pyridyl)indole derivatives from N-aryl-2-aminopyridines and internal alkynes.

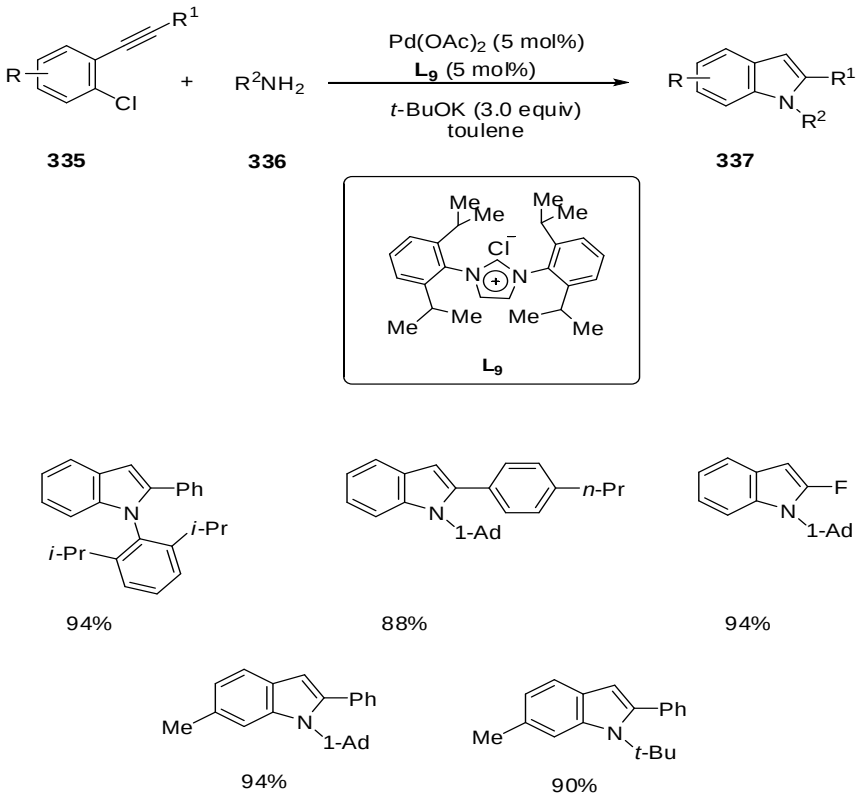
2.5. Indole Synthesis via Hydroamination or N-Arylation

In 2007, Sanz et al. carried out amination reactions of *o*-alkynyl-3-halophenyl ethers (**328**) and *m*-alkynyl-2-halophenyl ethers (**331**) with the benzylamine ($BnNH_2$) (**329**) using a catalytic system comprised of $Pd(OAc)_2$ and (1,3-bis(2,6-diisopropylphenyl)imidazolium chloride) (HIPrCl) with base KOt-Bu under refluxing conditions in toluene (Scheme 100). By this reaction, regioselective indole derivatives with the alkoxy (-OR) functional group at C–4 or C–7 (**330**) and (**332**) were afforded in excellent yields after 2 to 3 h of reaction via a cascade amination/annulation. This approach found its application in the synthesis of LY315920 (2-[3-(2-amino-2-oxoacetyl)-1-benzyl-2-ethyl-1H-indol-4-yloxy]-acetic acid) (**333**), an indole ring containing an inhibitor of PLA_2s (phospholipase A2). The PLA_2s were the secreted phospholipase ($sPLA_2$) present in high concentrations in patients with inflammatory disorders [250]. This methodology did not work well with the unprotected substrate. When derivatives of hydroxyl-2-chloro-3-(hex-1-yn-1-yl)phenol (**334**) were employed, the 7-hydroxyindole derivative was not afforded in a pure form. However, the starting substrate was consumed completely. This happened because the protection of hydroxyl group of 2,3-dihalophenol was necessary for the closure of the benzofuran (obtained as a result of the coupling of 2,3-dihalophenols with terminal C≡C under Cu/Pd-catalysis) [251].



Scheme 100. Synthesis of 4-alkoxy indole and 7-alkoxy indole by cascade amination/annulation.

In 2009, Ackermann et al. disclosed the synthesis of indoles (**337**) containing bulky N-aliphatic or N-aromatic substitutions via a Pd-catalyzed reaction involving an intermolecular N-annulation. This intramolecular reaction involved N-arylation and subsequent hydroamination, affording regioselective formation of the product (Scheme 101). The reaction was carried out between *o*-dihaloarenes or *o*-alkynylhaloarenes (**335**) and sterically crowded amines (**336**) using the catalyst Pd $(OAc)_2$. The Pd-complex generated from N-heterocyclic carbene ligands having unsaturated and sterically crowded imidazolium salt yielded the optimal results in the methodology. Thus, $Pd(OAc)_2$ together with the ligand (**L9**) afforded the respective indoles in moderate to high yields. The reaction tolerated 1-adamantylamine, *o*-alkynyl chloro arenes, and *t*-butylamine [$(CH_3)_3CNH_2$]. The reaction was worked smoothly with less-crowded anilines. The alkynes with a 1° an alkyl-group produced slightly poor results because 2° amine formed quantically underwent intramolecular hydroamination incompletely [252,253].

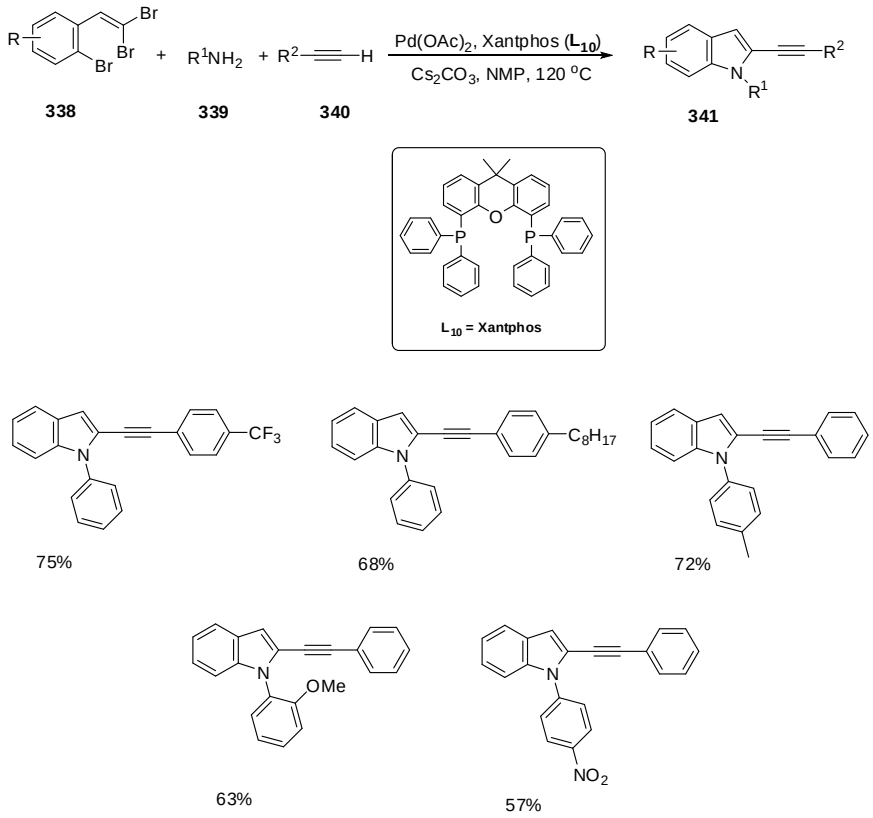


Scheme 101. Synthesis of indole derivatives by an intermolecular N-annulation.

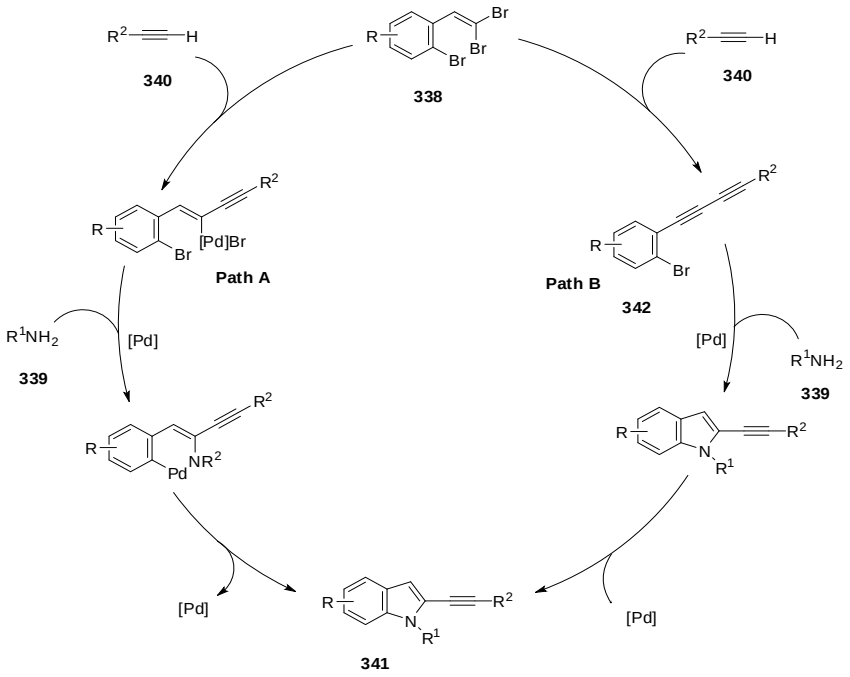
In 2011, Liang and co-workers synthesized alpha-Alkynyl indoles (**341**) by a single-pot coupling reaction employing three components, i.e., *o*-bromo-(2,2-dibromovinyl) benzenes (**338**), phenylamines (**339**), and terminal alkynes (**340**) under Pd-catalysis (Scheme 102). The three coupling components were added at the same time and exhibited a very high chemical selectivity, constructing one C–C and two C–N bonds. The mechanistic studies concluded that the reaction without adding aniline afforded the 1,3-diyne (**342**) (Scheme 103). The later reaction of (**342**) with aniline afforded the respective 2-alkynyl indole 68% yield. However, path **A** of the reaction as depicted was more preferable than path **B** of the reaction, though the latter should not be ruled out. The results showed that aromatic alkynes and anilines with electron-poor as well as electron-rich substituents were tolerated in this three-component coupling reaction. Alkynes with heteroatomic aromatic substituents were also suitable starting materials [254].

Alsabeh and co-workers reported a direct synthesis of 2-arylindoles (**345**) from ammonia (**344**) and 2-alkynyl bromoarenes (**343**) by a cascade cross-coupling reaction and subsequent amination of alkynes (Scheme 104). Herein, NH_3 or amines were used to provide the N-atom for the indole nucleus. The critical studies were performed to develop an effective catalytic system to achieve the highest yield of the desired indole. It was concluded that Hartwig and his colleagues used Josiphos (CyPFt-Bu) ligand (**L_{11}**), which was effective in this approach by using amines as well as ammonia in the cross-coupling reaction. Thus, in the presence of catalyst $[Pd(cinnamyl)Cl]_2$, ligand Josiphos (**L_{11}**), and base *t*-BuOK, the reaction afforded the best results, producing yields of indoles up to 89%. The yields of the products were influenced by loading of the catalyst $[Pd(cinnamyl)Cl]_2$; lower loading resulted in a lower yield of the product, although the starting substrate was fully consumed. In the presence of other bases, i.e., NaO*t*Bu, Cs_2CO_3, and KOH, the reaction did not afford the best results; additionally, they were sometimes in the presence of NaO*t*Bu such as 2-(phenylethynyl)aniline (**346**) was obtained in a high yield. This methodology has certain limitations; heterocyclic compounds having a heteroatom at the *o*-position to the alkyne or bromo resulted in lower yields. Alkyne groups attached to aryl with R^1 = silyl, alkenyl or alkyl (hexyl, propyl) tended to degrade under these reaction conditions, yielding

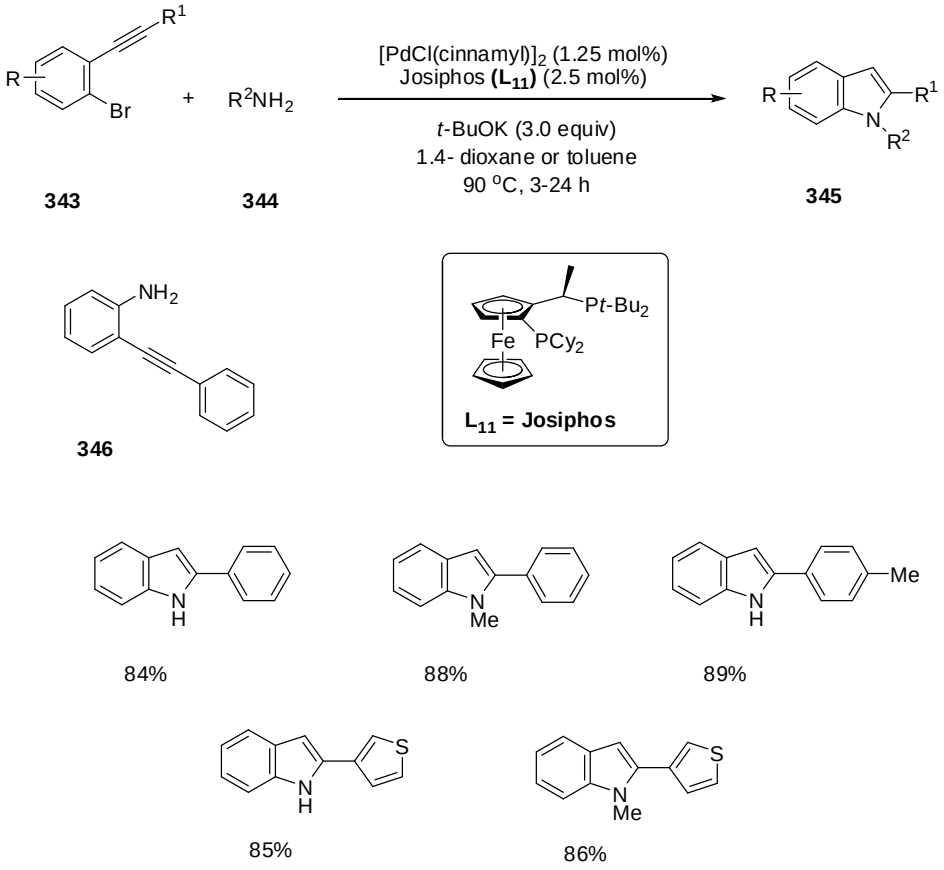
no satisfactory product results. This methodology worked smoothly for the preparation of N-metylated indole derivatives in a good quantity and CH_3NH_2 was used for the N-atom source instead of NH_3 [255].



Scheme 102. Synthesis of α-Alkynyl indoles by a one-pot coupling reaction.



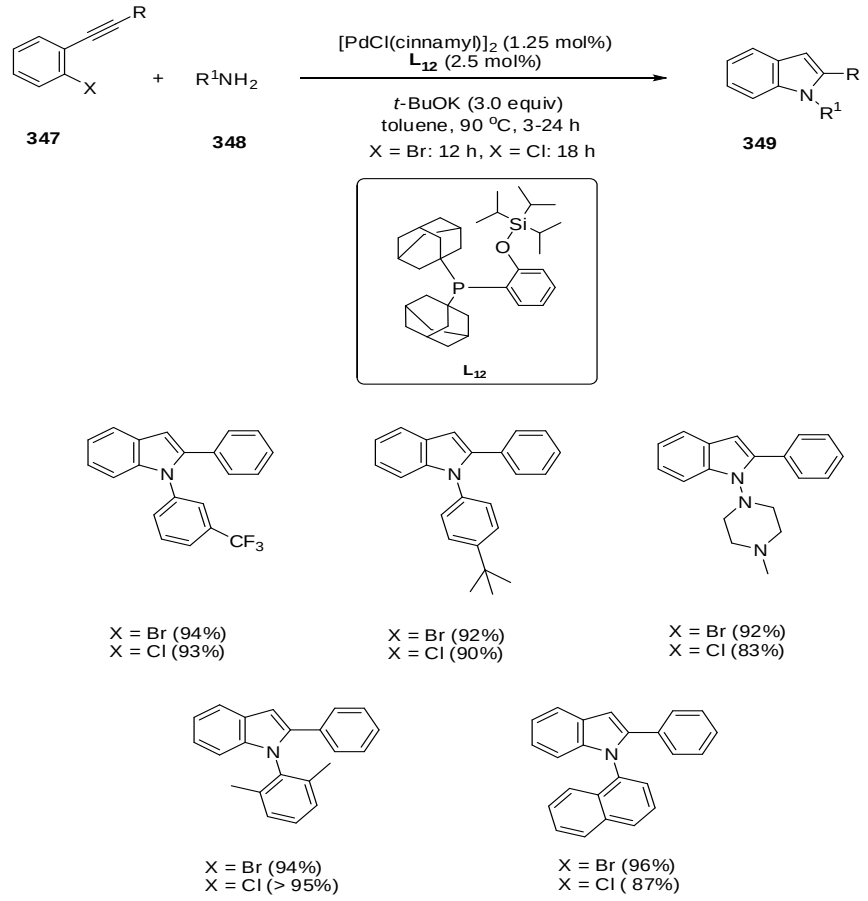
Scheme 103. The plausible pathway for the synthesis of alpha-Alkynyl indoles.



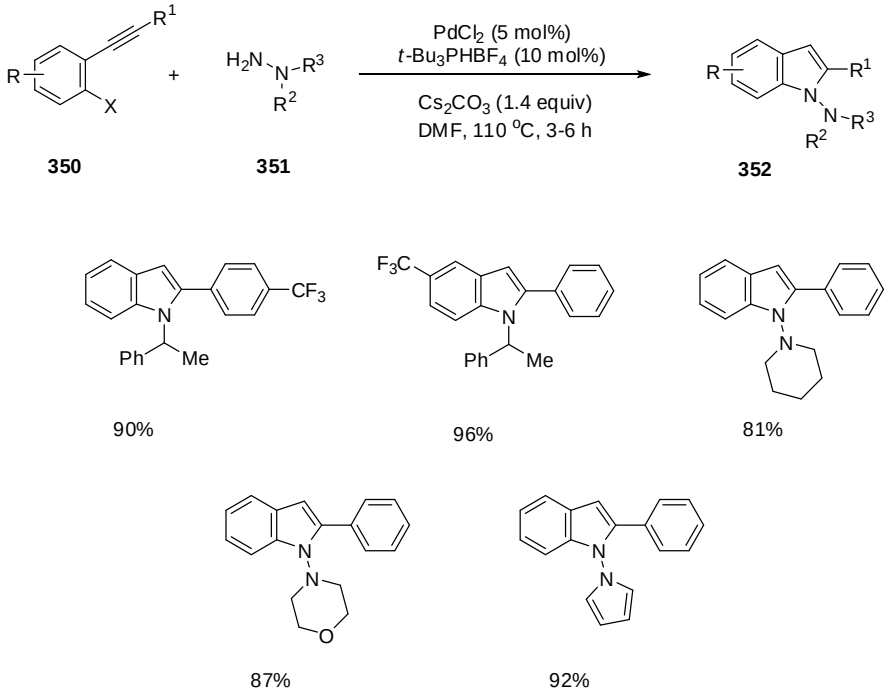
Scheme 104. Direct synthesis of 2-arylindoles via cascade cross-coupling/ amination reaction.

Furthermore, in 2012, Lavery and co-workers extended this methodology using (silanyloxyphenyl)phosphines as a ligand in the presence of a Pd-catalyst for the C-N cross-coupling reaction and subsequent annulation of *o*-alkynylhalo(hetero)arenes (**347**) with 1° amines (**348**), producing C–2 substituted indole derivatives (**349**) (Scheme 105). The study of experimental results concluded that di(1-adamantyl) -(2-triisopropylsiloxyphenyl)phosphine (OTips-DalPhos) (**L12**) was the best ligand under these reaction conditions. Thus, the catalyst using [Pd(cinnamyl)Cl]$_2$ and (**L12**) with a base such as *t*-BuOK in toluene as a solvent mediated the annulation of *o*-alkynylhalo(hetero)arenes (Scheme 105). The *o*-alkynylhalo(hetero)arene-having substituents, e.g., heteroaryl, aryl, and alkyl groups, were suitable for this reaction with the resultant indole having these substituents at C–2 in the indole ring. This reaction tolerated a wide range of amines such as small (methylamine), large (1-adamantylamine), sterically crowded or uncrowded aryl amines having either electron-rich or electron-deficient substituents, and N-methylpiperazine [256].

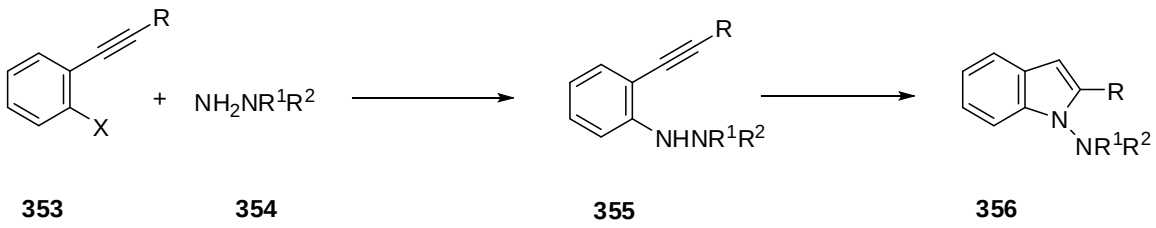
In 2011, Halland et al. synthesized substituted 1-aminoindoles (**352**) via a Pd-catalyzed cascade reaction of N,N-Disubstituted hydrazines (**351**) and 2-halophenylacetylenes (**350**). The reaction was conducted under relatively mild conditions, affording the desired product in 3–6 h. Herein, hydrazine was provided with the nitrogen for the indole ring (Scheme 106). The reaction mechanism is depicted in (Scheme 106). It involved the initial coupling reaction of the 2-halo(X)-phenylacetylene (**353**) and N,N′-disubstituted hydrazine (**354**) catalyzed by $PdCl_2$, affording N′-aryl-N,N-disubstituted hydrazine (**355**). Then, subsequent 5-endo-dig annulation in situ afforded the corresponding N,N-disubstituted-1-aminoindole (**356**) (Scheme 107). The 2-halophenyl acetylenes having either electron-rich or electron-poor groups underwent this reaction effectively. Quantitative yields of the required products were obtained using electron-rich hydrazine [257].



Scheme 105. Synthesis of C–2 substituted indole derivatives from *o*-alkynylhalo(hetero)arenes and 1º amines.



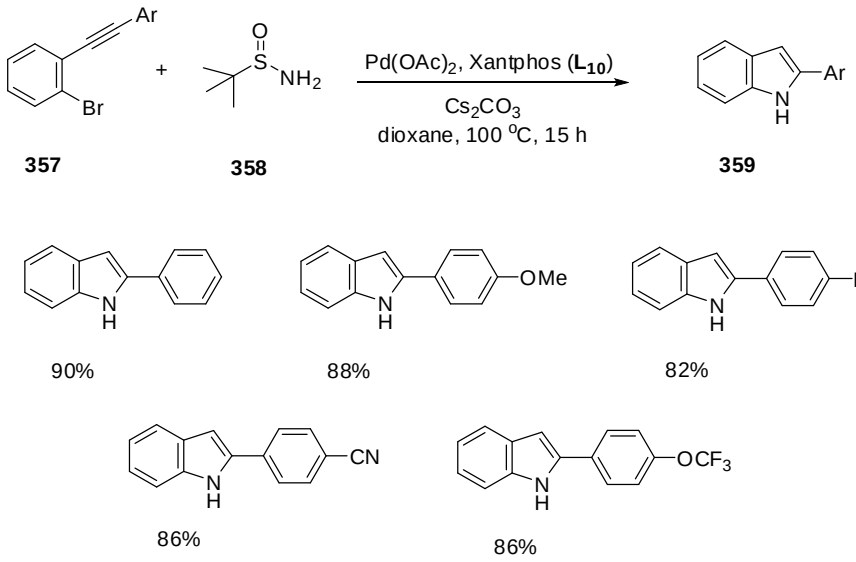
Scheme 106. Synthesis of 1-aminoindoles by 5-endo-dig annulation.



353 **354** **355** **356**

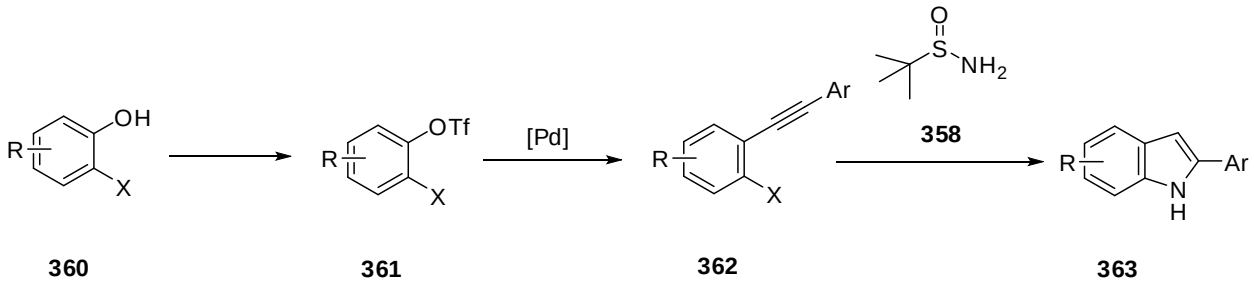
Scheme 107. The plausible mechanism for 5-endo-dig annulation.

Furthermore, Prakash and co-workers used tert-Butyl sulfinamide as the equivalent of nitrogen in the Pd-catalyzed amination. In the synthesis of 2-aryl-indoles (**359**), t-butyl sulfonamides (**358**) and *o*-alkynylbromoarene (**357**) under catalytic system Pd $(OAc)_2/Cs_2CO_3$/Xantphosin and 1,4-dioxane as a solvent at 110 °C produced a good to excellent yield of the products (Scheme 108). The preparation of 2-aryl substituted indoles (**363**) took place by three elementary steps: (a) *o*-halophenols (**360**) were transformed to phenol triflate (**361**) by Tf_2O and Et_3N in CH_2Cl_2 at 0 °C, (b) subsequent Sonogashira cross-coupling with the terminal alkynes afforded o-alkynylbromoarene (**362**), and (c) Buchwald coupling with tert-butyl sulfinamide (**358**) took place. Free N-H indole was obtained after the deprotection of sulfinamide moiety within the same reaction (Scheme 109). Aryl bromides (Ar–Br) and aryl chloride (Ar–Cl) having various substituents such as –CN, aldehyde, ester, and –OMe underwent this reaction smoothly without forming any side products, affording an excellent yield of the desired indole [258].



357 **358** **359**

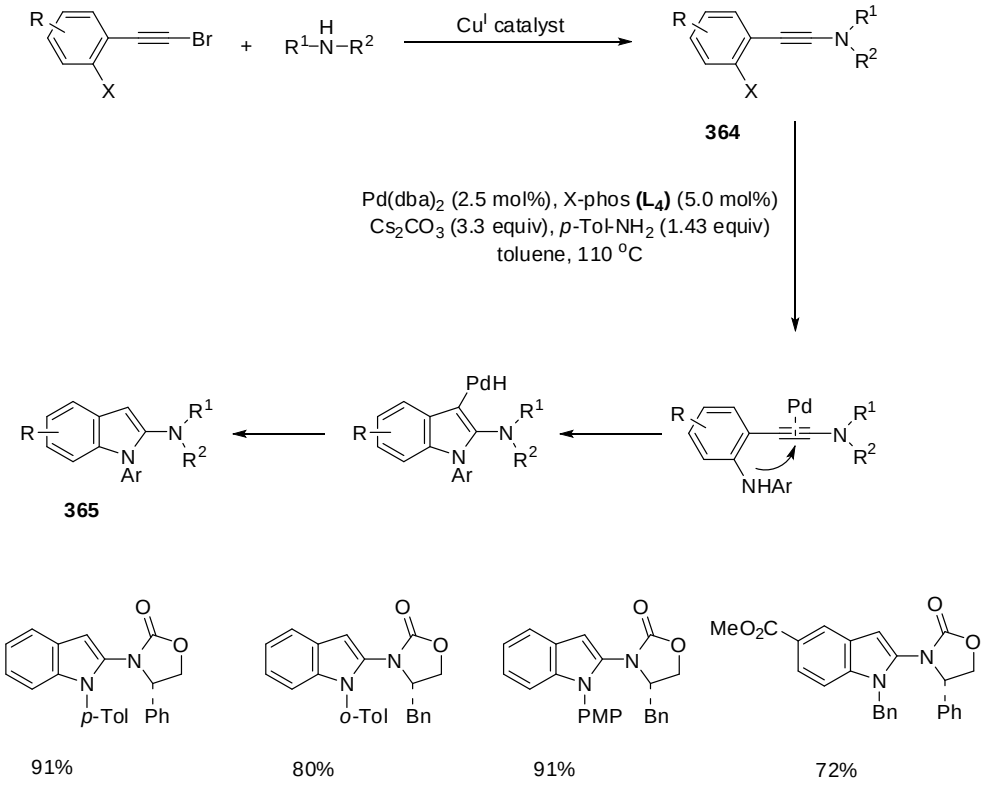
Scheme 108. Synthesis of 2-aryl-indoles from tert-Butyl sulfinamide.



360 **361** **362** **363**

Scheme 109. Mechanism for the synthesis of Free N-H indole.

Yao and colleagues reported Pd-catalyzed C–N bond development using *o*-haloaryl acetylenic bromides, amines, and amides. The highly selective Csp-N bond development instead of the Csp^2-N bond was performed by amidation, leading to o-haloaryl-substituted ynamides. These have been used as useful building blocks and for obtaining 2-amido-indoles (**365**) (Scheme 110). The reaction took place specifically between *o*-haloarylynamides (**364**) and *p*-tol-amine under a catalytic system comprised of a $Pd_2(dba)_3$ catalyst and X-phos ligand ($\mathbf{L_4}$) in toluene, affording 2-amido-indoles in high yields. Leeuwen's xantphos ligand was also employed, but better results were obtained using Buchwald's Xphos ligand ($\mathbf{L_4}$), requiring less reaction time. On the contrary, no satisfactory result was obtained using BINAP. It is worth noting that this annulation went better with Ar–Cl and Ar–Br than Ar–I. Additionally, cyclic or acyclic amides, as well as sulfonamides, worked smoothly for the N-alkynylation process, affording good yields of ynamides [259].



Scheme 110. Synthesis of 2-amido-indoles by Csp-N bond formation.

3. Conclusions

Indoles are found in bioactive and pharmaceutical compounds. Intermolecular or intramolecular cyclization of alkynes catalyzed by palladium is a strong technique for forming the indole moiety. Palladium-based complexes have been used to activate the terminal and internal alkynes as active catalysts. Palladium is an expensive and heavy transition metal that may adversely affect the environment. Therefore, it must be replaced by organocatalysts or metal-free synthesis.

Author Contributions: Conceptualization, N.R., A. and M.B.; data curation, S.G.K. and U.R.; software, M.B., A. and H.A.; writing—original draft preparation, A., M.B., H.A. and S.G.K.; writing—review and editing, U.R., N.R. and I.A.; visualization, N.R. and U.R.; supervision, N.R.; project administration, N.R. and I.A. All authors have read and agreed to the published version of the manuscript.

Funding: Article Processing Charges (APC) was funded by Research Management Center (RMC), Universiti Putra Malaysia (UPM), Malaysia.

Data Availability Statement: Not Applicable.

Acknowledgments: This research work was funded by Institutional Fund Projects under grant no. (IFPRP: 21-829-2021). Therefore, the authors gratefully acknowledge technical and financial support from the Ministry of Education and King Abdulaziz University, Jeddah, Saudi Arabia.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Van Order, R.H. Lindwall. Indole. *Chem. Rev.* **1942**, *30*, 69–96. [CrossRef]
2. Sharma, V.; Kumar, P.; Pathak, D. Biological importance of the indole nucleus in recent years: A comprehensive review. *J. Heterocycl. Chem.* **2010**, *47*, 491–502. [CrossRef]
3. Abele, E.; Abele, R.; Dzenitis, O.; Lukevics, E. Indole and Isatin Oximes: Synthesis, Reactions, and Biological Activity. *Chem. Heterocycl. Compd.* **2003**, *39*, 3–35. [CrossRef]
4. Aboul-Enein, H.Y.; Kruk, I.; Lichszteld, K.; Michalska, T.; Kladna, A.; Marczynski, S.; Ölgen, S. Scavenging of reactive oxygen species by N-substituted indole-2 and 3-carboxamides. *J. Lumin.* **2004**, *19*, 1–7. [CrossRef]
5. Al-Hiari, Y.M.; Qaisi, A.M.; El-Abadelah, M.M.; Voelter, W. Synthesis and antibacterial activity of some substituted 3-(aryl)-and 3-(heteroaryl) indoles. *Monatsh. Chem.* **2006**, *137*, 243–248. [CrossRef]
6. Barraja, P.; Sciabica, L.; Diana, P.; Lauria, A.; Montalbano, A.; Almerico, A.M.; Dattolo, G.; Cirrincione, G.; Disarò, S.; Basso, G. Synthesis and photochemotherapeutic activity of thiopyrano [2, 3-e] indol-2-ones. *Bioorgan. Med. Chem. Lett.* **2005**, *15*, 2291–2294. [CrossRef] [PubMed]
7. Hong, B.C.; Jiang, Y.F.; Chang, Y.L.; Lee, S.J. Synthesis and Cytotoxicity Studies of Cyclohepta [b] indoles, Benzo [6, 7] Cyclohepta [1, 2-b] Indoles, Indeno [1, 2-b] Indoles, and Benzo [a] Carbazoles. *J Chin Chem Soc.* **2006**, *53*, 647–662. [CrossRef]
8. Kalaskar, G.; Girisha, M.; Purohit, M.; Thippeswamy, B.; Patil, B. Synthesis and evaluation of in vivo antiinflammatory activity of indole-3-acetic acids. *Indian J. Heterocycl. Chem.* **2007**, *16*, 325–328.
9. Li, Y.-Y.; Wu, H.-S.; Tang, L.; Feng, C.-R.; Yu, J.-H.; Li, Y.; Yang, Y.-S.; Yang, B.; He, Q.-J. The potential insulin sensitizing and glucose lowering effects of a novel indole derivative in vitro and in vivo. *Pharmacol. Res.* **2007**, *56*, 335–343. [CrossRef]
10. Radwan, M.A.; Ragab, E.A.; Sabry, N.M.; El-Shenawy, S.M. Synthesis and biological evaluation of new 3-substituted indole derivatives as potential anti-inflammatory and analgesic agents. *Bioorgan. Med. Chem.* **2007**, *15*, 3832–3841. [CrossRef]
11. Talaz, O.; Gülçin, I.; Göksu, S.; Saracoglu, N. Antioxidant activity of 5, 10-dihydroindeno [1, 2-b] indoles containing substituents on dihydroindeno part. *Bioorgan. Med. Chem.* **2009**, *17*, 6583–6589. [CrossRef]
12. Bellemin, R.; Decerprit, J.; Festal, D. New indole derivatives as ACAT inhibitors: Synthesis and structure-activity relationships. *Eur. J. Med. Chem.* **1996**, *31*, 123–132. [CrossRef]
13. Grumel, V.; Mérour, J.-Y.; Lesur, B.; Giboulot, T.; Frydman, A.; Guillaumet, G. Design and synthesis of a series of indole glycoprotein IIb/IIIa inhibitors. *Eur. J. Med. Chem.* **2002**, *37*, 45–62. [CrossRef]
14. McKew, J.C.; Foley, M.A.; Thakker, P.; Behnke, M.L.; Lovering, F.E.; Sum, F.-W.; Tam, S.; Wu, K.; Shen, M.W.; Zhang, W. Inhibition of cytosolic phospholipase A2α: Hit to lead optimization. *J. Med. Chem.* **2006**, *49*, 135–158. [CrossRef]
15. Merino, I.; Monge, A.; Font, M.; de Irujo, J.J.M.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J.J.; Sarobe, P.; Borrás, F. Synthesis and anti-HIV-1 activities of new pyrimido [5, 4-b] indoles. *Farmaco* **1999**, *54*, 255–264. [CrossRef]
16. Takami, H.; Kishibayashi, N.; Ishii, A.; Kumazawa, T. Indole and benzimidazole derivatives as steroid 5α-reductase inhibitors in the rat prostate. *Bioorgan. Med. Chem.* **1998**, *6*, 2441–2448. [CrossRef]
17. Zheng, M.; Zheng, M.; Ye, D.; Deng, Y.; Qiu, S.; Luo, X.; Chen, K.; Liu, H.; Jiang, H. Indole derivatives as potent inhibitors of 5-lipoxygenase: Design, synthesis, biological evaluation, and molecular modeling. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2414–2420. [CrossRef]
18. Konkel, M.J.; Lagu, B.; Boteju, L.W.; Jimenez, H.; Noble, S.; Walker, M.W.; Chandrasena, G.; Blackburn, T.P.; Nikam, S.S.; Wright, J.L. 3-arylimino-2-indolones are potent and selective galanin GAL3 receptor antagonists. *J. Med. Chem.* **2006**, *49*, 3757–3758. [CrossRef]
19. Mahindroo, N.; Wang, C.-C.; Liao, C.-C.; Huang, C.-F.; Lu, I.-L.; Lien, T.-W.; Peng, Y.-H.; Huang, W.-J.; Lin, Y.-T.; Hsu, M.-C. Indol-1-yl acetic acids as peroxisome proliferator-activated receptor agonists: Design, synthesis, structural biology, and molecular docking studies. *J. Med. Chem.* **2006**, *49*, 1212–1216. [CrossRef]
20. Mewshaw, R.E.; Marquis, K.L.; Shi, X.; McGaughey, G.; Stack, G.; Webb, M.B.; Abou-Gharbia, M.; Wasik, T.; Scerni, R.; Spangler, T. New generation dopaminergic agents 4. Exploiting the 2-methyl chroman scaffold. Synthesis and evaluation of two novel series of 2-(aminomethyl)-3, 4, 7, 9-tetrahydro-2H-pyrano [2, 3-e] indole and indol-8-one derivatives. *Tetrahedron* **1998**, *54*, 7081–7108. [CrossRef]
21. Patil, N.T.; Yamamoto, Y. Coinage metal-assisted synthesis of heterocycles. *Chem. Rev.* **2008**, *108*, 3395–3442. [CrossRef]
22. Alonso, F.; Yus, M.; Beletskaya, I. Non-conventional methodologies for transition-metal catalysed carbon-carbon coupling: A critical overview. Part 2: The Suzuki reaction. *Tetrahedron* **2008**, *64*, 3047–3101. [CrossRef]
23. Doucet, H.; Hierso, J.C. Palladium-based catalytic systems for the synthesis of conjugated enynes by Sonogashira reactions and related alkynylations. *Angew. Chem. Int. Ed.* **2007**, *46*, 834–871. [CrossRef]
24. Enthaler, S. Palladium-catalysed hydroxylation and alkoxylation. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924. [CrossRef]

25. Feldman, K.S.; Bruendl, M.M.; Schildknegt, K.; Bohnstedt, A.C. Inter-and intramolecular addition/cyclizations of sulfonamide anions with alkynyliodonium triflates. Synthesis of dihydropyrrole, pyrrole, indole, and tosylenamide heterocycles. *J. Org. Chem.* **1996**, *61*, 5440–5452. [CrossRef]
26. Frisch, A.C.; Beller, M. Catalysts for cross-coupling reactions with non-activated alkyl halides. *Angew. Chem. Int. Ed.* **2005**, *44*, 674–688. [CrossRef]
27. Jana, R.; Pathak, T.P.; Sigman, M.S. Advances in transition metal (Pd, Ni, Fe)-catalyzed cross-coupling reactions using alkyl-organometallics as reaction partners. *Chem. Rev.* **2011**, *111*, 1417–1492. [CrossRef]
28. Kambe, N.; Iwasaki, T.; Terao, J. Pd-catalyzed cross-coupling reactions of alkyl halides. *Chem. Soc. Rev.* **2011**, *40*, 4937–4947. [CrossRef]
29. Knappke, C.E.; von Wangelin, A.J. 35 years of palladium-catalyzed cross-coupling with Grignard reagents: How far have we come? *Chem. Soc. Rev.* **2011**, *40*, 4948–4962. [CrossRef] [PubMed]
30. Molnar, A. Efficient, selective, and recyclable palladium catalysts in carbon− carbon coupling reactions. *Chem. Rev.* **2011**, *111*, 2251–2320. [CrossRef] [PubMed]
31. Nakao, Y.; Hiyama, T. Silicon-based cross-coupling reaction: An environmentally benign version. *Chem. Soc. Rev.* **2011**, *40*, 4893–4901. [CrossRef]
32. Negishi, E.-I.; Anastasia, L. Palladium-catalyzed alkynylation. *Chem. Rev.* **2003**, *103*, 1979–2018. [CrossRef]
33. Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. Diazonium salts as substrates in palladium-catalyzed cross-coupling reactions. *Chem. Rev.* **2006**, *106*, 4622–4643. [CrossRef] [PubMed]
34. Rollet, P.; Kleist, W.; Dufaud, V.; Djakovitch, L. Copper-free heterogeneous catalysts for the Sonogashira cross-coupling reaction: Preparation, characterisation, activity and applications for organic synthesis. *J. Mol. Catal. A Chem.* **2005**, *241*, 39–51. [CrossRef]
35. Selander, N.; Szabó, K.J. Catalysis by palladium pincer complexes. *Chem. Rev.* **2011**, *111*, 2048–2076. [CrossRef] [PubMed]
36. Surry, D.S.; Buchwald, S.L. Biaryl phosphane ligands in palladium-catalyzed amination. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361. [CrossRef] [PubMed]
37. Tucker, C.E.; de Vries, J.G. Homogeneous catalysis for the production of fine chemicals. Palladium-and nickel-catalysed aromatic carbon–carbon bond formation. *Top. Catal.* **2002**, *19*, 111–118. [CrossRef]
38. Zapf, A.; Beller, M. The development of efficient catalysts for palladium-catalyzed coupling reactions of aryl halides. *Chem. Commun.* **2005**, 431–440. [CrossRef]
39. Beletskaya, I.P. Palladium catalyzed CC and C-heteroatom bond formation reactions. *Pure Appl. Chem.* **1997**, *69*, 471–476. [CrossRef]
40. Wu, X.F.; Anbarasan, P.; Neumann, H.; Beller, M. From noble metal to Nobel prize: Palladium-catalyzed coupling reactions as key methods in organic synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 9047–9050. [CrossRef]
41. Zeni, G.; Larock, R.C. Synthesis of heterocycles via palladium π-olefin and π-alkyne chemistry. *Chem. Rev.* **2004**, *104*, 2285–2310. [CrossRef] [PubMed]
42. Suzuki, A. Cross-coupling reactions of organoboranes: An easy way to construct C—C bonds (Nobel Lecture). *Angew. Chem. Int. Ed.* **2011**, *50*, 6722–6737. [CrossRef]
43. Fischer, E.; Jourdan, F. Ueber die hydrazine der brenztraubensäure. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–2245. [CrossRef]
44. Wagaw, S.; Yang, B.H.; Buchwald, S.L. A palladium-catalyzed strategy for the preparation of indoles: A novel entry into the Fischer indole synthesis. *J. Am. Chem. Soc.* **1998**, *120*, 6621–6622. [CrossRef]
45. Gassman, P.G.; van Bergen, T.; Gruetzmacher, G. Use of halogen-sulfide complexes in the synthesis of indoles, oxindoles, and alkylated aromatic amines. *J. Am. Chem. Soc.* **1973**, *95*, 6508–6509. [CrossRef]
46. Thyagarajan, B.; Hillard, J.; Reddy, K.; Majumdar, K. A novel synthesis of indole derivatives via a claisen rearrangement. *Tetrahedron Lett.* **1974**, *15*, 1999–2002. [CrossRef]
47. Baudin, J.-B.; Julia, S.A. Synthesis of indoles from N-aryl-1-alkenylsulphinamides. *Tetrahedron Lett.* **1986**, *27*, 837–840. [CrossRef]
48. Houlihan, W.J.; Parrino, V.A.; Uike, Y. Lithiation of N-(2-alkylphenyl) alkanamides and related compounds. A modified Madelung indole synthesis. *J. Org. Chem.* **1981**, *46*, 4511–4515. [CrossRef]
49. Mayadeo, M.; Gandhi, S. Convenient general synthesis of alhpha-aminolusaturated ketones, nitrilesaed their use in nenitzescue indole synthesis. *J. Indian Chem. Soc.* **1994**, *71*, 281–282.
50. Bartoli, G.; Bosco, M.; Dalpozzo, R.; Palmieri, G.; Marcantoni, E. Reactivity of nitro- and nitroso-arenes with vinyl grignard reagents: Synthesis of 2-(trimethylsilyl)indoles. *J. Chem. Soc. Perkin Trans. I* **1991**, *11*, 2757–2761. [CrossRef]
51. Bosco, M.; Dalpozzo, R.; Bartoli, G.; Palmieri, G.; Petrini, M. Mechanistic studies on the reaction of nitro-and nitrosoarenes with vinyl Grignard reagents. *J. Chem. Soc. Perkin Trans. 2* **1991**, *5*, 657–663. [CrossRef]
52. Nenitzescu, C. Derivatives of 2-methyl-5-hydroxyindole. *Bull. Soc. Chim. Rom.* **1929**, *11*, 37–43.
53. Bailey, W.F.; Jiang, X.-L. Preparation of Substituted Indolines via Anionic Cyclization. *J. Org. Chem.* **1996**, *61*, 2596–2597. [CrossRef] [PubMed]
54. Zhang, D.; Liebeskind, L.S. A versatile synthesis of 3-substituted indolines and indoles. *J. Org. Chem.* **1996**, *61*, 2594–2595. [CrossRef] [PubMed]
55. Bischler, A. Ueber die entstehung einiger substituirter indole. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2860–2879. [CrossRef]
56. Hemetsberger, H.; Knittel, D. Synthese und Thermolyse von α-Azidoacrylestern. *Monatsh. Chem.* **1972**, *103*, 194–204. [CrossRef]

57. Molina, P.; Alcantara, J.; Lopez-Leonardo, C. Regiospecific intramolecular ring-closure of heterocumulene-substituted indoles: Formation of γ-carbolines and pyrimido [3, 4-a] indoles. *Tetrahedron Lett.* **1995**, *36*, 953–956. [CrossRef]
58. Feldman, K.S.; Bruendl, M.M.; Schildknegt, K. Preparation of Five-Membered Nitrogen-Containing Heterocycles via [Three-Atom+ Two-Atom] Combination of Tosylamide Anions with Phenyl (propynyl) iodonium Triflate. *J. Org. Chem.* **1995**, *60*, 7722–7723. [CrossRef]
59. Reissert, A. Einwirkung von oxalester und natriumäthylat auf nitrotoluole. synthese nitrirter phenylbrenztraubensäuren. *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1030–1053. [CrossRef]
60. Fukuyama, T.; Chen, X.; Peng, G. A novel tin-mediated indole synthesis. *J. Am. Chem. Soc.* **1994**, *116*, 3127–3128. [CrossRef]
61. Larock, R.C.; Yum, E.K. Synthesis of indoles via palladium-catalyzed heteroannulation of internal alkynes. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. [CrossRef]
62. Batcho, A.D.; Leimgruber, W. Indoles from 2-Methylnitrobenzenes by Condensation with Formamide Acetals Followed by Reduction: 4-Benzyloxyindole: 1H-Indole, 4-(phenylmethoxy)-. *Org. Synth.* **2003**, *63*, 214.
63. Enders, D.; Grondal, C.; Huettl, M.R. Asymmetric organocatalytic domino reactions. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581. [CrossRef]
64. Grigg, R.; Sridharan, V. Palladium catalysed cascade cyclisation-anion capture, relay switches and molecular queues. *J. Organomet. Chem.* **1999**, *576*, 65–87. [CrossRef]
65. Malacria, M. Selective preparation of complex polycyclic molecules from acyclic precursors via radical mediated-or transition metal-catalyzed cascade reactions. *Chem. Rev.* **1996**, *96*, 289–306. [CrossRef] [PubMed]
66. Miura, T.; Murakami, M. Formation of carbocycles through sequential carborhodation triggered by addition of organoborons. *Chem. Commun.* **2007**, 217–224. [CrossRef] [PubMed]
67. Montgomery, J. Nickel-catalyzed reductive cyclizations and couplings. *Angew. Chem. Int. Ed.* **2004**, *43*, 3890–3908. [CrossRef] [PubMed]
68. Negishi, E.-i.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. Cyclic carbopalladation. A versatile synthetic methodology for the construction of cyclic organic compounds. *Chem. Rev.* **1996**, *96*, 365–394. [CrossRef] [PubMed]
69. Nicolaou, K.; Edmonds, D.J.; Bulger, P.G. Cascade reactions in total synthesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186. [CrossRef]
70. Nicolaou, K.; Montagnon, T.; Snyder, S.A. Tandem reactions, cascade sequences, and biomimetic strategies in total synthesis. *Chem. Commun.* **2003**, 551–564. [CrossRef]
71. Tietze, L.F. Domino reactions in organic synthesis. *Chem. Rev.* **1996**, *96*, 115–136. [CrossRef]
72. Chen, Z.; Ding, Q.; Yu, X.; Wu, J. Silver Triflate-Catalyzed or Electrophile-Mediated Tandem Reaction of N′-(2-Alkynylbenzylidene) hydrazides with Dimethyl Acetylenedicarboxylate. *Adv. Synth. Catal.* **2009**, *351*, 1692–1698. [CrossRef]
73. Chen, Z.; Yang, X.; Wu, J. AgOTf-catalyzed tandem reaction of N′-(2-alkynylbenzylidene) hydrazide with alkyne. *Chem. Commun.* **2009**, 3469–3471. [CrossRef]
74. Chen, Z.; Yu, X.; Su, M.; Yang, X.; Wu, J. Multicatalytic Tandem Reactions of 2-Alkynylbenzaldoximes with Isocyanides. *Adv. Synth. Catal.* **2009**, *351*, 2702–2708. [CrossRef]
75. Ding, Q.; He, X.; Wu, J. Synthesis of 2-aminobenzothiazole via copper (I)-catalyzed Tandem Reaction of 2-iodobenzenamine with isothiocyanate. *J. Comb. Chem.* **2009**, *11*, 587–591. [CrossRef]
76. Ding, Q.; Huang, X.-G.; Wu, J. Facile synthesis of benzothiazoles via cascade reactions of 2-iodoanilines, acid chlorides and Lawesson's reagent. *J. Comb. Chem.* **2009**, *11*, 1047–1049. [CrossRef] [PubMed]
77. Ding, Q.; Wang, Z.; Wu, J. Tandem Electrophilic Cyclization−[3+2] Cycloaddition− Rearrangement Reactions of 2-Alkynylbenzaldoxime, DMAD, and Br2. *J. Org. Chem.* **2009**, *74*, 921–924. [CrossRef] [PubMed]
78. Ding, Q.; Wang, Z.; Wu, J. Tandem cyclization-[3+ 3] cycloaddition reactions of 2-alkynylbenzaldoxime: Synthesis of fused 1, 2-dihydroisoquinolines. *Tetrahedron Lett.* **2009**, *50*, 198–200. [CrossRef]
79. Ding, Q.; Wu, J. Access to Functionalized Isoquinoline N-Oxides via Sequential Electrophilic Cyclization/Cross-Coupling Reactions. *Adv. Synth. Catal.* **2008**, *350*, 1850–1854. [CrossRef]
80. Ye, S.; Gao, K.; Wu, J. Three-Component Reactions of 2-Alkynylbenzaldoximes and α, β-Unsaturated Carbonyl Compounds with Bromine or Iodine Monochloride. *Adv. Synth. Catal.* **2010**, *352*, 1746–1751. [CrossRef]
81. Yu, X.; Chen, Z.; Yang, X.; Wu, J. Tandem Reactions of N′-(2-Alkynylbenzylidene) hydrazides with Silyl Enolates: A Facile Route to H-Pyrazolo [5, 1-a] isoquinolines. *J. Comb. Chem.* **2010**, *12*, 374–378. [CrossRef]
82. Yu, X.; Wu, J. Synthesis of functionalized isoquinolines via sequential cyclization/cross-coupling reactions. *J. Comb. Chem.* **2009**, *11*, 895–899. [CrossRef] [PubMed]
83. Yu, X.; Wu, J. Synthesis of 1-(1 H-Indol-3-yl)-1, 2-dihydroisoquinolines via AgOTf-Catalyzed Three-Component Reactions of 2-Alkynylbenzaldehydes, Amines, and Indoles. *J. Comb. Chem.* **2010**, *12*, 238–244. [CrossRef] [PubMed]
84. Kurti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis, ed.*; Elsevier: Amsterdam, The Netherlands, 2005.
85. Narasaka, K.; Kusama, H.; Yamashita, Y.; Sato, H. Org. React. Org. React. 35, 1, 1988. *Chem. Lett.* **1993**, *1993*, 489–492. [CrossRef]
86. Qiu, G.; Ding, Q.; Ren, H.; Peng, Y.; Wu, J. Multicatalytic one-pot reaction of 1-(2-alkynylphenyl) ketoximes for generation of indole derivatives. *Org. Lett.* **2010**, *12*, 3975–3977. [CrossRef] [PubMed]
87. Alkorta, I.; Elguero, J.; Roussel, C.; Vanthuyne, N.; Piras, P. Atropisomerism and axial chirality in heteroaromatic compounds. *Adv. Heterocycl. Chem.* **2012**, *105*, 1–188.

88. Ayitou, A.J.-L.; Jesuraj, J.L.; Barooah, N.; Ugrinov, A.; Sivaguru, J. Enantiospecific photochemical Norrish/Yang type II reaction of nonbiaryl atropchiral α-oxoamides in solution—Axial to point chirality transfer. *J. Am. Chem. Soc.* **2009**, *131*, 11314–11315. [CrossRef]
89. Bock, L.; Adams, R. The stereochemistry of N-phenylpyrroles. The preparation and Resolution of N-2-Carboxyphenyl-2, 5-dimethyl-3-carboxypyrrole. XIII. *J. Am. Chem. Soc.* **1931**, *53*, 374–376. [CrossRef]
90. Clayden, J. Tetrahedron Symposium-in-print on Axially Chiral Amides (Atropisomerism). *Tetrahedron* **2004**, *60*, 4325.
91. Curran, D.P.; Qi, H.; Geib, S.J.; DeMello, N.C. Atroposelective thermal reactions of axially twisted amides and imides. *J. Am. Chem. Soc.* **1994**, *116*, 3131–3132. [CrossRef]
92. Dai, X.; Wong, A.; Virgil, S.C. Synthesis and resolution of quinazolinone atropisomeric phosphine ligands. *J. Org. Chem.* **1998**, *63*, 2597–2600. [CrossRef]
93. Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. Asymmetric Synthesis of Axially Chiral Anilides by Enantiotopic Lithiation of Tricarbonyl (N-methyl-N-acyl-2, 6-dimethylanilide) chromium Complex. *Org. Lett.* **2000**, *2*, 1907–1910. [CrossRef]
94. Kawabata, T.; Jiang, C.; Hayashi, K.; Tsubaki, K.; Yoshimura, T.; Majumdar, S.; Sasamori, T.; Tokitoh, N. Axially Chiral Binaphthyl Surrogates with an Inner N− H− N Hydrogen Bond. *J. Am. Chem. Soc.* **2009**, *131*, 54–55. [CrossRef]
95. Kawamoto, T.; Tomishima, M.; Yoneda, F.; Hayami, J.-I. Synthesis and reaction of novel 5-deazaflavins with axial chirality at pyrimidine ring moiety. *Tetrahedron Lett.* **1992**, *33*, 3169–3172. [CrossRef]
96. Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. Optically active axially chiral anilide and maleimide derivatives as new chiral reagents: Synthesis and application to asymmetric Diels−Alder reaction. *J. Org. Chem.* **1998**, *63*, 2634–2640. [CrossRef]
97. Kondo, K.; Iida, T.; Fujita, H.; Suzuki, T.; Yamaguchi, K.; Murakami, Y. A Chiral Axis due to an Acyclic Imide–Ar Bond: A study of steric effects of Acyl groups on racemization. *Tetrahedron* **2000**, *56*, 8883–8891. [CrossRef]
98. Mannschreck, A.; Koller, H.; Stuhler, G.; Davies, M.; Traber, J. The enantiomers of methaqualone and their unequal anticonvulsive activity. *Eur. J. Med. Chem.* **1984**, *19*, 381–383.
99. Mino, T.; Komatsu, S.; Wakui, K.; Yamada, H.; Saotome, H.; Sakamoto, M.; Fujita, T. N-Aryl indole-derived C–N bond axially chiral phosphine ligands: Synthesis and application in palladium-catalyzed asymmetric allylic alkylation. *Tetrahedron Asymmetry* **2010**, *21*, 711–718. [CrossRef]
100. Mintas, M.; Mihaljević, V.; Koller, H.; Schuster, D.; Mannschreck, A. Sterically hindered N-aryl-2 (1 H)-quinolones and N-aryl-6 (5 H)-phenanthridinones: Separation of enantiomers and barriers to racemization. *J. Chem. Soc. Perkin Trans. 2* **1990**, *4*, 619–624. [CrossRef]
101. Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. Comparison of racemization processes in 1-arylpyrimidine-2-thione and 3-arylthiazoline-2-thione atropisomers and their oxygen analogs. *J. Org. Chem.* **1988**, *53*, 5076–5080. [CrossRef]
102. Sakamoto, M.; Utsumi, N.; Ando, M.; Saeki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishio, T.; Kashima, C. Breaking the Symmetry of Axially Chiral N-Aryl-2 (1H)-pyrimidinones by Spontaneous Crystallization. *Angew. Chem. Int. Ed.* **2003**, *42*, 4360–4363. [CrossRef] [PubMed]
103. Tokitoh, T.; Kobayashi, T.; Nakada, E.; Inoue, T.; Yokoshima, S.; Takahashi, H.; Natsugarib, H. Diastereoselective synthesis of atropisomeric 3-(2-substituted aryl) quinazolin-4-ones and their stereochemical properties. *Heterocycles* **2006**, *70*, 93–99.
104. Tracey, M.R. *Synthesis and Reactions of Ynamides and Allenamides*; University of Minnesota: Minneapolis, MN, USA, 2005.
105. Yılmaz, E.M.; Doğan, İ. Axially chiral N-(o-aryl)-2-thioxo-oxazolidine-4-one and rhodanine derivatives: Enantiomeric separation and determination of racemization barriers. *Tetrahedron Asymmetry* **2008**, *19*, 2184–2191. [CrossRef]
106. Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K.A. Chirally Aminated 2-Naphthols—Organocatalytic synthesis of non-biaryl atropisomers by asymmetric Friedel–Crafts amination. *Angew. Chem.* **2006**, *118*, 1165–1169. [CrossRef]
107. Clayden, J.; Turner, H. Enantiomerically enriched atropisomeric N, N′-diaryl ureas by oxidative kinetic resolution of their 2-sulfanyl derivatives. *Tetrahedron Lett.* **2009**, *50*, 3216–3219. [CrossRef]
108. Di Iorio, N.; Righi, P.; Mazzanti, A.; Mancinelli, M.; Ciogli, A.; Bencivenni, G. Remote control of axial chirality: Aminocatalytic desymmetrization of N-arylmaleimides via vinylogous Michael addition. *J. Am. Chem. Soc.* **2014**, *136*, 10250–10253. [CrossRef]
109. Duan, W.-L.; Imazaki, Y.; Shintani, R.; Hayashi, T. Asymmetric construction of chiral C–N axes through rhodium-catalyzed 1, 4-addition. *Tetrahedron* **2007**, *63*, 8529–8536. [CrossRef]
110. Guo, R.; Li, K.-N.; Liu, B.; Zhu, H.-J.; Fan, Y.-M.; Gong, L.-Z. Asymmetric synthesis of heteroaryl atropisomers via a gold-catalyzed cycloisomerization–amination cascade reaction. *Chem. Comm.* **2014**, *50*, 5451–5454. [CrossRef]
111. Kamikawa, K.; Arae, S.; Wu, W.Y.; Nakamura, C.; Takahashi, T.; Ogasawara, M. Simultaneous induction of axial and planar chirality in arene–chromium complexes by molybdenum-catalyzed enantioselective ring-closing metathesis. *Chem. Eur. J.* **2015**, *21*, 4954–4957. [CrossRef]
112. Kitagawa, O.; Kohriyama, M.; Taguchi, T. Catalytic asymmetric synthesis of optically active atropisomeric anilides through enantioselective N-allylation with chiral Pd-tol-BINAP catalyst. *J. Org. Chem.* **2002**, *67*, 8682–8684. [CrossRef]
113. Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. Efficient synthesis of optically active atropisomeric anilides through catalytic asymmetric N-arylation reaction. *J. Am. Chem. Soc.* **2005**, *127*, 3676–3677. [CrossRef]
114. Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. Highly enantioselective synthesis of atropisomeric anilide derivatives through catalytic asymmetric N-arylation: Conformational analysis and application to asymmetric enolate chemistry. *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931. [CrossRef]

115. Liu, H.; Feng, W.; Kee, C.W.; Leow, D.; Loh, W.T.; Tan, C.H. Brønsted base-catalyzed tandem isomerization–Michael reactions of alkynes: Synthesis of oxacycles and azacycles. *Adv. Synth. Catal.* **2010**, *352*, 3373–3379. [CrossRef]
116. Liu, Y.; Feng, X.; Du, H. Asymmetric synthesis of axially chiral anilides by Pd-catalyzed allylic substitutions with P/olefin ligands. *Org. Biomol. Chem.* **2015**, *13*, 125–132. [CrossRef]
117. Onodera, G.; Suto, M.; Takeuchi, R. Iridium-Catalyzed [2+ 2+ 2] Cycloaddition of α, ω-Diynes with Isocyanates. *J. Org. Chem.* **2012**, *77*, 908–920. [CrossRef]
118. Oppenheimer, J.; Hsung, R.P.; Figueroa, R.; Johnson, W.L. Stereochemical control of both C− C and C− N axial chirality in the synthesis of chiral N, O-biaryls. *Org. Lett.* **2007**, *9*, 3969–3972. [CrossRef]
119. Shirakawa, S.; Liu, K.; Maruoka, K. Catalytic asymmetric synthesis of axially chiral o-iodoanilides by phase-transfer catalyzed alkylations. *J. Am. Chem. Soc.* **2012**, *134*, 916–919. [CrossRef] [PubMed]
120. Takahashi, I.; Morita, F.; Kusagaya, S.; Fukaya, H.; Kitagawa, O. Catalytic enantioselective synthesis of atropisomeric 2-aryl-4-quinolinone derivatives with an N–C chiral axis. *Tetrahedron Asymmetry* **2012**, *23*, 1657–1662. [CrossRef]
121. Takahashi, I.; Suzuki, Y.; Kitagawa, O. Asymmetric Synthesis of Atropisomeric Compounds with an N-C Chiral Axis. *Org. Prep. Proced. Int.* **2014**, *46*, 1–23. [CrossRef]
122. Takahashi, M.; Kitagawa, O. Catalytic enantioselective synthesis of novel atropisomeric compounds having an NC chiral axis and their application to asymmetric reaction. *J. Syn. Org. Chem. Jpn.* **2011**, *69*, 985–993. [CrossRef]
123. Takahashi, M.; Tanabe, H.; Nakamura, T.; Kuribara, D.; Yamazaki, T.; Kitagawa, O. Atropisomeric lactam chemistry: Catalytic enantioselective synthesis, application to asymmetric enolate chemistry and synthesis of key intermediates for NET inhibitors. *Tetrahedron* **2010**, *66*, 288–296. [CrossRef]
124. Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. Synthesis of enantioenriched N-aryl-2-pyridones with chiral CN axes by rhodium-catalyzed [2+ 2+ 2] cycloaddition of alkynes with isocyanates. *Synlett* **2008**, *2008*, 1724–1728. [CrossRef]
125. Tanaka, K.; Takeishi, K.; Noguchi, K. Enantioselective synthesis of axially chiral anilides through rhodium-catalyzed [2+ 2+ 2] cycloaddition of 1, 6-diynes with trimethylsilylynamides. *J. Am. Chem. Soc.* **2006**, *128*, 4586–4587. [CrossRef]
126. Terauchi, J.; Curran, D.P. N-Allylation of anilides with chiral palladium catalysts: The first catalytic asymmetric synthesis of axially chiral anilides. *Tetrahedron Asymmetry* **2003**, *14*, 587–592. [CrossRef]
127. Cacchi, S.; Fabrizi, G. Synthesis and functionalization of indoles through palladium-catalyzed reactions. *Chem. Rev.* **2005**, *105*, 2873–2920. [CrossRef]
128. Humphrey, G.R.; Kuethe, J.T. Practical methodologies for the synthesis of indoles. *Chem. Rev.* **2006**, *106*, 2875–2911. [CrossRef] [PubMed]
129. Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. InBr3-promoted divergent approach to polysubstituted indoles and quinolines from 2-ethynylanilines: Switch from an intramolecular cyclization to an intermolecular dimerization by a type of terminal substituent group. *J. Org. Chem.* **2008**, *73*, 4160–4165. [CrossRef]
130. Taylor, E.C.; Katz, A.H.; Salgado-Zamora, H.; McKillop, A. Thallium in organic synthesis. 68. A convenient synthesis of 2-phenylindoles from anilides. *Tetrahedron Lett.* **1985**, *26*, 5963–5966. [CrossRef]
131. Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. Catalytic Enantioselective Synthesis of Atropisomeric Indoles with an N—C Chiral Axis. *Chem. Eur. J.* **2010**, *16*, 6752–6755. [CrossRef] [PubMed]
132. Morimoto, Y.; Shimizu, S.; Mokuya, A.; Ototake, N.; Saito, A.; Kitagawa, O. Enantioselective synthesis of N–C axially chiral indoles through chiral palladium-catalyzed 5-endo-hydroaminocyclization. *Tetrahedron* **2016**, *72*, 5221–5229. [CrossRef]
133. Sakai, H.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. One-Pot/Four-Step/Palladium-Catalyzed Synthesis of Indole Derivatives: The Combination of Heterogeneous and Homogeneous Systems. *Adv. Synth. Catal.* **2008**, *350*, 2498–2502. [CrossRef]
134. Holenz, J.; Mercè, R.; Díaz, J.L.; Guitart, X.; Codony, X.; Dordal, A.; Romero, G.; Torrens, A.; Mas, J.; Andaluz, B. Medicinal chemistry driven approaches toward novel and selective serotonin 5-HT6 receptor ligands. *J. Med. Chem.* **2005**, *48*, 1781–1795. [CrossRef]
135. Leclerc, V.; Yous, S.; Delagrange, P.; Boutin, J.A.; Renard, P.; Lesieur, D. Synthesis of nitroindole derivatives with high affinity and selectivity for melatoninergic binding sites MT3. *J. Med. Chem.* **2002**, *45*, 1853–1859. [CrossRef]
136. Owa, T.; Okauchi, T.; Yoshimatsu, K.; Sugi, N.H.; Ozawa, Y.; Nagasu, T.; Koyanagi, N.; Okabe, T.; Kitoh, K.; Yoshino, H. A focused compound library of novel N-(7-indolyl) benzenesulfonamides for the discovery of potent cell cycle inhibitors. *Bioorgan. Med. Chem. Lett.* **2000**, *10*, 1223–1226. [CrossRef]
137. Xu, Y.-C.; Johnson, K.W.; Phebus, L.A.; Cohen, M.; Nelson, D.L.; Schenck, K.; Walker, C.D.; Fritz, J.E.; Kaldor, S.W.; LeTourneau, M.E. N-[3-(2-Dimethylaminoethyl)-2-methyl-1 H-indol-5-yl]-4-fluorobenzamide: A Potent, Selective, and Orally Active 5-HT1F Receptor Agonist Potentially Useful for Migraine Therapy. *J. Med. Chem.* **2001**, *44*, 4031–4034. [CrossRef]
138. Sanz, R.; Guilarte, V.; Pérez, A. Straightforward selective preparation of nitro-or amino-indoles from 2-halonitroanilines and alkynes. First synthesis of 7-amino-5-nitroindoles. *Tetrahedron Lett.* **2009**, *50*, 4423–4426. [CrossRef]
139. Djakovitch, L.; Dufaud, V.; Zaidi, R. Heterogeneous Palladium Catalysts Applied to the Synthesis of 2-and 2, 3-Functionalised Indoles. *Adv. Synth. Catal.* **2006**, *348*, 715–724. [CrossRef]
140. Dooleweerdt, K.; Ruhland, T.; Skrydstrup, T. Application of Ynamides in the Synthesis of 2-Amidoindoles. *Org. Lett.* **2009**, *11*, 221–224. [CrossRef]
141. Fang, Y.-Q.; Lautens, M. A highly selective tandem cross-coupling of gem-dihaloolefins for a modular, efficient synthesis of highly functionalized indoles. *J. Org. Chem.* **2008**, *73*, 538–549. [CrossRef] [PubMed]

142. Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. Palladium-Catalyzed Aryl Amination–Heck Cyclization Cascade: A One-Flask Approach to 3-Substituted Indoles. *Angew. Chem. Int. Ed.* **2008**, *47*, 888–890. [CrossRef]
143. Jia, Y.; Zhu, J. Palladium-catalyzed, modular synthesis of highly functionalized indoles and tryptophans by direct annulation of substituted o-haloanilines and aldehydes. *J. Org. Chem.* **2006**, *71*, 7826–7834. [CrossRef] [PubMed]
144. Liu, J.; Shen, M.; Zhang, Y.; Li, G.; Khodabocus, A.; Rodriguez, S.; Qu, B.; Farina, V.; Senanayake, C.H.; Lu, B.Z. A New entry to polycyclic indole skeletons via palladium-catalyzed intramolecular heteroannulation. *Org. Lett.* **2006**, *8*, 3573–3575. [CrossRef]
145. Terrasson, V.; Michaux, J.; Gaucher, A.; Wehbe, J.; Marque, S.; Prim, D.; Campagne, J.M. *Iron–Palladium Association in the Preparation of Indoles and One-Pot Synthesis of Bis (Indolyl) Methanes*; Wiley Online Library: Hoboken, NJ, USA, 2007.
146. Zhao, J.; Larock, R.C. Synthesis of substituted carbazoles, indoles, and dibenzofurans by vinylic to aryl palladium migration. *J. Org. Chem.* **2006**, *71*, 5340–5348. [CrossRef] [PubMed]
147. Rodriguez, A.L.; Koradin, C.; Dohle, W.; Knochel, P. Versatile indole synthesis by a 5-endo-dig cyclization mediated by potassium or cesium bases. *Angew. Chem. Int. Ed.* **2000**, *39*, 2488. [CrossRef]
148. Dai, W.-M.; Sun, L.-P.; Guo, D.-S. Chemistry of aminophenols. Part 2: A general and efficient synthesis of indoles possessing a nitrogen substituent at the C4, C5, C6, and C7 positions. *Tetrahedron Lett.* **2002**, *43*, 7699–7702. [CrossRef]
149. Alonso, F.; Beletskaya, I.P.; Yus, M. Transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes. *Chem. Rev.* **2004**, *104*, 3079–3160. [CrossRef]
150. Chemler, S.R.; Fuller, P.H. Heterocycle synthesis by copper facilitated addition of heteroatoms to alkenes, alkynes and arenes. *Chem. Soc. Rev.* **2007**, *36*, 1153–1160. [CrossRef] [PubMed]
151. Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. Efficient construction of indole rings from 2-ethynylaniline derivatives catalyzed by copper (II) salts and its application to the tandem cyclization reactions. *Tetrahedron Lett.* **2002**, *43*, 1277–1280. [CrossRef]
152. Lu, B.Z.; Zhao, W.; Wei, H.-X.; Dufour, M.; Farina, V.; Senanayake, C.H. A practical mild, one-pot, regiospecific synthesis of 2, 3-disubstituted indoles via consecutive Sonogashira and Cacchi reactions. *Org. Lett.* **2006**, *8*, 3271–3274. [CrossRef] [PubMed]
153. Shimada, T.; Nakamura, I.; Yamamoto, Y. Intramolecular C− N Bond Addition of Amides to Alkynes Using Platinum Catalyst. *J. Am. Chem. Soc.* **2004**, *126*, 10546–10547. [CrossRef]
154. Rao, R.M.; CH, U.R.; Mulakayala, N.; Alvala, M.; Arunasree, M.; Poondra, R.R.; Iqbal, J.; Pal, M. Sequential coupling/desilylation–coupling/cyclization in a single pot under Pd/C–Cu catalysis: Synthesis of 2-(hetero) aryl indoles. *Org. Biomol. Chem.* **2011**, *9*, 3808–3816. [CrossRef] [PubMed]
155. Ahmed, A.; Ghosh, M.; Sarkar, P.; Ray, J.K. ZnCl2 and Pd/C catalyzed synthesis of 2-substituted indoles. *Tetrahedron Lett.* **2013**, *54*, 6691–6694. [CrossRef]
156. Ahmed, A.; Ghosh, M.; Dhara, S.; Ray, J.K. A Mild Approach for the Synthesis of Indoles from N-(2-Iodo-aryl) formamides and Phenylacetylene by a Copper (I)-and Palladium-Catalyzed Cascade Process. *Synlett* **2014**, *25*, 2455–2458. [CrossRef]
157. Yamaguchi, M.; Manabe, K. One-pot synthesis of 2, 4-disubstituted indoles from N-tosyl-2, 3-dichloroaniline using palladium–dihydroxyterphenylphosphine catalyst. *Org. Lett.* **2014**, *16*, 2386–2389. [CrossRef]
158. Bruneau, A.; Gustafson, K.P.; Yuan, N.; Tai, C.-W.; Persson, I.; Zou, X.; Bäckvall, J.-E. Synthesis of benzofurans and indoles from terminal alkynes and iodoaromatics catalyzed by recyclable palladium nanoparticles immobilized on siliceous mesocellular foam. *Chem. Eur. J.* **2017**, *23*, 12886–12891. [CrossRef] [PubMed]
159. He, Y.P.; Wu, H.; Wang, Q.; Zhu, J. Palladium-Catalyzed Enantioselective Cacchi Reaction: Asymmetric Synthesis of Axially Chiral 2, 3-Disubstituted Indoles. *Angew. Chem.* **2020**, *132*, 2121–2125. [CrossRef]
160. Chen, Y.; Markina, N.A.; Larock, R.C. An efficient, microwave-assisted, one-pot synthesis of indoles under Sonogashira conditions. *Tetrahedron* **2009**, *65*, 8908–8915. [CrossRef] [PubMed]
161. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. 2, 3-Disubstituted indoles via palladium-catalyzed reaction of 2-alkynyltrifluoroacetanilides with arenediazonium tetrafluoroborates. *Org. Lett.* **2010**, *12*, 3279–3281. [CrossRef]
162. Guilarte, V.; Castroviejo, M.P.; García-García, P.; Fernández-Rodríguez, M.A.; Sanz, R. Approaches to the synthesis of 2, 3-dihaloanilines. Useful precursors of 4-functionalized-1 H-indoles. *J. Org. Chem.* **2011**, *76*, 3416–3437. [CrossRef] [PubMed]
163. Lu, B.Z.; Wei, H.-X.; Zhang, Y.; Zhao, W.; Dufour, M.; Li, G.; Farina, V.; Senanayake, C.H. One-pot and regiospecific synthesis of 2, 3-disubstituted indoles from 2-bromoanilides via consecutive palladium-catalyzed sonogashira coupling, amidopalladation, and reductive elimination. *J. Org. Chem.* **2013**, *78*, 4558–4562. [CrossRef] [PubMed]
164. Staudinger, H.; Meyer, J. Über neue organische phosphorverbindungen III. Phosphinmethylenderivate und phosphinimine. *Helv. Chim. Acta* **1919**, *2*, 635–646. [CrossRef]
165. Zhou, Q.; Zhang, Z.; Zhou, Y.; Li, S.; Zhang, Y.; Wang, J. Palladium-Catalyzed Synthesis of Indoles and Isoquinolines with in Situ Generated Phosphinimine. *J. Org. Chem.* **2017**, *82*, 48–56. [CrossRef] [PubMed]
166. Minami, H.; Kanayama, T.; Tanaka, R.; Okamoto, N.; Sueda, T.; Yanada, R. Regioselective Arylative Ring-Closing Reaction of 2-Alkynylphenyl Derivatives: Formation of Arylated Benzoxazin-2-ones, Benzoxazin-2-amines and 2, 3-Disubstituted Indoles. *Eur. J. Org. Chem.* **2016**, *2016*, 5990–6000. [CrossRef]
167. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Iazzetti, A.; Verdiglione, R. 2-(Aminomethyl)-3-arylindoles from 3-(o-Trifluoroacetamidoaryl)-1-propargylic alcohols, aryl Halides, and amines: A domino palladium-catalyzed three-component approach. *Synthesis* **2017**, *49*, 4163–4172.

168. Arcadi, A.; Cianci, R.; Ferrara, G.; Marinelli, F. 3-(2-Alken-1-one-2-yl) indoles through the palladium-catalyzed reaction of 2-alkynyltrifluoroacetanilides with cyclic α-iodoenones. *Tetrahedron* **2010**, *66*, 2378–2383. [CrossRef]
169. Álvarez, R.; Martínez, C.; Madich, Y.; Denis, J.G.; Aurrecoechea, J.M.; de Lera, Á.R. A General Synthesis of Alkenyl-Substituted Benzofurans, Indoles, and Isoquinolones by Cascade Palladium-Catalyzed Heterocyclization/Oxidative Heck Coupling. *Chem. Eur. J.* **2010**, *16*, 12746–12753. [CrossRef]
170. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. Heck reaction of arenediazonium salts with N, N-diprotected allylamines. Synthesis of cinnamylamines and indoles. *Org. Biomol. Chem.* **2011**, *9*, 1727–1730. [CrossRef] [PubMed]
171. Wang, Q.; Huang, L.; Wu, X.; Jiang, H. Nucleopalladation triggering the oxidative heck reaction: A general strategy to diverse β-indole ketones. *Org. Lett.* **2013**, *15*, 5940–5943. [CrossRef]
172. Janreddy, D.; Kavala, V.; Kuo, C.-W.; Kuo, T.-S.; He, C.-H.; Yao, C.-F. The PdCl2-catalyzed sequential heterocyclization/Michael addition cascade in the synthesis of 2, 3-disubstituted indoles. *Tetrahedron* **2013**, *69*, 3323–3330. [CrossRef]
173. Reddy, V.; Vijaya Anand, R. Expedient access to unsymmetrical diarylindolylmethanes through palladium-catalyzed domino electrophilic cyclization–extended conjugate addition approach. *Org. Lett.* **2015**, *17*, 3390–3393. [CrossRef]
174. Chen, J.; Han, X.; Lu, X. Enantioselective Synthesis of Tetrahydropyrano [3, 4-b] indoles: Palladium (II)-Catalyzed Aminopalladation/1, 4-Addition Sequence. *Angew. Chem.* **2017**, *129*, 14890–14893. [CrossRef]
175. Tang, S.; Xie, Y.-X.; Li, J.-H.; Wang, N.-X. PdX2/CuX2-Catalyzed annulation of 2-Ethynylbenzeneamines: Selective synthesis of 2-Substituted 3-Halo-1H-indoles. *Synthesis* **2007**, *2007*, 1841–1847. [CrossRef]
176. Zhang, H.-P.; Yu, S.-C.; Liang, Y.; Peng, P.; Tang, B.-X.; Li, J.-H. Halopalladation Cyclization of Alkynes with Azides: Selective Synthesis of 4-Haloisoquinolines and 3-Haloindoles. *Synlett* **2011**, *2011*, 982–988.
177. Han, X.; Lu, X. Cationic Pd (II)-Catalyzed Tandem Reaction of 2-Arylethynylanilines and Aldehydes: An Efficient Synthesis of Substituted 3-Hydroxymethyl Indoles. *Org. Lett.* **2010**, *12*, 3336–3339. [CrossRef]
178. Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. Palladium-catalyzed difunctionalization of alkynes via C–N and S–N cleavages: A versatile approach to highly functional indoles. *Org. Lett.* **2014**, *16*, 5124–5127. [CrossRef] [PubMed]
179. Gabriele, B.; Veltri, L.; Salerno, G.; Mancuso, R.; Costa, M. Multicomponent Cascade Reactions: A novel and expedient approach to functionalized Indoles by an unprecedented nucleophilic addition-heterocyclization-oxidative alkoxycarbonylation sequence. *Adv. Synth. Catal.* **2010**, *352*, 3355–3363. [CrossRef]
180. Gabriele, B.; Veltri, L.; Mancuso, R.; Salerno, G.; Costa, M. A general synthesis of Indole-3-carboxylic esters by Palladium-catalyzed direct oxidative carbonylation of 2-Alkynylaniline derivatives. *Eur. J. Org. Chem.* **2012**, *2012*, 2549–2559. [CrossRef]
181. Chen, J.; Han, X.; Lu, X. Atom-economic synthesis of pentaleno [2, 1-b] indoles via Tandem cyclization of alkynones initiated by aminopalladation. *J. Org. Chem.* **2017**, *82*, 1977–1985. [CrossRef]
182. Xia, X.-F.; Zhang, L.-L.; Song, X.-R.; Niu, Y.-N.; Liu, X.-Y.; Liang, Y.-M. Palladium–copper-cocatalyzed intramolecular oxidative coupling: An efficient and atom-economical strategy for the synthesis of 3-acylindoles. *Chem. Comm.* **2013**, *49*, 1410–1412. [CrossRef]
183. Zhang, X.; Li, P.; Lyu, C.; Yong, W.; Li, J.; Zhu, X.; Rao, W. Synthesis of 1 H-indole-3-sulfonates via palladium-catalyzed tandem reactions of 2-alkynyl arylazides with sulfonic acids. *Org. Biomol. Chem.* **2017**, *15*, 6080–6083. [CrossRef]
184. Qiu, G.; Chen, C.; Yao, L.; Wu, J. An efficient route to 3-Amidylindoles via a Palladium-Catalyzed tandem reaction of 2-alkynylanilines with isocyanides. *Adv. Synth. Catal.* **2013**, *355*, 1579–1584. [CrossRef]
185. Hu, Z.; Wang, J.; Liang, D.; Zhu, Q. Synthesis of 1H-Indole-3-carboxamidines through a Palladium-Catalyzed Three-Component Reaction Involving Isocyanide Insertion as a Key Step. *Adv. Synth. Catal.* **2013**, *355*, 3290–3294. [CrossRef]
186. Qiu, G.; Qiu, X.; Liu, J.; Wu, J. Switchable Synthesis of 3-Cyanoindoles and 3-Amidylindoles via a Palladium-Catalyzed Reaction of N, N-Dimethyl-2-alkynylaniline with Isocyanide. *Adv. Synth. Catal.* **2013**, *355*, 2441–2446. [CrossRef]
187. Hu, Z.; Luo, S.; Zhu, Q. Aminopalladation-Triggered Carbene Insertion Reaction: Synthesis of 2-(1H-Indol-3-yl) acetates. *Adv. Synth. Catal.* **2015**, *357*, 1060–1064. [CrossRef]
188. Yao, B.; Wang, Q.; Zhu, J. Palladium-Catalyzed Coupling of ortho-Alkynylanilines with Terminal Alkynes Under Aerobic Conditions: Efficient Synthesis of 2, 3-Disubstituted 3-Alkynylindoles. *Angew. Chem. Int. Ed.* **2012**, *51*, 12311–12315. [CrossRef]
189. Yao, B.; Wang, Q.; Zhu, J. Pd/C-Catalyzed Cyclizative Cross-Coupling of Two ortho-Alkynylanilines under Aerobic Conditions: Synthesis of 2, 3′-Bisindoles. *Chem. Eur. J.* **2015**, *21*, 7413–7416. [CrossRef] [PubMed]
190. Huang, J.; Macdonald, S.J.; Harrity, J.P. A borylative cyclisation towards indole boronic esters. *Chem. Comm.* **2010**, *46*, 8770–8772. [CrossRef]
191. Guo, Y.J.; Tang, R.Y.; Li, J.H.; Zhong, P.; Zhang, X.G. Palladium-Catalyzed Annulation of 2-(1-Alkynyl) benzenamines with Disulfides: Synthesis of 3-Sulfenylindoles. *Adv. Synth. Catal.* **2009**, *351*, 2615–2618. [CrossRef]
192. Li, J.; Yang, S.; Huang, L.; Chen, H.; Jiang, H. Highly efficient and practical synthesis of functionalized 1, 5-dienes via Pd (II)-catalyzed halohomoallylation of alkynes. *RSC Adv.* **2013**, *3*, 11529–11532. [CrossRef]
193. Li, J.; Yang, S.; Jiang, H.; Wu, W.; Zhao, J. Palladium-catalyzed coupling of alkynes with unactivated alkenes in ionic liquids: A regio-and stereoselective synthesis of functionalized 1, 6-dienes and their analogues. *J. Org. Chem.* **2013**, *78*, 12477–12486. [CrossRef]
194. Li, J.; Yang, S.; Wu, W.; Jiang, H. Novel palladium-catalyzed cascade carboxylative annulation to construct functionalized γ-lactones in ionic liquids. *Chem. Comm.* **2014**, *50*, 1381–1383. [CrossRef]

195. Li, J.; Yang, S.; Wu, W.; Qi, C.; Deng, Z.; Jiang, H. Synthesis of 1, 4-dienes by Pd (II)-catalyzed haloallylation of alkynes with allylic alcohols in ionic liquids. *Tetrahedron* **2014**, *70*, 1516–1523. [CrossRef]
196. Li, J.; Yang, W.; Yang, S.; Huang, L.; Wu, W.; Sun, Y.; Jiang, H. Palladium-Catalyzed Cascade Annulation To Construct Functionalized β-and γ-Lactones in Ionic Liquids. *Angew. Chem. Int. Ed.* **2014**, *53*, 7219–7222. [CrossRef] [PubMed]
197. Li, J.; Zhu, Z.; Yang, S.; Zhang, Z.; Wu, W.; Jiang, H. Palladium-catalyzed tandem annulation: A strategy to construct 2, 3-difunctionalized benzofuran derivatives in ionic liquids. *J. Org. Chem.* **2015**, *80*, 3870–3879. [CrossRef] [PubMed]
198. Wu, W.; Jiang, H. Haloalkynes: A powerful and versatile building block in organic synthesis. *Acc. Chem. Res.* **2014**, *47*, 2483–2504. [CrossRef] [PubMed]
199. Yang, S.-R.; Jiang, H.-F.; Li, Y.-Q.; Chen, H.-J.; Luo, W.; Xu, Y.-B. Protonolysis of the carbon–palladium bond in palladium (II)-catalyzed enyne cyclization in imidazolium-type ionic liquids. *Tetrahedron* **2008**, *64*, 2930–2937. [CrossRef]
200. Chaplin, J.H.; Flynn, B.L. A multi-component coupling approach to benzo [b] furans and indolesElectronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for 14a–h, 15a and 16. *Chem. Commun.* **2001**, 1594–1595. [CrossRef]
201. Zhou, R.; Wang, W.; Jiang, Z.-j.; Wang, K.; Zheng, X.-l.; Fu, H.-y.; Chen, H.; Li, R.-X. One-pot synthesis of 2-substituted benzo [b] furans via Pd–tetraphosphine catalyzed coupling of 2-halophenols with alkynes. *Chem. Comm.* **2014**, *50*, 6023–6026. [CrossRef]
202. Chen, C.; Xie, Y.; Chu, L.; Wang, R.W.; Zhang, X.; Qing, F.L. Copper-Catalyzed Oxidative Trifluoromethylthiolation of Aryl Boronic Acids with TMSCF3 and Elemental Sulfur. *Angew. Chem.* **2012**, *124*, 2542–2545. [CrossRef]
203. Chu, L.; Qing, F.-L. Copper-mediated oxidative trifluoromethylation of boronic acids. *Org. Lett.* **2010**, *12*, 5060–5063. [CrossRef]
204. Helton, M.E.; Chen, P.; Paul, P.P.; Tyeklár, Z.; Sommer, R.D.; Zakharov, L.N.; Rheingold, A.L.; Solomon, E.I.; Karlin, K.D. Reaction of elemental sulfur with a copper (I) complex forming a trans-μ-1, 2 end-on disulfide complex: New directions in copper− sulfur chemistry. *J. Am. Chem. Soc.* **2003**, *125*, 1160–1161. [CrossRef] [PubMed]
205. Posner, G. Direct and convenient preparation of lithium phenylthio (alkyl) cuprate reagents. *Synthesis* **1974**, 662–663. [CrossRef]
206. Senecal, T.D.; Parsons, A.T.; Buchwald, S.L. Room temperature aryl trifluoromethylation via copper-mediated oxidative cross-coupling. *J. Org. Chem.* **2011**, *76*, 1174–1176. [CrossRef] [PubMed]
207. Li, J.; Li, C.; Yang, S.; An, Y.; Wu, W.; Jiang, H. Assembly of 3-sulfenylbenzofurans and 3-sulfenylindoles by palladium-catalyzed cascade annulation/arylthiolation reaction. *J. Org. Chem.* **2016**, *81*, 2875–2887. [CrossRef]
208. Sheng, J.; Li, S.; Wu, J. Synthesis of 3-((trifluoromethyl) thio) indoles via a reaction of 2-alkynylaniline with trifluoromethanesulfanylamide. *Chem. Comm.* **2014**, *50*, 578–580. [CrossRef] [PubMed]
209. Wu, C.; Zhao, F.; Du, Y.; Zhao, L.; Chen, L.; Wang, J.; Liu, H. Highly selective intramolecular addition of C–N and S–N bonds to alkynes catalyzed by palladium: A practical access to two distinct functional indoles. *RSC Adv.* **2016**, *6*, 70682–70690. [CrossRef]
210. Gabriele, B.; Mancuso, R.; Salerno, G.; Lupinacci, E.; Ruffolo, G.; Costa, M. Versatile synthesis of quinoline-3-carboxylic esters and indol-2-acetic esters by palladium-catalyzed carbonylation of 1-(2-aminoaryl)-2-yn-1-ols. *J. Org. Chem.* **2008**, *73*, 4971–4977. [CrossRef]
211. Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. Efficient synthesis of ureas by direct palladium-catalyzed oxidative carbonylation of amines. *J. Org. Chem.* **2004**, *69*, 4741–4750. [CrossRef]
212. Nishiyama, Y.; Kawamatsu, H.; Sonoda, N. A facile method for the synthesis of thiocarbamates: Palladium-catalyzed reaction of disulfide, amine, and carbon monoxide. *J. Org. Chem.* **2005**, *70*, 2551–2554. [CrossRef] [PubMed]
213. Cacchi, S.; Fabrizi, G.; Filisti, E. Palladium-catalyzed synthesis of free-NH indole 2-acetamides and derivatives from ethyl 3-(o-trifluoroacetamidoaryl)-1-propargylic carbonates. *Synlett* **2009**, *2009*, 1817–1821. [CrossRef]
214. Ambrogio, I.; Cacchi, S.; Fabrizi, G.; Prastaro, A. 3-(o-Trifluoroacetamidoaryl)-1-propargylic esters: Common intermediates for the palladium-catalyzed synthesis of 2-aminomethyl-, 2-vinylic, and 2-alkylindoles. *Tetrahedron* **2009**, *65*, 8916–8929. [CrossRef]
215. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Molinaro, C.; Verdiglione, R. Palladium-catalyzed synthesis of 2-(aminomethyl) indoles from 3-(o-trifluoroacetamidoaryl)-1-propargylic alcohols and amines. *J. Org. Chem.* **2014**, *79*, 401–407. [CrossRef] [PubMed]
216. Thirupathi, N.; Babu, M.H.; Dwivedi, V.; Kant, R.; Reddy, M.S. Palladium-Catalyzed Tandem Intramolecular Oxy/Amino-Palladation/Isocyanide Insertion: Synthesis of α-Benzofuranyl/Indolylacetamides. *Org. Lett.* **2014**, *16*, 2908–2911. [CrossRef]
217. Liu, Y.; Huang, Y.; Song, H.; Liu, Y.; Wang, Q. Regio-and Chemoselective N-1 Acylation of Indoles: Pd-Catalyzed Domino Cyclization to Afford 1, 2-Fused Tricyclic Indole Scaffolds. *Chem. Eur. J.* **2015**, *21*, 5337–5340. [CrossRef]
218. Das, B.; Kundu, P.; Chowdhury, C. Facile synthesis of 2-arylmethylindoles and 2-vinylic indoles through palladium-catalyzed heteroannulations of 2-(2-propynyl) aniline and 2-(2-propynyl) tosylanilide. *Org. Biomol. Chem.* **2014**, *12*, 741–748. [CrossRef] [PubMed]
219. Chowdhury, C.; Das, B.; Mukherjee, S.; Achari, B. Palladium-catalyzed approach for the general synthesis of (E)-2-arylmethylidene-N-tosylindolines and (E)-2-arylmethylidene-N-tosyl/nosyltetrahydroquinolines: Access to 2-substituted indoles and quinolines. *J. Org. Chem.* **2012**, *77*, 5108–5119. [CrossRef] [PubMed]
220. Cui, X.; Li, J.; Fu, Y.; Liu, L.; Guo, Q.-X. Regioselective Pd-catalyzed indolization of 2-bromoanilines with internal alkynes using phosphine-free ligands. *Tetrahedron Lett.* **2008**, *49*, 3458–3462. [CrossRef]
221. Batail, N.; Bendjeriou, A.; Lomberget, T.; Barret, R.; Dufaud, V.; Djakovitch, L. First Heterogeneous Ligand-and Salt-Free Larock Indole Synthesis. *Adv. Synth. Catal.* **2009**, *351*, 2055–2062. [CrossRef]
222. Batail, N.; Dufaud, V.; Djakovitch, L. Larock heteroannulation of 2-bromoanilines with internal alkynes via ligand and salt free Pd/C catalysed reaction. *Tetrahedron Lett.* **2011**, *52*, 1916–1918. [CrossRef]

223. Monguchi, Y.; Mori, S.; Aoyagi, S.; Tsutsui, A.; Maegawa, T.; Sajiki, H. Palladium on carbon-catalyzed synthesis of 2-and 2, 3-substituted indoles under heterogeneous conditions. *Org. Biomol. Chem.* **2010**, *8*, 3338–3342. [CrossRef]
224. Ang, W.J.; Tai, C.-H.; Lo, L.-C.; Lam, Y. Palladium-catalyzed annulation of internal alkynes in aqueous medium. *RSC Adv.* **2014**, *4*, 4921–4929. [CrossRef]
225. Denmark, S.E.; Baird, J.D. Preparation of 2, 3-disubstituted indoles by sequential Larock heteroannulation and silicon-based cross-coupling reactions. *Tetrahedron* **2009**, *65*, 3120–3129. [CrossRef] [PubMed]
226. Danner, P.; Morkunas, M.; Maier, M.E. Synthesis of d-Abrines by Palladium-catalyzed Reaction of ortho-Iodoanilines with N-Boc-N-methylalanyl-substituted Acetaldehyde and Acetylene. *Org. Lett.* **2013**, *15*, 2474–2477. [CrossRef]
227. Kondoh, A.; Yorimitsu, H.; Oshima, K. Synthesis of 2-indolylphosphines by palladium-catalyzed annulation of 1-alkynylphosphine sulfides with 2-iodoanilines. *Org. Lett.* **2010**, *12*, 1476–1479. [CrossRef]
228. Goswami, K.; Duttagupta, I.; Sinha, S. Synthesis of optically active 2-and 3-indolylglycine derivatives and their oxygen analogues. *J. Org. Chem.* **2012**, *77*, 7081–7085. [CrossRef] [PubMed]
229. Hao, W.; Geng, W.; Zhang, W.X.; Xi, Z. Palladium-catalyzed one-pot three-or four-component coupling of aryl iodides, alkynes, and amines through C—N bond cleavage: Efficient synthesis of indole derivatives. *Chem. Eur. J.* **2014**, *20*, 2605–2612. [CrossRef] [PubMed]
230. Hao, W.; Wei, J.; Geng, W.; Zhang, W.X.; Xi, Z. Transfer of Aryl Halide to Alkyl Halide: Reductive elimination of alkylhalide from alkylpalladium halides containing syn-β-Hydrogen atoms. *Angew. Chem.* **2014**, *126*, 14761–14765. [CrossRef]
231. Hao, W.; Wang, H.; Walsh, P.J.; Xi, Z. Combining Pd (π-allyl) Cp and PPh 3 as a unique catalyst for efficient synthesis of alkyliodo indoles via C (sp 3)–I reductive elimination. *Org. Chem. Front.* **2015**, *2*, 1080–1084. [CrossRef]
232. Zhu, C.; Ma, S. Coupling and cyclization of o-iodoanilines and propargylic bromides via allenes: An efficient entry to indomethacin. *Org. Lett.* **2013**, *15*, 2782–2785. [CrossRef]
233. Panyam, P.K.R.; Gandhi, T. Palladium (II)/N-heterocyclic carbene-catalyzed regioselective heteroannulation of tertiary propargyl alcohols and o-Haloanilines to form 2-Alkenylindoles. *Adv. Synth. Catal.* **2017**, *359*, 1144–1151. [CrossRef]
234. Onishi, K.; Oikawa, K.; Yano, H.; Suzuki, T.; Obora, Y. N, N-Dimethylformamide-stabilized palladium nanoclusters as a catalyst for Larock indole synthesis. *RSC Adv.* **2018**, *8*, 11324–11329. [CrossRef]
235. Zhang, H.; Wang, H.-Y.; Luo, Y.; Chen, C.; Cao, Y.; Chen, P.; Guo, Y.-L.; Lan, Y.; Liu, G. Regioselective palladium-catalyzed CH Bond trifluoroethylation of indoles: Exploration and mechanistic insight. *ACS Catal.* **2018**, *8*, 2173–2180. [CrossRef]
236. Alberico, D.; Scott, M.E.; Lautens, M. Aryl− aryl bond formation by transition-metal-catalyzed direct arylation. *Chem. Rev.* **2007**, *107*, 174–238. [CrossRef]
237. Chen, X.; Li, X.; Wang, N.; Jin, J.; Lu, P.; Wang, Y. Palladium-Catalyzed reaction of arylamine and diarylacetylene: Solvent-controlled construction of 2, 3-diarylindoles and pentaarylpyrroles. *Eur. J. Org. Chem.* **2012**, *2012*, 4380–4386. [CrossRef]
238. Shen, D.; Han, J.; Chen, J.; Deng, H.; Shao, M.; Zhang, H.; Cao, W. Mild and efficient one-pot synthesis of 2-(perfluoroalkyl) indoles by means of sequential Michael-type addition and Pd (II)-catalyzed cross-dehydrogenative coupling (CDC) reaction. *Org. Lett.* **2015**, *17*, 3283–3285. [CrossRef] [PubMed]
239. Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. Indoles from simple anilines and alkynes: Palladium-catalyzed C H activation using dioxygen as the oxidant. *Angew. Chem.* **2009**, *121*, 4642–4646. [CrossRef]
240. Nakamura, I.; Nemoto, T.; Shiraiwa, N.; Terada, M. Palladium-catalyzed indolization of N-aroylbenzotriazoles with disubstituted alkynes. *Org. Lett.* **2009**, *11*, 1055–1058. [CrossRef]
241. Katritzky, A.R.; Kirichenko, K. Acyl anion synthons: Benzotriazole stabilized compared to classical. *Arkivoc* **2006**, *4*, 119–151. [CrossRef]
242. Katritzky, A.R.; Lan, X.; Yang, J.Z.; Denisko, O.V. Properties and synthetic utility of N-substituted benzotriazoles. *Chem. Rev.* **1998**, *98*, 409–548. [CrossRef]
243. Katritzky, A.R.; Suzuki, K.; Wang, Z. Acylbenzotriazoles as advantageous N-, C-, S-, and O-acylating agents. *Synlett* **2005**, *2005*, 1656–1665. [CrossRef]
244. Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. Intramolecular Pd-mediated processes of amino-tethered aryl halides and ketones: Insight into the ketone α-arylation and carbonyl-addition dichotomy. A new class of four-membered azapalladacycles. *J. Am. Chem. Soc.* **2003**, *125*, 1587–1594. [CrossRef]
245. Horino, H.; Inoue, N. Ortho vinylation of aromatic amides via cyclopalladation complexes. *J. Org. Chem.* **1981**, *46*, 4416–4422. [CrossRef]
246. Tremont, S.J.; Rahman, H.U. Ortho-alkylation of acetanilides using alkyl halides and palladium acetate. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760. [CrossRef]
247. Zhou, F.; Han, X.; Lu, X. Synthesis of indoles via palladium-catalyzed C–H activation of N-aryl amides followed by coupling with alkynes. *Tetrahedron Lett.* **2011**, *52*, 4681–4685. [CrossRef]
248. Chen, J.; Pang, Q.; Sun, Y.; Li, X. Synthesis of N-(2-pyridyl) indoles via Pd (II)-catalyzed oxidative coupling. *J. Org. Chem.* **2011**, *76*, 3523–3526. [CrossRef] [PubMed]
249. Chen, J.; He, L.; Natte, K.; Neumann, H.; Beller, M.; Wu, X.F. Palladium@ Cerium (IV) Oxide-Catalyzed Oxidative Synthesis of N-(2-Pyridyl) indoles via C—H Activation Reaction. *Adv. Synth. Catal.* **2014**, *356*, 2955–2959. [CrossRef]

250. Sanz, R.; Castroviejo, M.P.; Guilarte, V.; Pérez, A.; Fananas, F.J. Regioselective Synthesis of 4-and 7-alkoxyindoles from 2, 3-dihalophenols: Application to the preparation of indole inhibitors of phospholipase A2. *J. Org. Chem.* **2007**, *72*, 5113–5118. [CrossRef] [PubMed]
251. Sanz, R.; Castroviejo, M.P.; Fernández, Y.; Fañanás, F.J. A new and efficient synthesis of 4-functionalized benzo [b] furans from 2, 3-dihalophenols. *J. Org. Chem.* **2005**, *70*, 6548–6551. [CrossRef] [PubMed]
252. Ackermann, L.; Sandmann, R.; Kondrashov, M.V. Thieme Chemistry Journal Awardees-Where Are They Now? Palladium-Catalyzed N-Arylation-Hydroamination Sequence for the Synthesis of Indoles with Sterically Demanding N-Substituents. *Synlett* **2009**, *2009*, 1219–1222. [CrossRef]
253. Ackermann, L.; Sandmann, R.; Schinkel, M.; Kondrashov, M.V. Palladium-catalyzed sequential indole synthesis using sterically hindered amines. *Tetrahedron* **2009**, *65*, 8930–8939. [CrossRef]
254. Liang, Y.; Meng, T.; Zhang, H.-J.; Xi, Z. Palladium-catalyzed, one-pot, three-component approach to α-alkynyl indoles from o-bromo-(2, 2-dibromovinyl) benzenes, terminal alkynes and arylamines. *Synlett* **2011**, *2011*, 911–914. [CrossRef]
255. Alsabeh, P.G.; Lundgren, R.J.; Longobardi, L.E.; Stradiotto, M. Palladium-catalyzed synthesis of indoles via ammonia cross-coupling–alkyne cyclization. *Chem. Comm.* **2011**, *47*, 6936–6938. [CrossRef]
256. Lavery, C.B.; McDonald, R.; Stradiotto, M. Efficient palladium-catalyzed synthesis of substituted indoles employing a new (silanyloxyphenyl) phosphine ligand. *Chem. Comm.* **2012**, *48*, 7277–7279. [CrossRef]
257. Halland, N.; Nazaré, M.; Alonso, J.; R'kyek, O.; Lindenschmidt, A. A general and mild domino approach to substituted 1-aminoindoles. *Chem. Comm.* **2011**, *47*, 1042–1044. [CrossRef] [PubMed]
258. Prakash, A.; Dibakar, M.; Selvakumar, K.; Ruckmani, K.; Sivakumar, M. Efficient indoles and anilines syntheses employing tert-butyl sulfinamide as ammonia surrogate. *Tetrahedron Lett.* **2011**, *52*, 5625–5628. [CrossRef]
259. Yao, P.-Y.; Zhang, Y.; Hsung, R.P.; Zhao, K. A sequential metal-catalyzed C− N bond formation in the synthesis of 2-amido-indoles. *Org. Lett.* **2008**, *10*, 4275–4278. [CrossRef] [PubMed]