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Exploring the capabilities of 2-alkynyl aryl/benzyl azides: synthesis approaches for indoles, quinolines, and their derivatives *via* transition metal catalysis

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In recent research, quinoline and indole structures have gained recognition for their significant clinical relevance and effectiveness. These compounds are known for their wide-ranging pharmacological effects, which include anticancer, antibacterial, antifungal, antiviral, and anti-inflammatory properties. Researchers have successfully implemented a variety of innovative synthetic strategies, leading to the creation of numerous compounds that display fascinating biological activities in diverse fields. This has sparked growing interest in developing quinoline and indole-based analogues, given their impressive variety of biological effects. Over the past few years, new, efficient, and more accessible synthetic

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techniques—such as green chemistry and microwave-assisted synthesis—have been introduced to produce a diverse array of quinoline and indole structures. This development reflects an expanding area of interest in both academic and industrial settings, making it easier to investigate their biological capabilities. In this review, we examine the intriguing transformations of 2-alkynyl aryl and benzyl azide derivatives into indoles and quinolines, emphasizing the role of metal catalysts such as Au, Cu, Rh, Pd, and Ag, from 2011 to 2024. We showcase the variety of substrates involved, highlight notable advancements in this area of research, and address the limitations faced by chemists. Additionally, we offer insights into the mechanisms driving these important reactions, aiming to enhance understanding and inspire future work in this dynamic field.

1 Introduction

In recent decades, heterocyclic compounds have garnered significant interest for various reasons, with their biological activity and their application as drug molecules being particularly noteworthy. Additionally, these compounds are recognized for their presence in a wide array of functional molecules, natural products, organic materials, and pharmaceuticals.[1–4] Quinolines represent a significant class of nitrogen-containing heterocyclic aromatic compounds. Recently, researchers have increasingly focused on quinolines due to their extensive array of biological activities and their diverse range of applications. Quinoline is predominantly derived from several primary sources, including petroleum, the processing of coal, the preservation of wood, and the extraction of oil from shale. Additionally, derivatives of quinoline are found in various natural products, particularly in alkaloids. This versatile heterocyclic structure is prevalent in numerous areas, including natural products, pharmaceuticals, agrochemicals, functional materials, and as ligands in transition metal catalysts (Fig. 1).[5–7]

Indole is a prevalent heterocyclic structure commonly encountered in nature. It holds an important position in the formulation of a diverse array of dyes, fragrances, pharmaceuticals, and agricultural chemicals (Fig. 2). Consequently, the synthesis of the indole core and its subsequent functionalization represent critical areas of research within heterocyclic chemistry. This topic has garnered the interest of synthetic organic chemists for more than 150 years.[8]

In addition, cross-coupling reactions catalyzed by transition metals that utilize C–H activation present an alternative approach to conventional synthetic methods. Recently, these reactions have gained significant importance for the formation of C–C and C–N bonds.[5–18]

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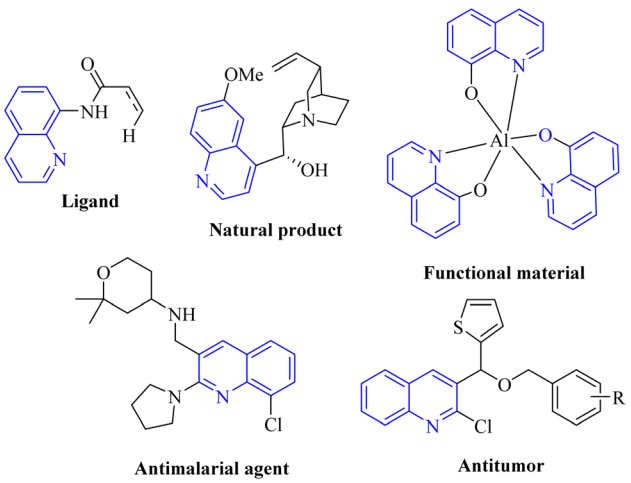


Fig. 1 Compounds that exemplify the quinoline framework demonstrate various properties.

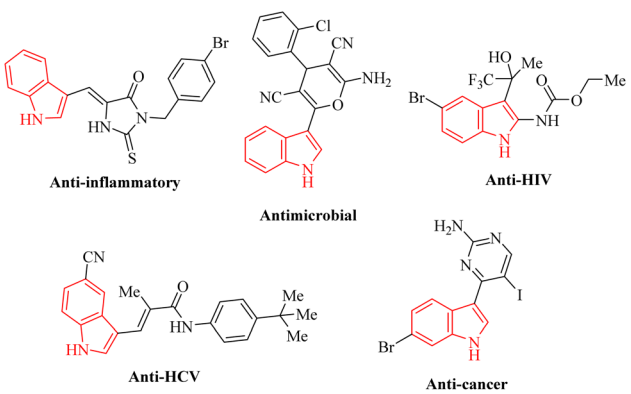


Fig. 2 Compounds that illustrate the indole structure exhibit a diverse range of properties.

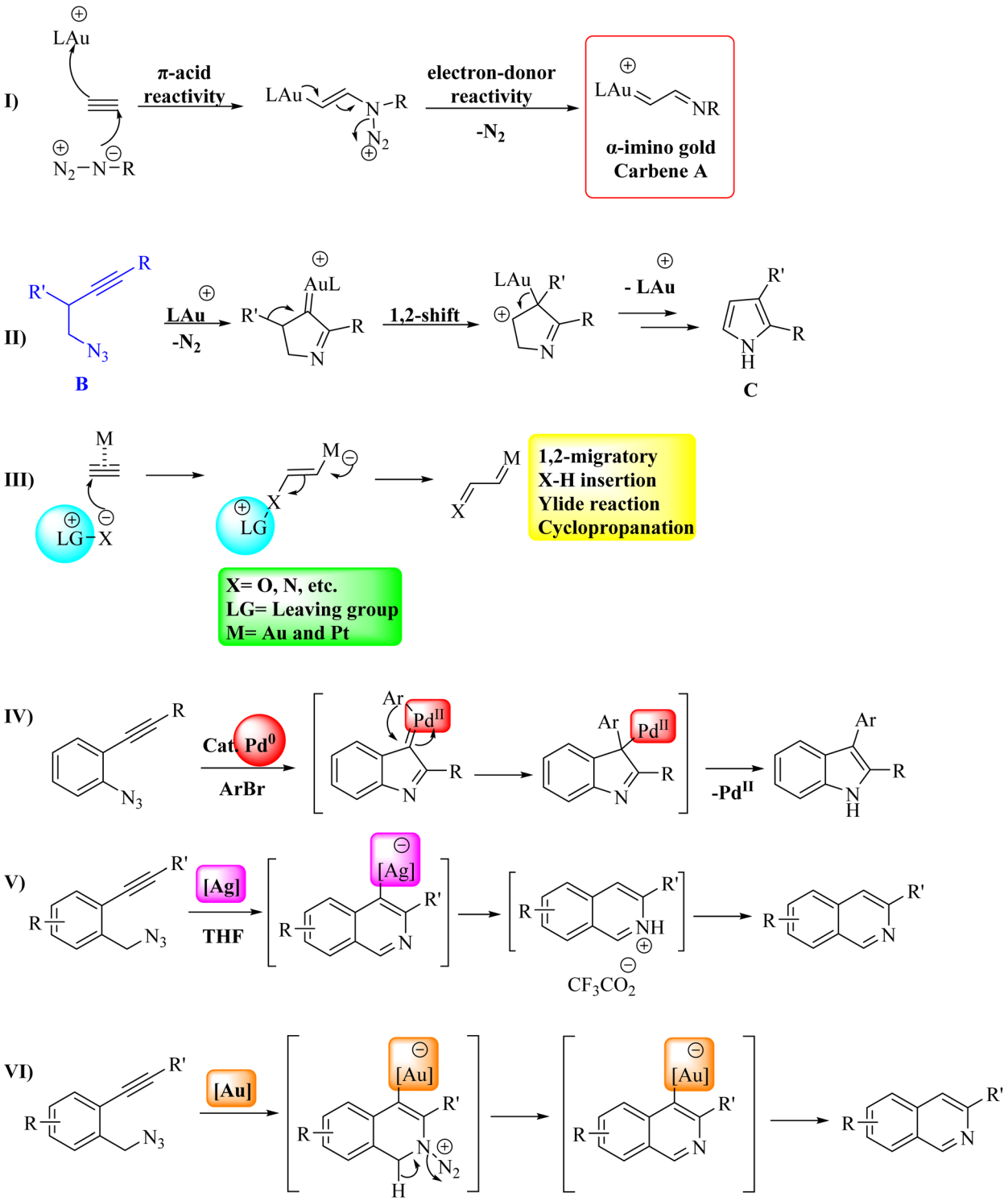
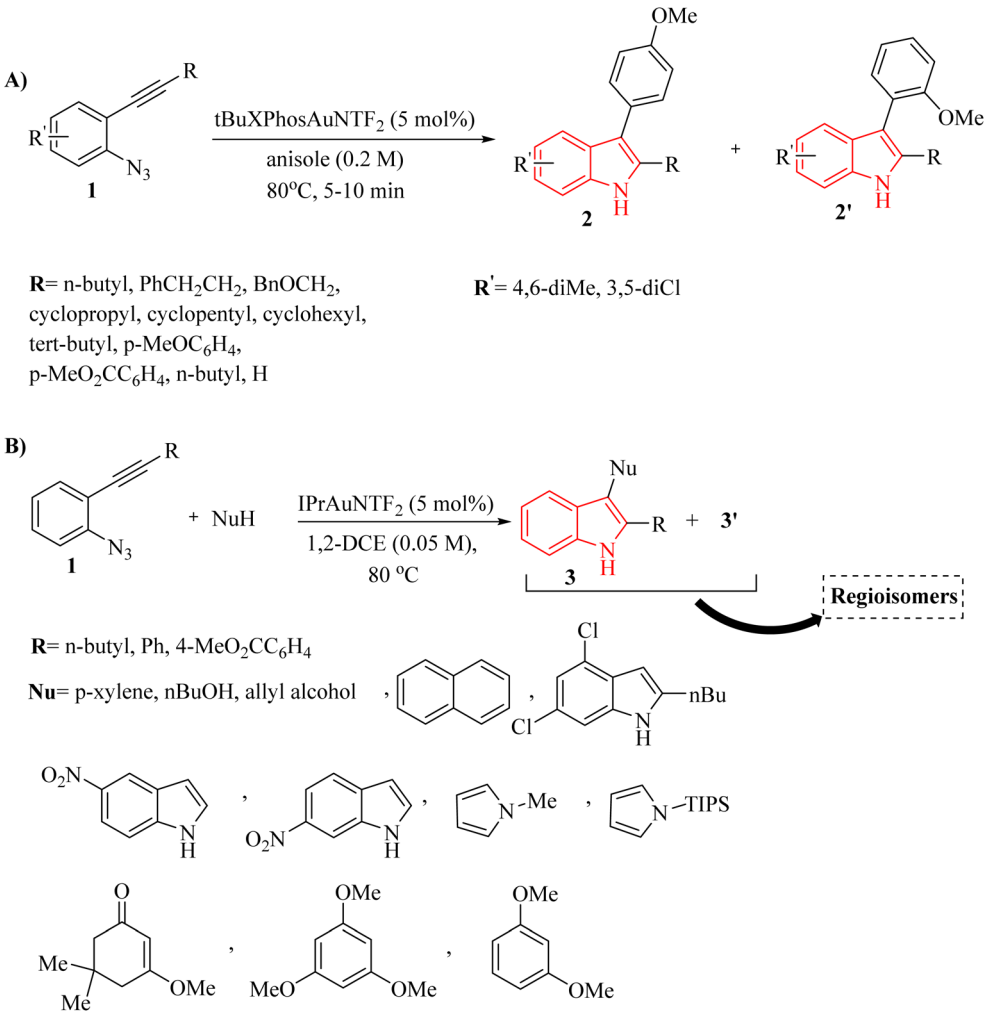


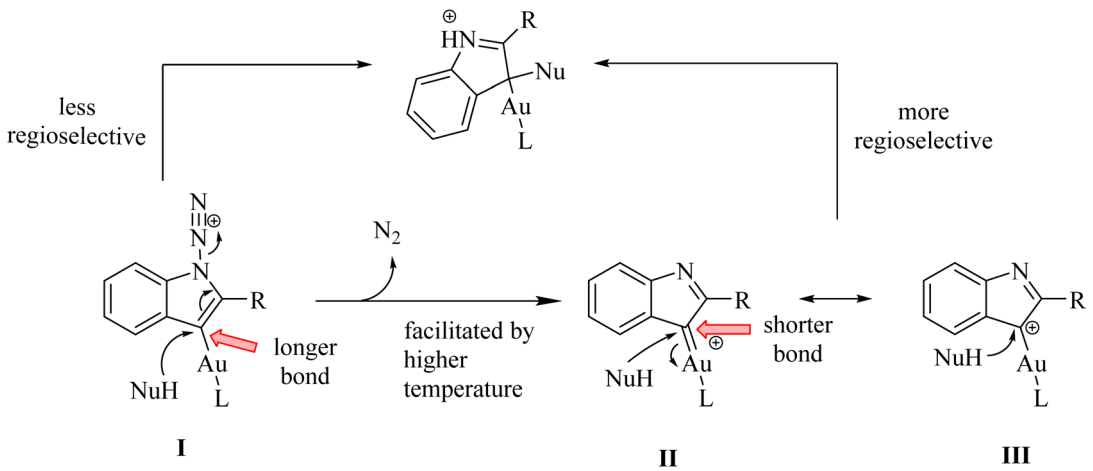
Fig. 3 (I) The design of synthetic methods to capture α-imino gold carbene intermediates, (II) Au(I)-catalyzed intramolecular acetylenic Schmidt reaction, (III) alkynes as sources for metal carbene formation, (IV) the suggested method for synthesizing indole catalyzed by Pd, (V) cyclization of 2-alkynylbenzyl azide by Ag catalyst. (VI) Cyclization of 2-alkynylbenzyl azide by Au catalyst.

Au catalysis has become a convenient method for creating diverse and complex molecules.[19,20] These catalysts have demonstrated significant utility in activating π systems, including alkynes and allene derivatives, for nucleophile addition.[21] Much of the synthetic chemistry in this field is closely associated with the Lewis acidic behavior of electrophilic Au species.[22–26] Apart from its acidic properties, Au can act as an electron donor, which helps stabilize intermediate cationic species and enhances reaction pathways that cannot be promoted by other Lewis acids.[27] In the Au(I)-catalyzed reaction



Scheme 1 (A) The range of *o*-azidoarylalkyne substrates **1**, (B) the range of various nucleophiles.

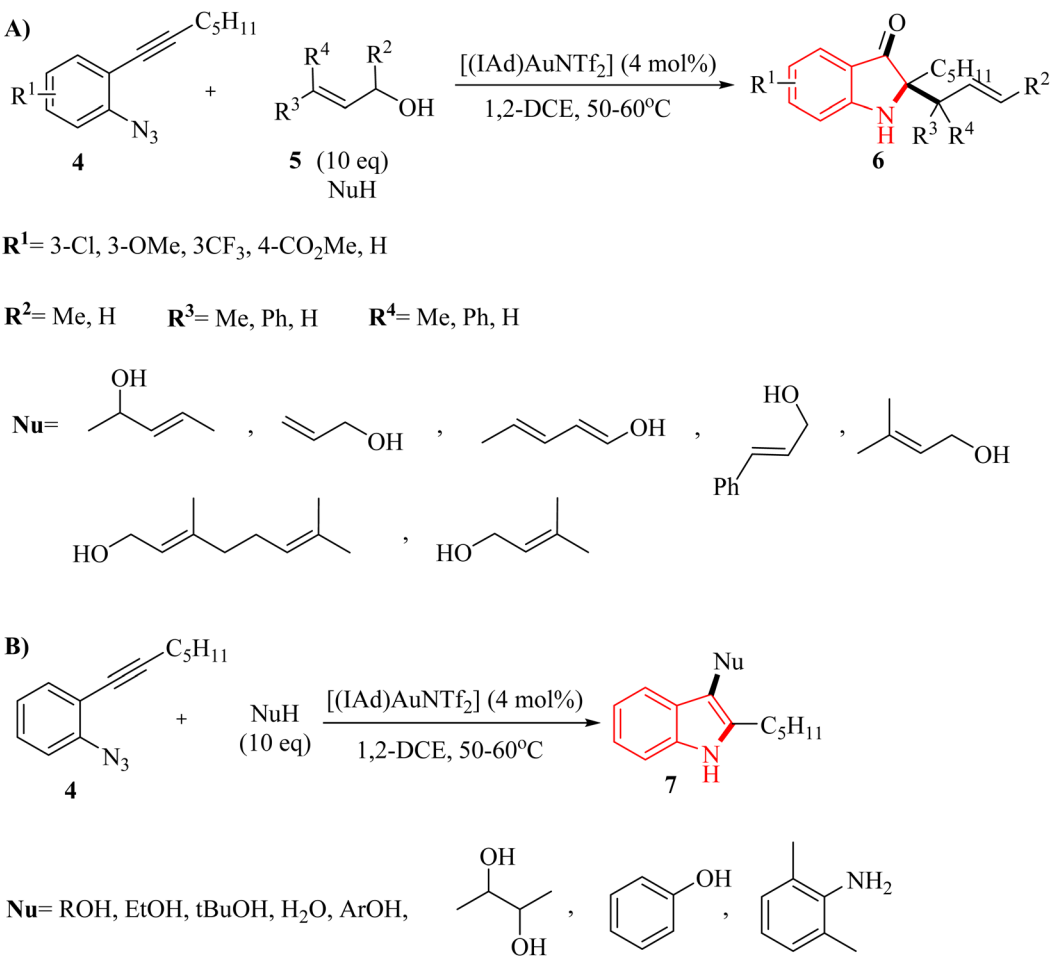
between an alkyne and an azide, the dual reactivity of the pi acid/electron donor is emphasized. This process involves nucleophilic azide addition, leading to the generation of an alpha-imino Au carbene **A**, followed by the Au-assisted expulsion of N_2 (Fig. 3I).[21] Toste and colleagues harnessed this reactivity pattern to create an Au(I)-catalyzed intramolecular



Scheme 2 The inverse correlation between regioselectivities and reaction temperatures.

acetylenic Schmidt reaction. In this process, a homopropargylazide **B** is transformed into a pyrrole **C** (Fig. 3II).[28] Recent studies have extensively examined Au-catalyzed tandem reactions, where Au-carbenoid species[29–35] act as key intermediates in reactions involving diyne derivatives,[36–39] enyne derivatives,[40–42] and alkyne derivatives with *N*-oxides,[43–48] as well as in the rearrangement of 1,2-propargylic ester derivatives.[49,50] However, the *in situ* generation of α-imino Au carbenoids from azide derivatives and alkyne derivatives remains largely unexplored.[51–65] Specifically, alkyne derivatives can act as sources of carbenes when they react with nucleophiles that have a leaving group, under the catalysis of Au or Pt (Fig. 3III).[43,51] Alkyne derivatives have various applications in the transformation of organic compounds[2] and can also act as starting materials for producing alpha-oxo and alpha-imino Au carbenes, which participate in common carbene reactions like 1,2-migration, X–H bond insertion, ylide formation, cyclopropanation, and more.[66] When using 2-alkynyl arylazide derivatives as substrates, the resulting Pd carbene can participate in cross-coupling reactions to synthesize polysubstituted indoles,[67–72] as illustrated in Fig. 3IV. While the formation of Pd carbene from alkynes is documented.[73–75] Complexes of Ag(I) are commonly employed as stoichiometric oxidants for oxidizing a range of organic and inorganic substrates. Numerous studies have utilized the complexes of Ag(I) as catalysts in oxidation and group-transfer reactions.[76–82] Recent research has demonstrated that Ag species display notable catalytic activities, acting as a transition metal catalyst.[76,83–96] Ag catalysts, when viewed as transition metals, are generally seen as less efficient and not as effective as other late transition metals.[97] Cyclization of 2-alkynylbenzyl azide catalyzed by Ag and Au have been shown in Fig. 3V and VI. Using Cu catalysts is significantly more attractive for forming Cu carbene intermediates or activating alkyne species due to their lower cost, reduced toxicity, and greater availability.[98] Common transformations in this field encompass alkynylation,[99–103] cycloaddition,[104–108] allene formation,[109–113] among various others.[114–118]

Given the widespread use of 2-alkynyl aryl/benzyl azide derivatives in organic transformations, we explore the fascinating conversions of 2-alkynyl aryl and benzyl azide derivatives into indole derivatives and quinoline derivatives, focusing on the use of metal catalysts like Au, Cu, Rh, Pd, and Ag. Also, we highlight the diverse range of substrates used, significant breakthroughs in the field, and the challenges faced by chemists. Furthermore, we delve into the mechanisms behind these



Scheme 3 (A) Range of substrates of 2-alkynyl arylazide derivatives **4** and **5**, (B) generation of 3-substituted indole derivatives **7**.

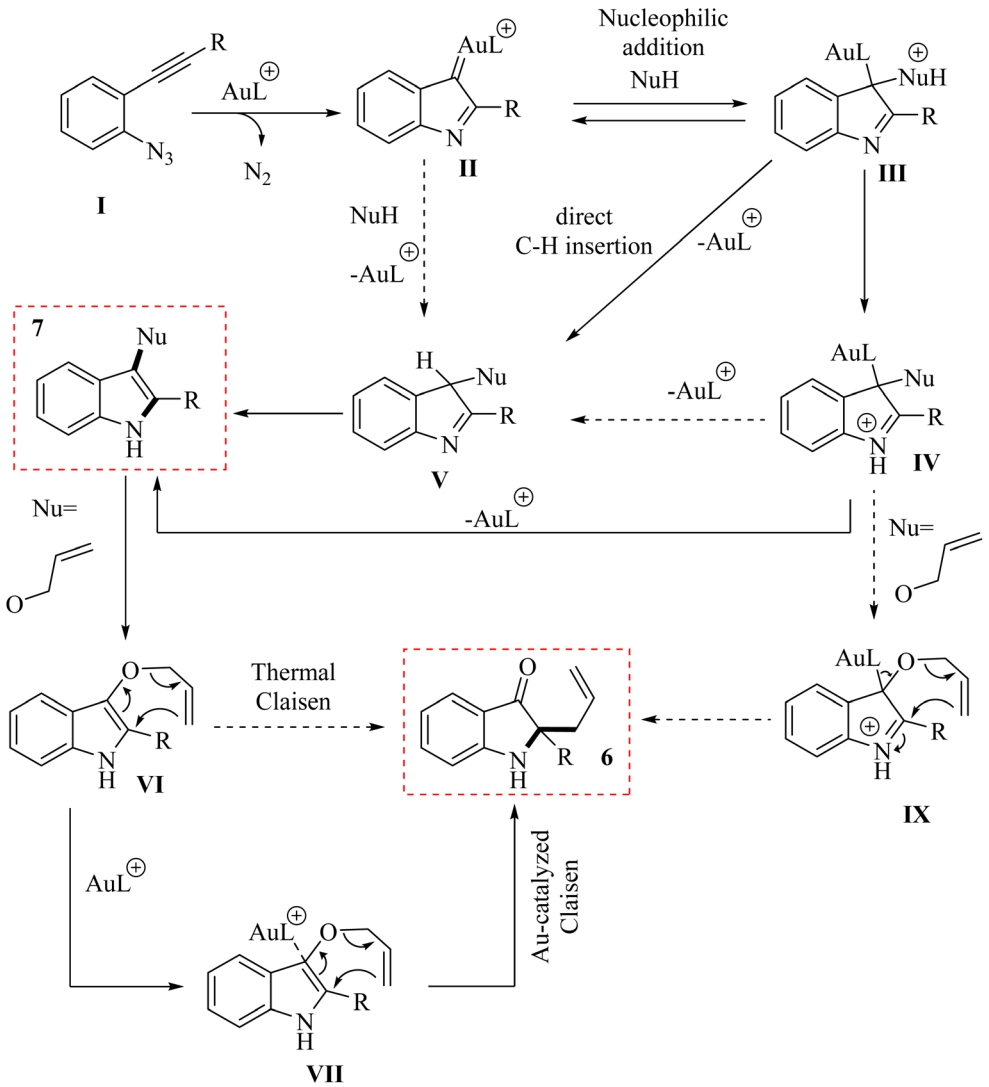
important reactions to improve understanding and inspire future exploration in this vibrant area of research.

2 2-Alkynylaryl azides

2.1 Synthesis of indoles

2.1.1 Au-catalyzed transformation. In 2011, Lu *et al.*[119] introduced a novel method for achieving umpolung reactivity of indole at the 3-position (**2**, **2′** and **3**, **3′**) through the use of tBuXPhosAuNTf$_2$ catalysis. Their approach involved the utilization of an *ortho*-azido group **1** to facilitate the delivery of a nitrene intramolecularly, thereby leading to the formation of a highly electrophilic indole skeleton at the 3-position. This electrophilic intermediate subsequently underwent a reaction with various nucleophiles in 1,2-dichloroethane or anisole at 80 °C, resulting in the efficient synthesis of a diverse array of functional indole derivatives. The desired products were obtained with yields of up to 95%. In the case of the azidophenylalkyne derivatives **1** were reacted with corresponding catalyst, in all instances, the regioselectivities showed a strong correlation with the substituent's bulkiness, and the optimal **2**/**2′** ratio was achieved using *tert*-butyl alkyne (Scheme 1A). To naphthalene which tested as a nucleophile, the alpha-position was favoured due to its higher nucleophilicity (Scheme 1B). In the case of *N*-methylpyrrole, it appeared that electronic and steric factors were in conflict, resulting in the absence of regioselectivity. It should be noted that competing reactions with electrophilic intermediates were required excess nucleophiles and regioselectivity issues arise with varying reaction temperatures. Also, solvent participation was interfered with desired reactions. Some important gaps regarding the research should be considering such as (1) need for broader application of Au-catalyzed nitrene transfer, (2) there is insufficient understanding of regioselectivity at varying temperatures, and (3) exploration of alternative nucleophiles and their efficiencies is required.

A mechanism underlying this transformation is depicted in Scheme 2. The formation of **II**/**III** at a higher temperature (*e.g.*,



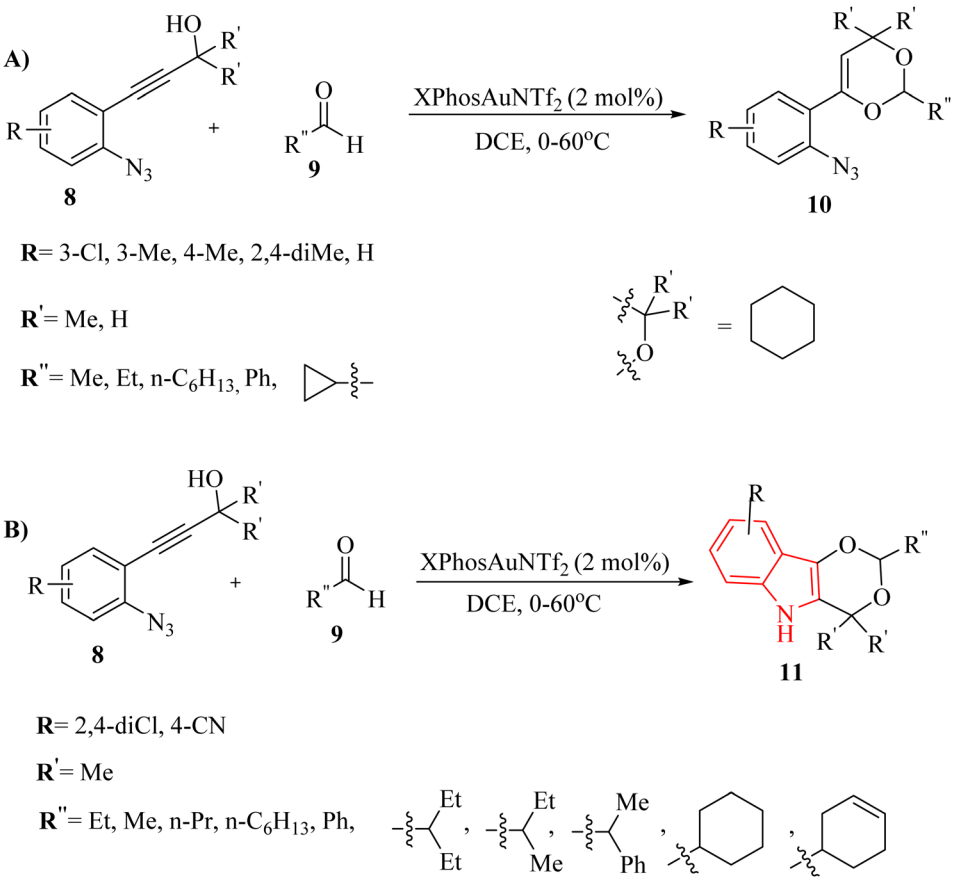
Scheme 4 A mechanism for the Au-catalyzed **4** into indole derivatives (**7** and **6**).

80 °C) is facilitated while its precursor (**I**) at a lower temperature (*e.g.*, −20 °C) may persist. Then, it plays a role by reacting with nucleophile derivatives. This reaction is carried out *via* an SN2′ process. When the reaction is proceeded *via* **II**/**III**, it showed greater regioselectivity due to the short bond of Au–C length. It should be noted that Au–C bond length in I longer than the bond of Au–C in **II**/**III**.[119]

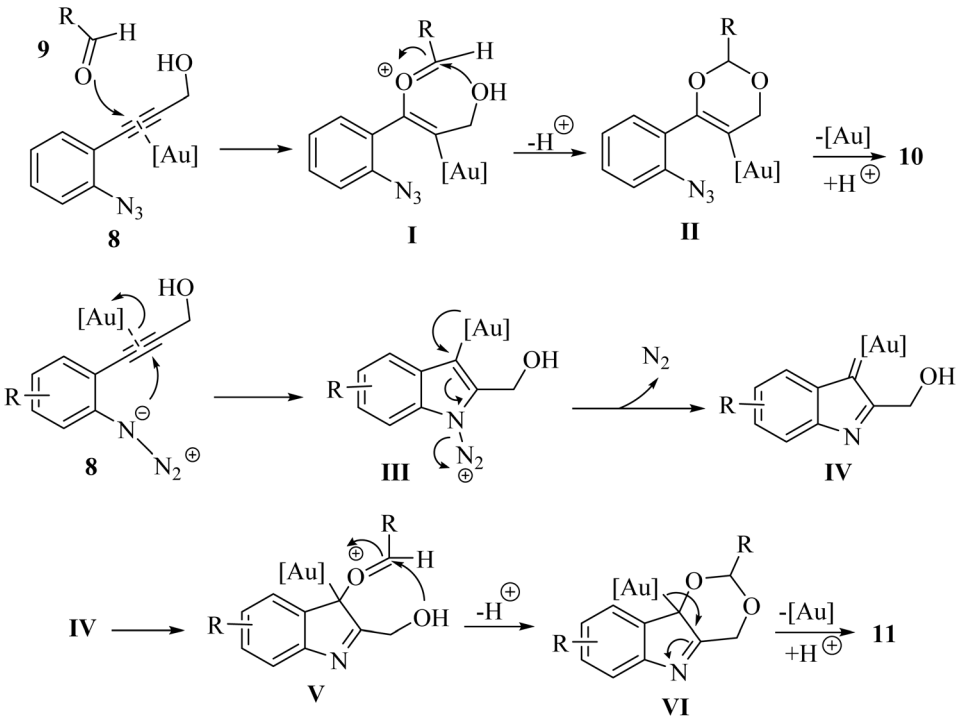
In 2011, Wetzel and Gagosz[120] reported a novel Au(I)-catalyzed reaction for the conversion of 2-alkynyl arylazide derivatives **4** into indolin-3-one derivatives **6** (Scheme 3A) and 3-substituted indole derivatives **7** (Scheme 3B). This reaction, conducted in 1,2-DCE at 50–60 °C, was demonstrated rapid and efficient performance, while also exhibiting tolerance towards various functional groups. Notably, the potential to generate indolin-3-one derivatives containing two vicinal asymmetric quaternary carbon canters is of particular interest due to its prospective utility in the synthesis of pseudoindoxyl alkaloid derivatives. The desired products gave with impressive yields of up to 99%. When allylic alcohol derivatives with substitutions at the C3-position were employed, an extra asymmetric canter was formed. When phenol was tested, it did not lead to the formation of the desired product. In an unexpected result, even the poorly nucleophilic *tert*-butanol formed the corresponding product. The desired reaction had some challenges such as (1) difficulty in isolating expected products during reactions, (2) because of steric effects there was moderate selectivity in Claisen products, and (3) inability to observe intermediates *via* the reaction monitoring. There were inadequate studies on reaction mechanisms for type of nucleophiles as well as a limited understanding of selectivity in Claisen rearrangements.

A mechanism underlying this transformation is depicted in Scheme 4. The Au(I) complex can activate the alkyne moiety in compound **I**. After the extrusion of N2, this activation may result in the formation of an intermediate alpha-imino Au carbene, denoted as compound **II**. The species undergoes a nucleophilic addition, resulting in the formation of a product labelled as **III**. Indole **7** could be generated from compound **V** through two distinct pathways. First, it can form *via* iminium intermediate **IV** using a prototropy/demetalation sequence. Alternatively, it can also be produced directly from compound **V** through a protodemetalation/tautomerization sequence. Through a direct insertion of **II** into the Nu–H bond, the intermediate **V** is generated. In the following, when an allylic alcohol is acted as the nucleophile, compound **6** is formed, which could be explained by a Claisen rearrangement of compound **VI**. Compound **6** could also be generated through an alternative pathway, starting from **IV** and proceeding *via* intermediate **IX**.[120]

Zhang *et al.*[121] introduced a study detailing an effective Au-catalyzed ($XPhosAuNTf_2$) chemoselective synthetic pathway to



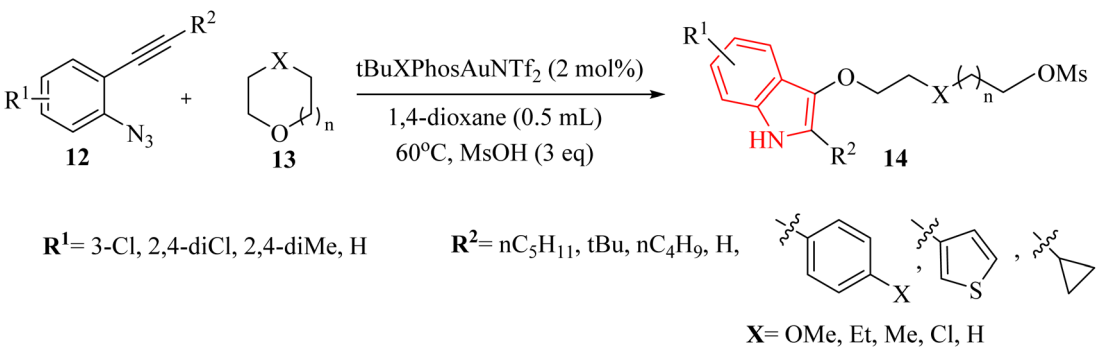
Scheme 5 (A) Generation of dioxine derivatives **10**, (B) generation of dioxino-indole derivatives **11**.



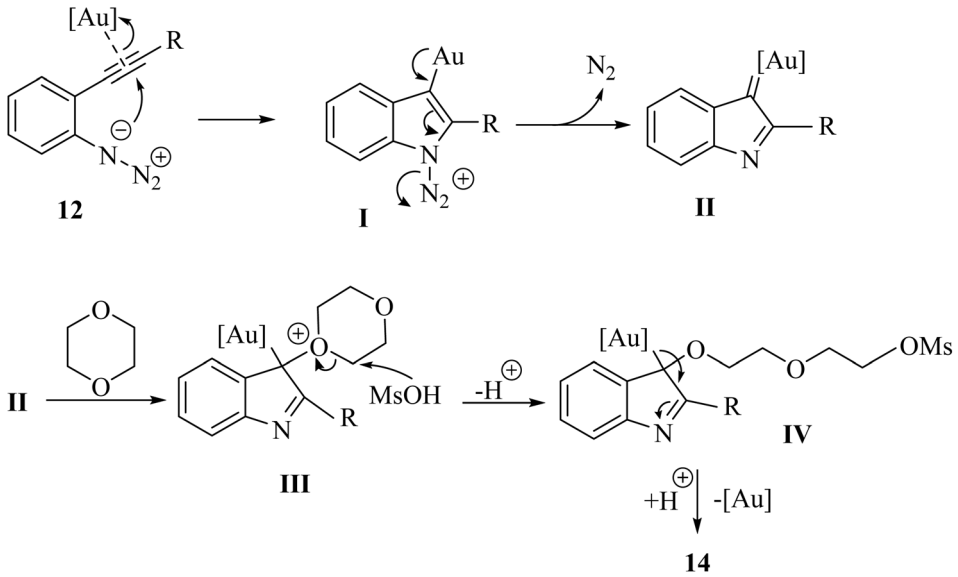
Scheme 6 A proposed mechanism for the reaction catalyzed by Au between compounds **8** and **9**.

produce 4*H*-1,3-dioxine derivatives **10** (Scheme 5A) and indole derivatives **11** (Scheme 5B). This process involved the tandem annulation of **8** with aldehyde derivatives **9**. Notably, the reactions exhibited high efficiency and precise control over product chemoselectivity when various **8** were used in conjunction with desired Au catalyst in DCE at 0–60 °C. In the case of **8**, the desired products generated in 34–75% yields. Nevertheless, when cyclopropanecarbaldehyde, 4-(2-azidophenyl)but-3-yn-1-ol, and benzaldehyde were employed as substrates, they generated a blend of decomposition products that remained unidentified, even after analyzing the crude mixture with ^{1}H NMR. Authors observed that the **10** was not produced when starting material (ArN_3), which contained 3,5-dichloro-substituted groups on the aryl ring, underwent the standard reaction conditions. In the case of **11**, the desired products gave in 54–94% yields. Benzaldehyde was also investigated; however, it yielded a blend of decomposition products that remained unidentified. There were some gaps regarding the reaction, such as (1) inadequate understanding of product chemoselectivity based on substituent groups, (2) limited investigation of alpha-imino Au carbenoids from azide derivatives and alkyne derivatives. It should be noted that decomposition products were observed with certain substrates and conditions.

A proposed mechanism underlying this transformation is depicted in Scheme 6. This process may entail the activation of compound **8** by coordinating with an Au catalyst through its alkyne moiety. Subsequently, compound **9** attacks to form complex **I**, which then undergoes intramolecular alkoxylation to yield **II**. Finally, a protodemetalation step leads to the formation compound **10**. When **8** is used as the substrate the intermediate **IV** is produced *in situ*. This intermediate is subsequently trapped by **9**, resulting in the formation of **V**. Following



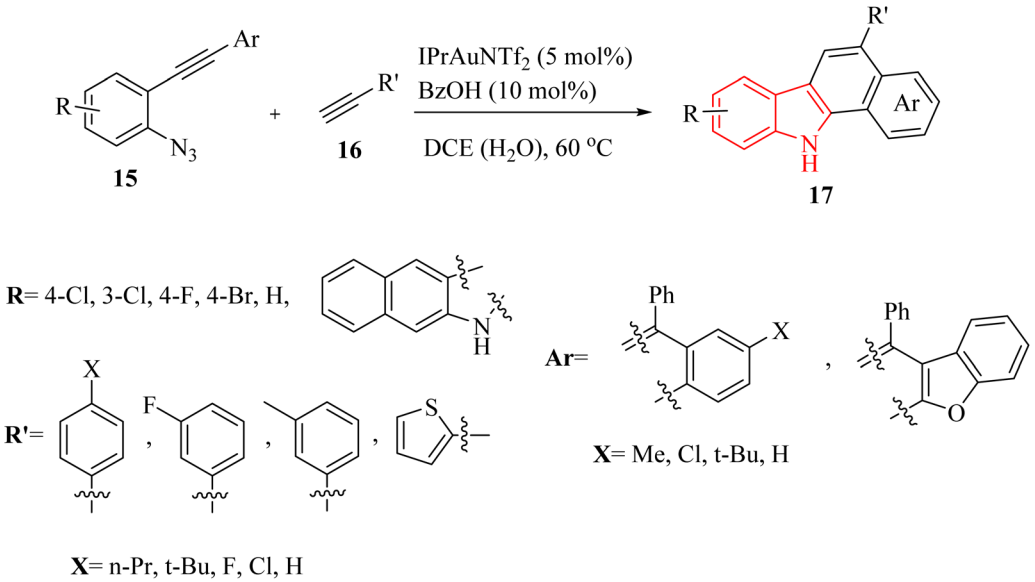
Scheme 7 Scope of 2-alkynyl arylazide derivatives **12** and oxygen-containing heterocycles **13**.



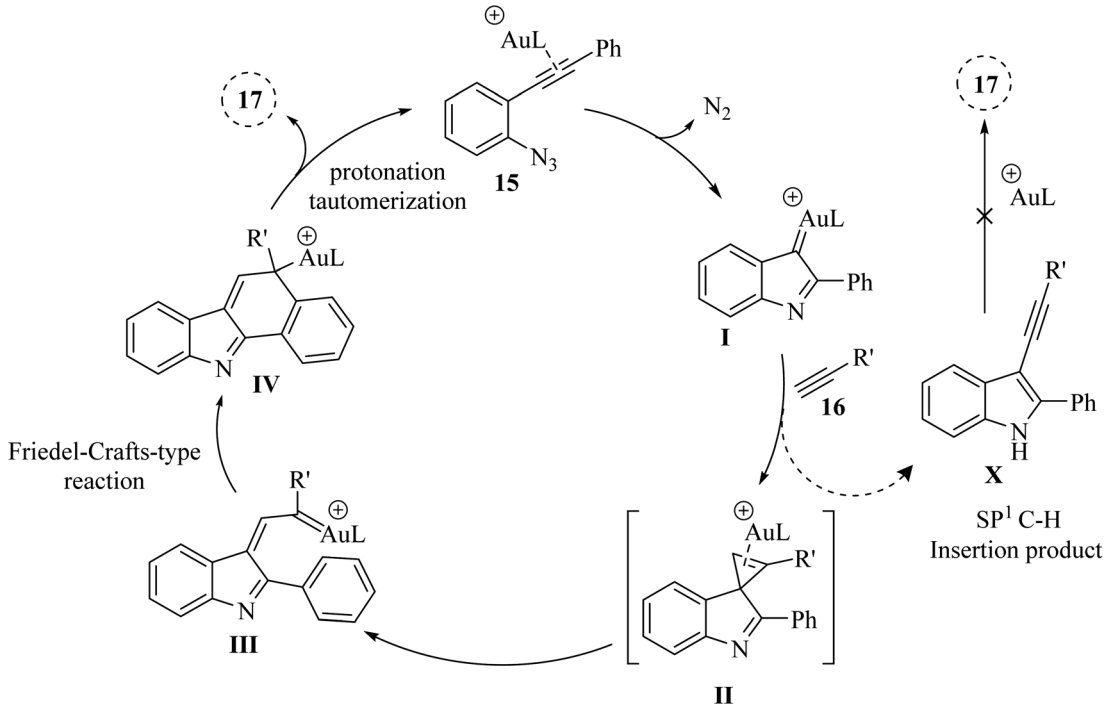
Scheme 8 A mechanism for the Au-catalyzed ring-opening reactions of **12** with **13**.

intramolecular alkoxylation of **V**, the tricyclic ring–Au complex **VI** is emerged. Finally, a subsequent protodemetalation step leads to the production of compound **11**.[121]

Zhang *et al.*[122] introduced a notable discovery in the field of organic synthesis. Authors illustrated an unforeseen Au-catalyzed (tBuXPhosAuNTf$_2$) method for producing indole derivatives through the ring-opening reaction of 2-alkynyl arylazide derivatives **12** with oxygen-containing heterocycles **13**, in the presence of methanesulfonic acid in 1,4-dioxane at 60 °C (Scheme 7). This innovative approach exhibited a remarkable tolerance for a diverse range of substrates of **12**, which can be conveniently prepared in just two steps from readily available materials. Furthermore, the Au-catalysed tandem reactions proved to be practical, as they did not necessitate inert or moisture-free conditions. The corresponding products generated in 28–95% yields. However, when using substrates containing a cyclopropyl group or a terminal alkyne moiety, and reacting compound **12** with oxetane, tetrahydrofuran, or 2-phenyloxirane, only a mixture of unknown side products was obtained. These products could not be identified. There were some challenges regarding the reaction, such as (1) some substrates were yielded unknown side products, (2) inert and moisture-free conditions were not always practical, and (3) the reaction was required specific conditions for optimal yields. It should be noted that the mechanism of Au-catalyzed reactions remains speculative.



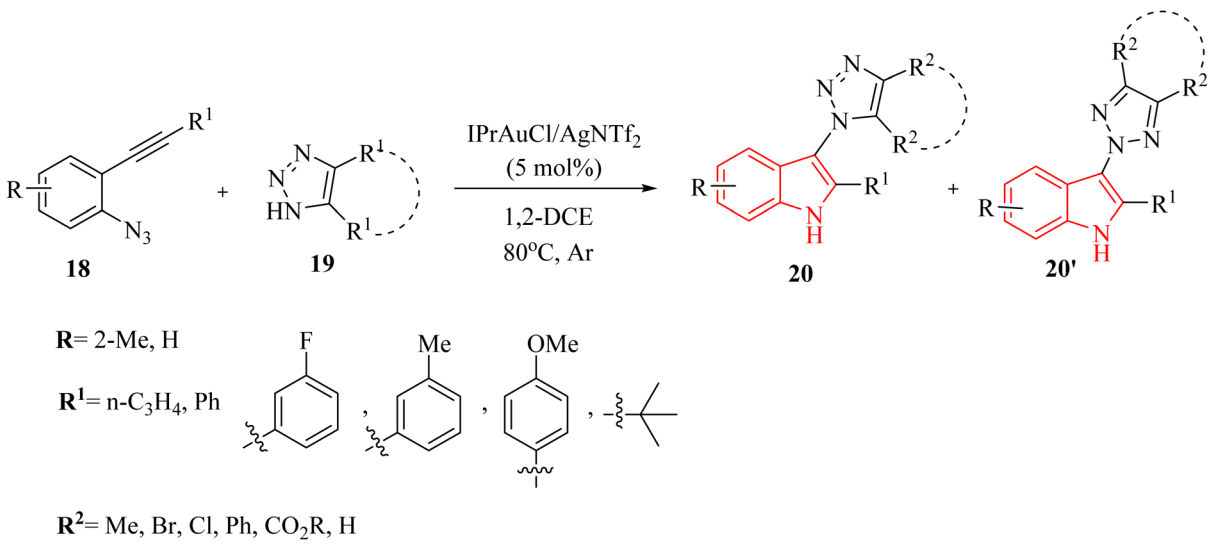
Scheme 9 Scope of azido alkyne derivatives **15** and alkyne derivatives **16**.



Scheme 10 A mechanism for the cyclization reactions of **15** with **16** catalyzed by Au.

A mechanism underlying this transformation is depicted in Scheme 8. In this process, **12** is activated by coordinating it with an Au catalyst. The azide attacks the alkyne, forming intermediate **I**. Subsequently, alpha-imino Au carbene **II** is generated after N_2 expulsion, facilitates by the Au catalyst. This intermediate is further attacked by 1,4-dioxane, resulting in the release of intermediate **III**. Finally, ring opening of **III** using MsOH is produced complex **IV**, which undergoes a protodemetalation step to yield **14**.[122]

Li *et al.*[123] introduced a novel synthetic approach, catalysed by Au, for the efficient formation of aryl-fused carbazole derivatives **20**. This method starts with 2-alkynyl arylazide derivatives **15** and alkyne derivatives **16** and progresses through a series of reactions (Scheme 9). The process includes cyclopropenation followed by an intramolecular reaction similar to the Friedel–Crafts reaction involving metal carbene and arene. This sequence was facilitated by two distinct Au carbene intermediates and occurred in a DCE/H_2O mixture at a temperature of 60 °C. The results illustrated that this reaction can accommodate diverse azido alkyne derivatives (up to 85% yield) and alkyne derivatives (up to 70% yield). The tolerance of the Br group, which was typically incompatible with Pd-catalysed

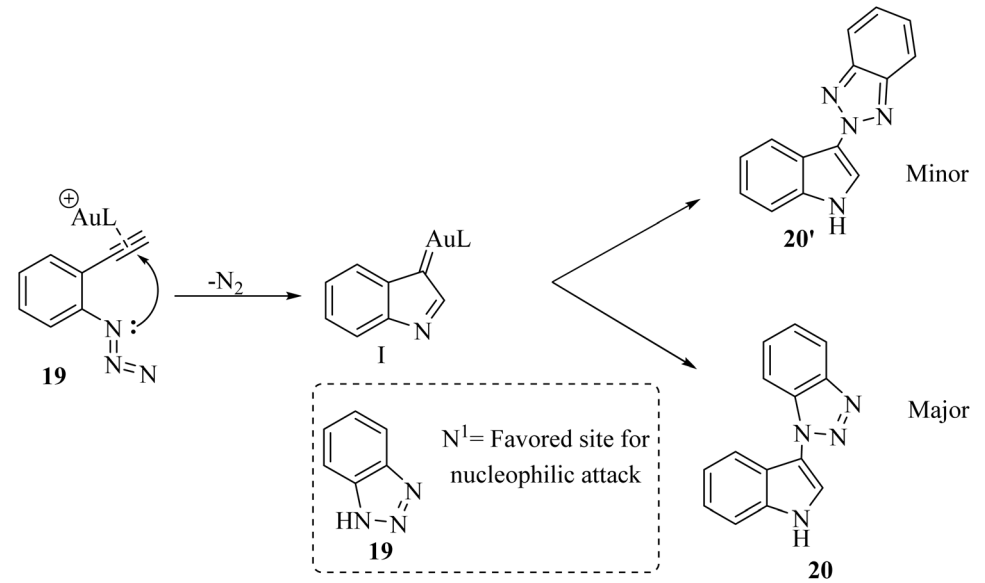


Scheme 11 Scope of 2-alkynyl arylazide derivatives **18** and benzotriazole derivatives **19**.

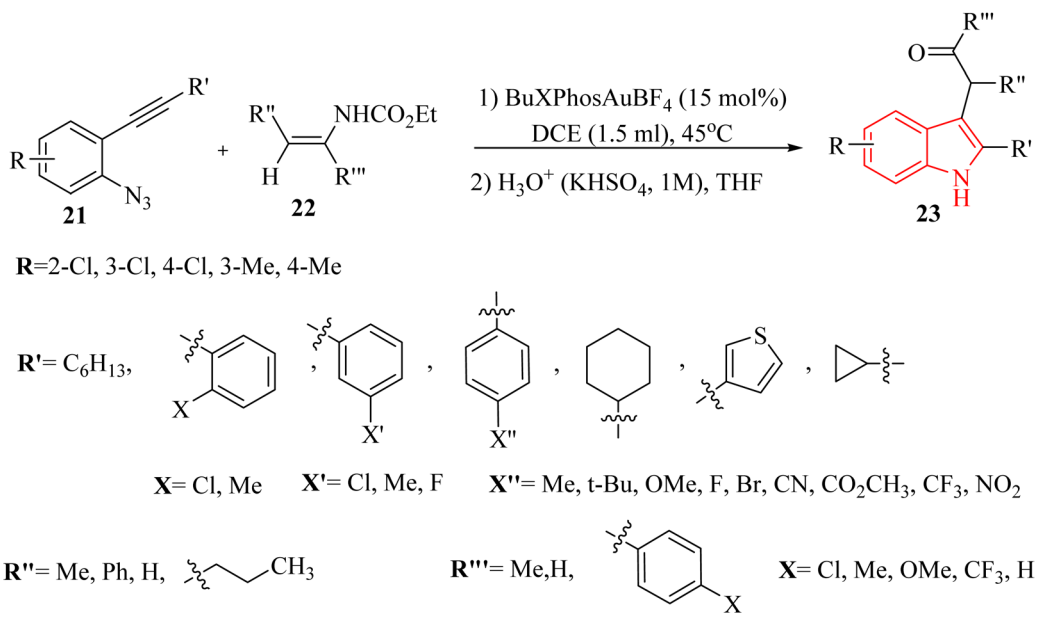
methodologies for carbazole synthesis, provided an opportunity to modulate the structure of related products through cross-coupling reactions, thereby enhancing their structural complexity. In the mentioned reaction aliphatic alkyne derivatives could not undergo the reaction. There were some challenges in the mentioned reaction, such as (1) the role of H_2O in reactions was not fully understood, (2) inadequate investigation of aliphatic alkyne derivatives in reactions.

A mechanism underlying this transformation is depicted in Scheme 10. Initially, **15** is generated the alpha-imino Au carbene **I**, which could undergo cyclopropenation with an acetylene to yield **II**. Compound **II** in the presence of the desired catalyst is transformed into intermediate **III** (Au carbene). Subsequent **IV** is generated after an intramolecular metal carbene/arene Friedel–Crafts-type reactions, which after protonation and tautomerization then is converted to compound **17**. In addition to the main reaction, a potential side reaction might be occurring, leading to the formation of compound **X** through the alkynyl C–H insertion of **I**. However, a control experiment revealed that pre-synthesized compound **X** did not convert into **17** under the given reaction conditions.[123]

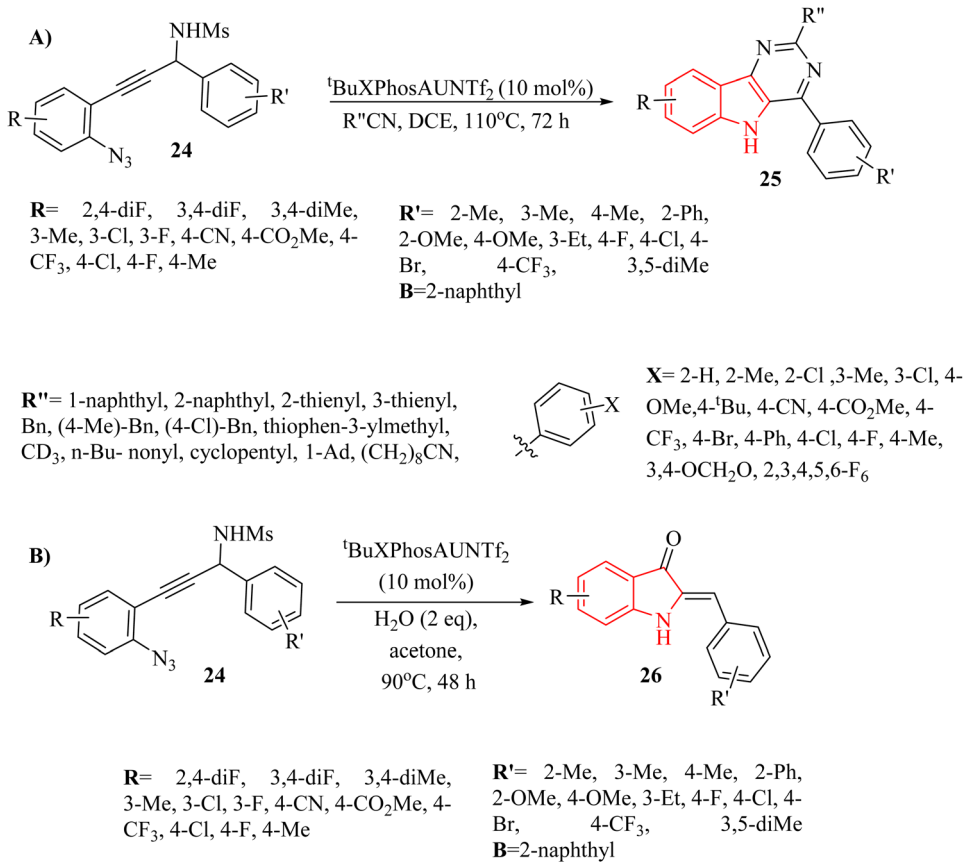
In 2020, Li *et al.*[124] developed a groundbreaking technique for synthesizing N_1 and N_2-indol-3-yl 1,2,3-triazole compounds (**20** and **20′**, respectively). This was achieved using an Au-



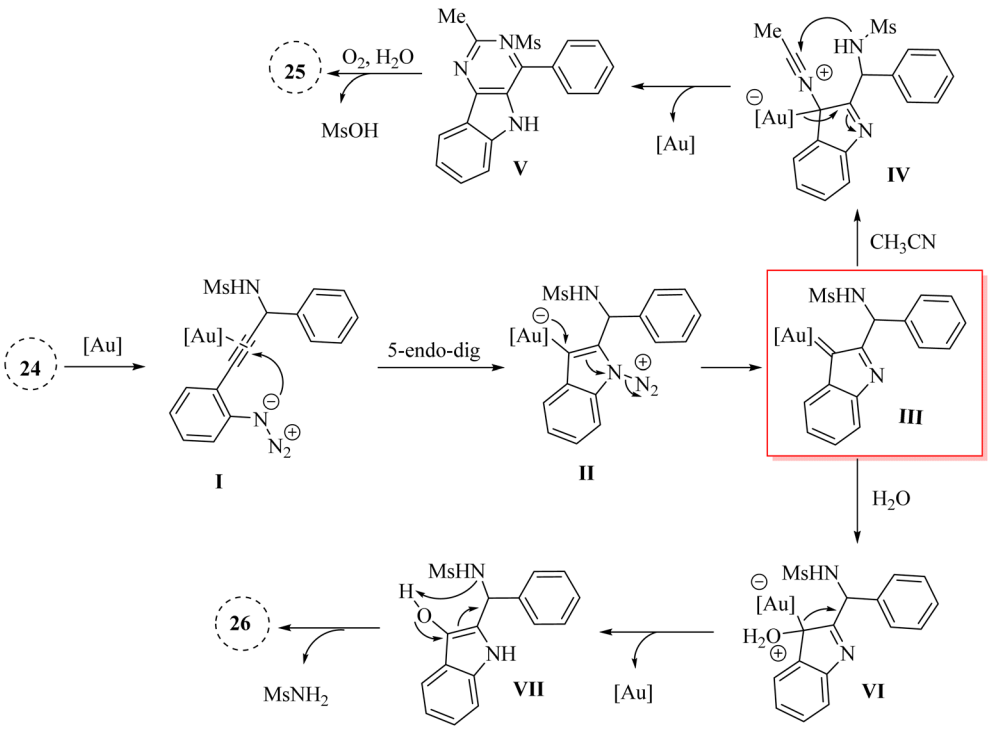
Scheme 12 A proposed mechanism for the reaction of **18** with **19** catalyzed by Au.



Scheme 13 Scope of 2-(alkynyl)phenyl azide derivatives **21** and enecarbamate derivatives **22**.



Scheme 14 (A) Generation of indoles **25** and (B) 2-benzylideneindolin-3-one derivatives **26**.

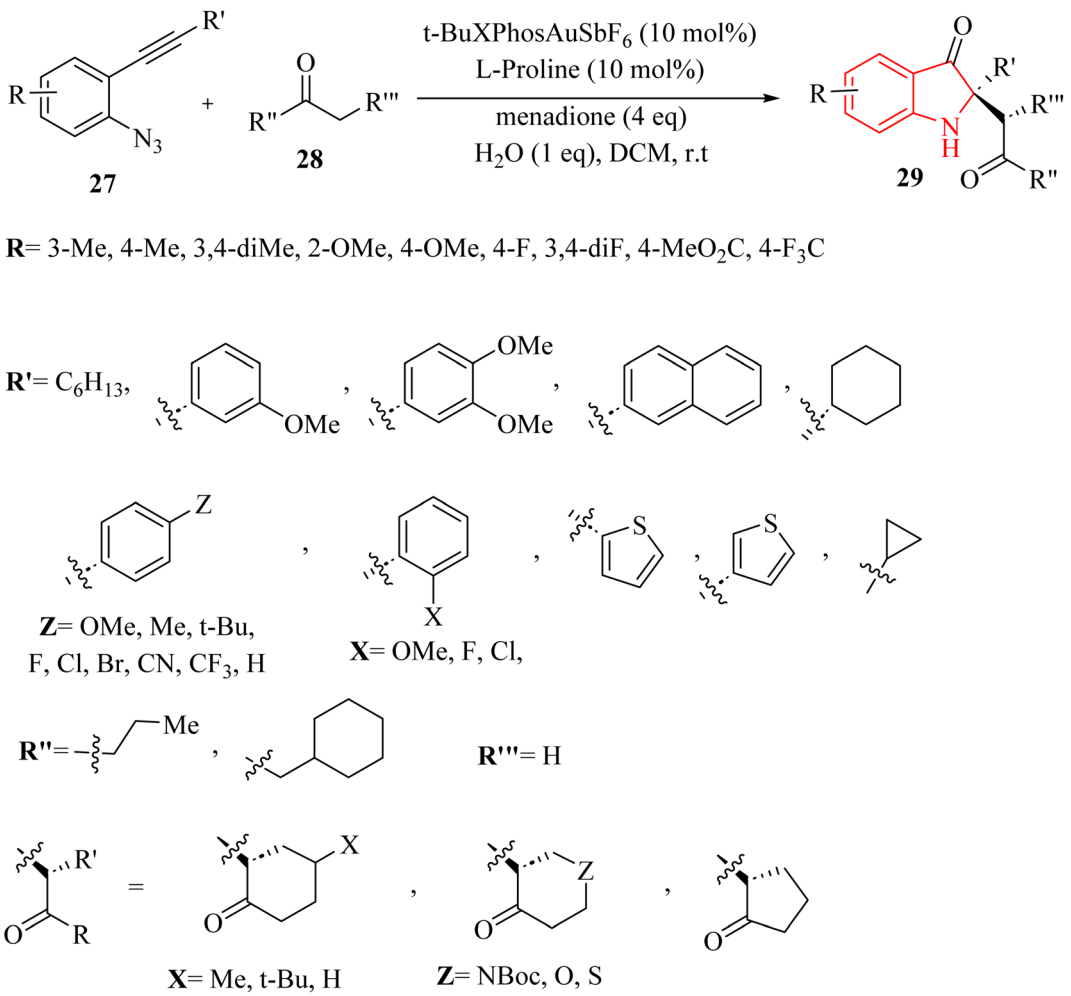


Scheme 15 A mechanism for the reaction of 2-alkynyl arylazide derivatives **24** into indole derivatives **25** and indolinone derivatives **26** catalyzed by Au.

catalyzed (IPrAuCl/$AgNTf_2$) cascade reaction that combines *ortho*-alkynyl arylazide derivatives **18** with 1,2,3-triazole derivatives **19** (Scheme 11). The process took place in 1,2-DCE at 80 °C under Ar. During this reaction, an amino Au carbene intermediate was formed *in situ* and then captured by different triazole molecules. The reaction tends to preferentially undergo N_1-selective nucleophilic attack, resulting in moderate to high selectivity between N_1 and N_2 products. There were some challenges regarding the reaction, such as (1) ineffective performance of type of Ag salts with respect to $AgNTf_2$, and (2) temperature and solvent adjustments did not improve reaction yields.

A mechanism underlying this transformation is depicted in Scheme 12. Initially, **18** is generated the alpha-imino Au carbene **I** which could be intercepted by azole nucleophile derivatives. N_1-selective nucleophilic attack is favored when compound **19** is used due to the relatively higher electron density at the N1 nitrogen with respect to the internal N_2 nitrogen.[124]

In 2023, Xie *et al.*[125] devised an innovative method for directly creating alpha-(3-indolyl) ketone derivatives **23** (Scheme 13). This method involved an Au-catalyzed (*t*BuXPhosAuBF$_4$) cascade reaction that combines 2-alkynyl aryl azide derivatives **21** with enecarbamate derivatives **22**, which allowed for the umpolung (reversal of polarity) of the indole's 3-position. The process was highly efficient, utilizing a catalyst in DCE at 45 °C under a N_2 atmosphere. This technique offered a straightforward and alternative pathway for the direct production of alpha-(3-indolyl) ketone derivatives. In the case of **21** derivatives, the desired products generated in 21–85% yields, as well as derivatives of **22** produced the desired products in 10–61% yields. In this study, various terminal alkynyl derivatives were evaluated. Interestingly, the transformation was compatible with both electron-donating and -withdrawing groups on the phenyl group, resulting in the corresponding products. In the case of the derivatives of **22**, the experimental findings illustrated that the electronic characteristics of the substituents had a significant effect on the product yields. Notably, the presence of a potent electron-donating substituent (such as the methoxy group) markedly enhanced the reaction. In the case of the reaction limitations, there was inadequate evaluation of reaction scalability beyond 1.0 mmol scale as well as required to comparative studies with other catalytic systems. It should be noted that steric bulkiness affected reaction outcomes with certain substituents.

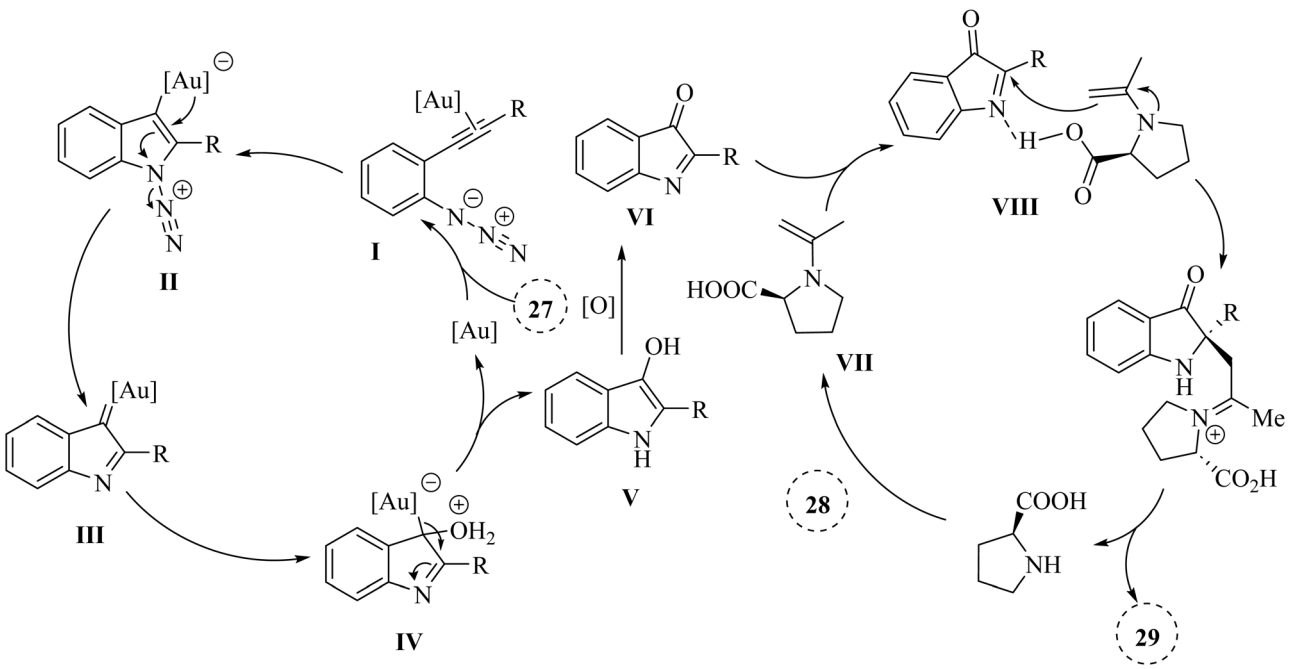


Scheme 16 Synthesis of 3-carbonyl indole derivatives **29**.

In 2024, Zhu *et al.*[126] reported innovative an Au-catalyzed method to synthesize indole derivatives **25** and indolinone derivatives **26** (Scheme 14). This was achieved by trapping Au carbene intermediates with nitriles and water in DCE at 110 °C. The critical intermediate, bata-sulfonamido-alpha-imino Au carbene, was produced *via* Au-catalyzed cyclization of *N*-(2-azidophenyl-ynyl)-methanesulfonamides. This intermediate then engaged in a formal [4 + 2] cascade annulation with nitrile derivatives and an intramolecular SN2′ type reaction with H_2O, led to the formation of **25** and **26** with high yields. Additionally, the created **25** exhibited notable fluorescence characteristics. This study explored the applicability of Au-catalyzed [4 + 2]-annulation reactions involving diverse derivatives of **24** in conjunction with acetonitrile. According to this process, the substrate with an unreactive CN group which not involved in the annulation reaction, led to the corresponding product. In the following, using 5 equivalents of the nitrile in DCE, the corresponding products were obtained with a satisfactory yield. There were some limitations and challenges regarding the reaction, such as (1) the scalability of the technique was required further investigation, (2) limited evaluations on diverse nitrile substrates was presented, (3) mechanistic details of Au carbene intermediates were required more clarity, and (4) effects of types of solvents on reaction outcomes were not investigated.

A mechanism underlying this transformation is depicted in Scheme 15. Firstly, the Au catalyst is coordinated with the alkyne by π-coordination. Then, intermediate **II** is formed *via* the triggers a cyclization reaction involving an ionic nitrogen of the azide and the Au-activated alkyne. Next, **III** is formed *via* the back-bonding from the Au canter along with lose N2. After that, intermediate **IV** is generated from **III** in the presence of nitrile. In the following, product **V** is generated *via* the nucleophilic attack of the nitrogen of sulfonamide to the nitrile carbon. Lastly, compounds **25** is produced from **V** in the presence of H_2O and O_2 *via* the further aromatization of **V**. Also, compound **VI** could be formed from **III** which it could be trapped by H_2O. In the following, it is converted to product VII (O–H insertion) and is regenerated the corresponding catalyst. Finally, product **26** is formed from the enol **VII** *via* the intramolecular SN2′ type reaction.[126]

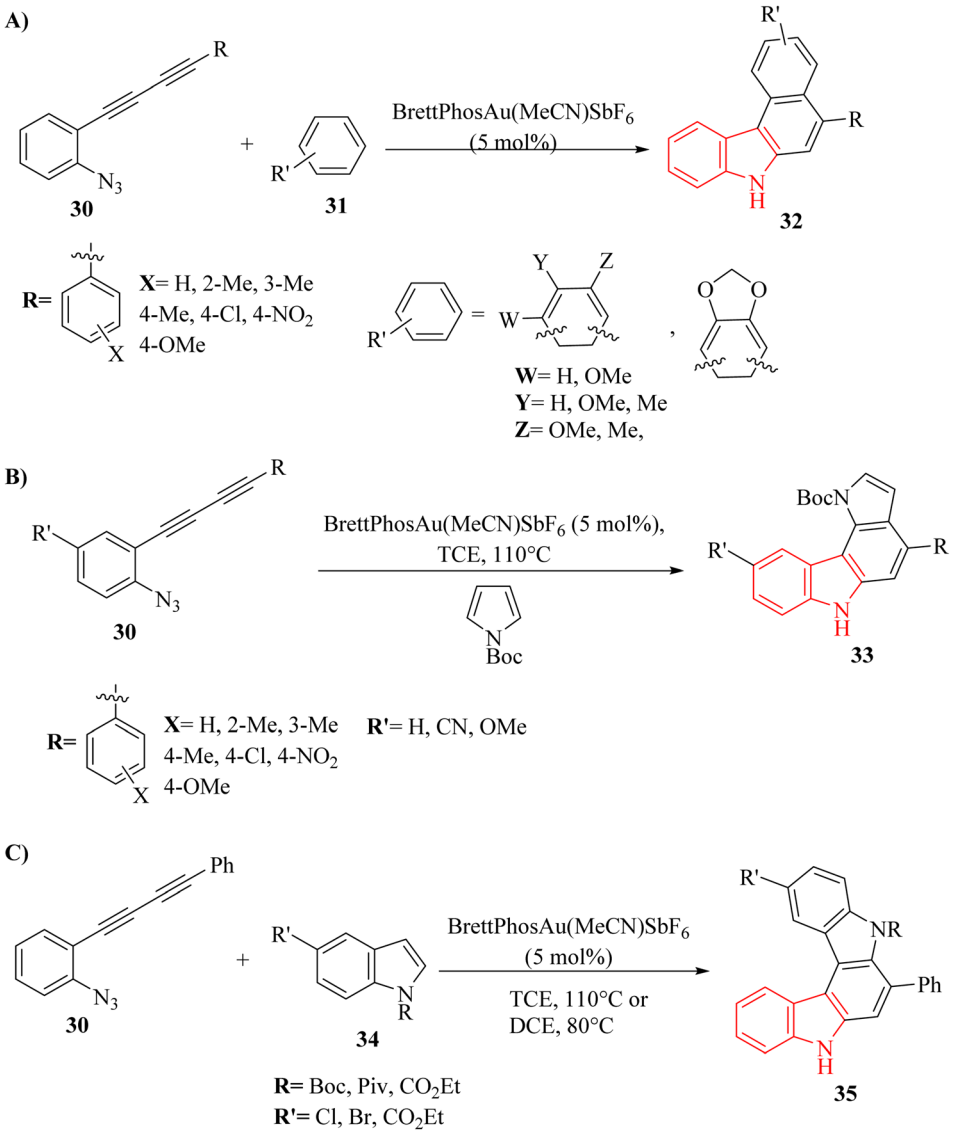
In 2024, Wang *et al.*[127] introduced a novel asymmetric catalysis approach using Au (*t*-BuXPhosAuSbF$_6$) and L-proline. This method facilitated the direct creation of chiral 2,2-disubstituted 3-carbonyl indole derivatives **29** featuring quaternary carbon canters with stereochemistry, starting from 2-alkynyl arylazide derivatives **27** and ketone derivatives **28** (Scheme 16). The process involved generating key 2-phenyl-3*H*-indol-3-one intermediates and conducting an asymmetric Mannich reaction with H_2O in DCM at room temperature, leading to satisfactory yields and outstanding enantioselectivity and diastereoselectivity. The desired catalysis reaction illustrated broad functional group tolerance across a wide range of the derivatives of **27**. In addition, electron-donating groups substantially enhanced yields and significantly reduced reaction times. Conversely, electron-withdrawing groups resulted in longer reaction times and diminished yields. There were some challenges and limitations regarding the reaction, such as (1) inadequate investigations on reaction mechanisms and intermediates, (2) lack of comprehensive optimization for type of reaction conditions, (3) more diverse substrate applications were required in asymmetric synthesis, and (4) limited investigation of Au/chiral amine relay catalysis compatibility.



Scheme 17 A mechanism for the reaction of 2-alkynyl arylazide derivatives **27** with ketone derivatives **28** catalyzed by Au.

A mechanism underlying this transformation is depicted in Scheme 17. Initially, the 2-alkynyl arylazide substrate **27** is activated by Au catalyst and is formed the Au-coordinated intermediate **I**. Next, compound **II** is formed from intermediate **I** *via* the cyclization. After that, complex **III** is formed from compound **II** along with lose of N_2 and immediately trapped by H_2O which this action is produced complex **IV**. Then, intermediate **V** is obtained from **IV** *via* the proton demetalation. In the following, intermediate **VI** is generated in the presence of the oxidant. In the next step, transition state **VIII** is formed *via* the reaction between enamine **VII** and imine intermediate **VI** which **VII** itself is obtained from *via* the reaction between proline and acetone. Finally, the corresponding product **29** is produced *via* the Mannich reaction.[127]

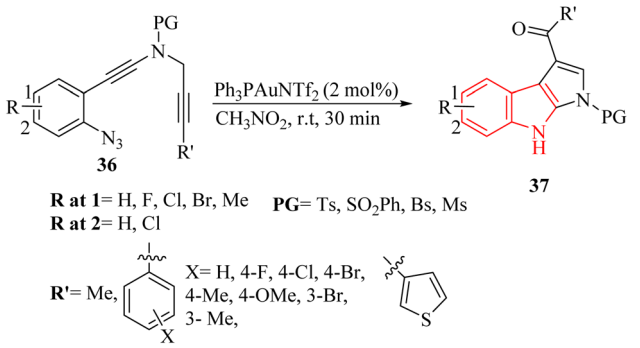
A novel strategy was developed for synthesizing aryl-annulated [*c*]carbazole derivatives *via* Au-catalyzed cascade cyclization of azido-diyne derivatives by Kawada and co-workers.[128] When reacting with electron-rich benzene derivatives like anisole and xylene, benzo[*c*]carbazole derivatives **32** (Scheme 18A) were formed by functionalizing two benzene C–H bonds. Additionally, using *N*-boc-pyrrole and indole derivatives as coupling partners selectively produced heteroaryl-annulated carbazole derivatives—specifically pyrrolo[2,3-*c*]carbazole derivatives **33** (Scheme 18B) and indolo-carbazole derivatives **35** (Scheme 18C). The reaction involved an internal nucleophilic attack by the N_3 on the nearby alkyne, resulting in the formation of an Au carbenoid species. The process was completed by the nucleophilic attack of arene derivatives on the carbenoid, followed by a 6-*endo*-dig cyclization of the introduced arene to the other alkyne. DFT calculations, competition experiments, and deuterium-labelling experiments provided evidence for the proposed reaction mechanism. Notably, a *N*,*N*′-dimethylated derivative of compound **35** showed both fluorescence and UV-vis-NIR spectral changes during electrolysis, demonstrating



Scheme 18 (A) Synthesis of carbazole derivatives **32**, (B) synthesis of pyrrolo-carbazole derivatives **33**, (C) synthesis of indolo-carbazole derivatives **35**.

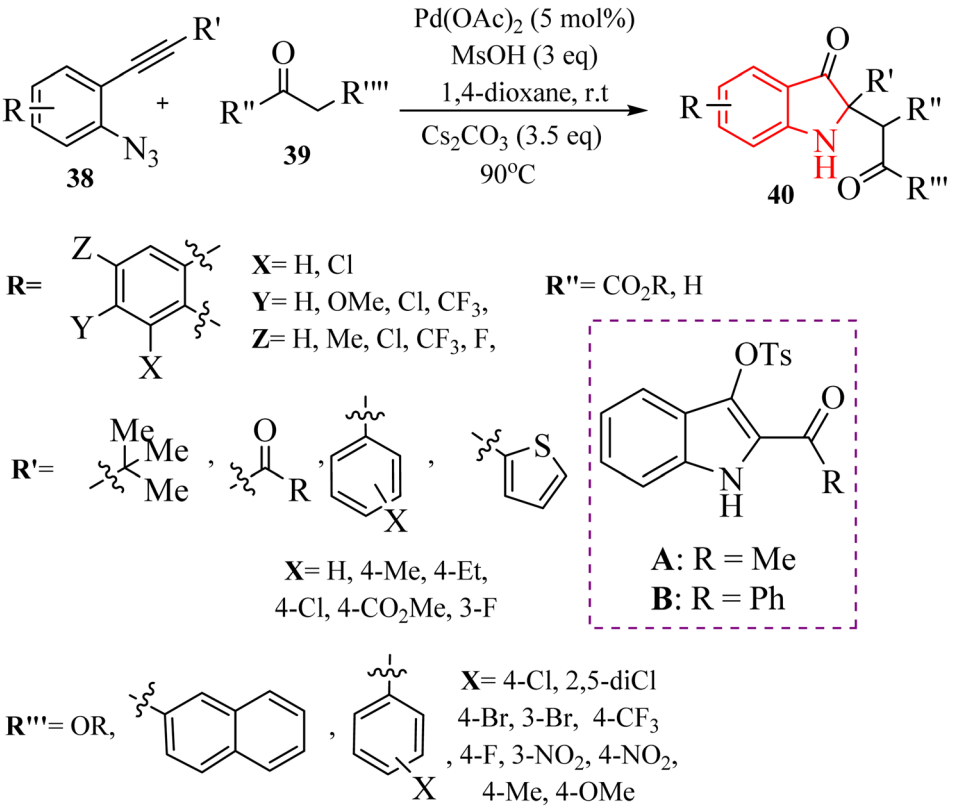
the potential usefulness of this reaction in materials chemistry. There were some limitations and challenges regarding the reactions, such as (1) separation of minor isomers from by-products was difficult, (2) electrophilic aromatic substitution was more likely than C–H insertion, (3) the relative reactivity of arene derivatives with *N*-Boc-pyrrole was unclear, (4) limited understanding of side reactions with indole derivatives, and (5) further investigation of electron-withdrawing groups on indole derivatives was required. It should be noted that deprotonation was not the rate-determining step for product formation.

Shen *et al.*[129] documented an Au-catalyzed cascade cyclization resulted in the diverse creation of synthetically valuable derivatives of pyrrolo-indole **37** (up to 95% yield) (Scheme 19).

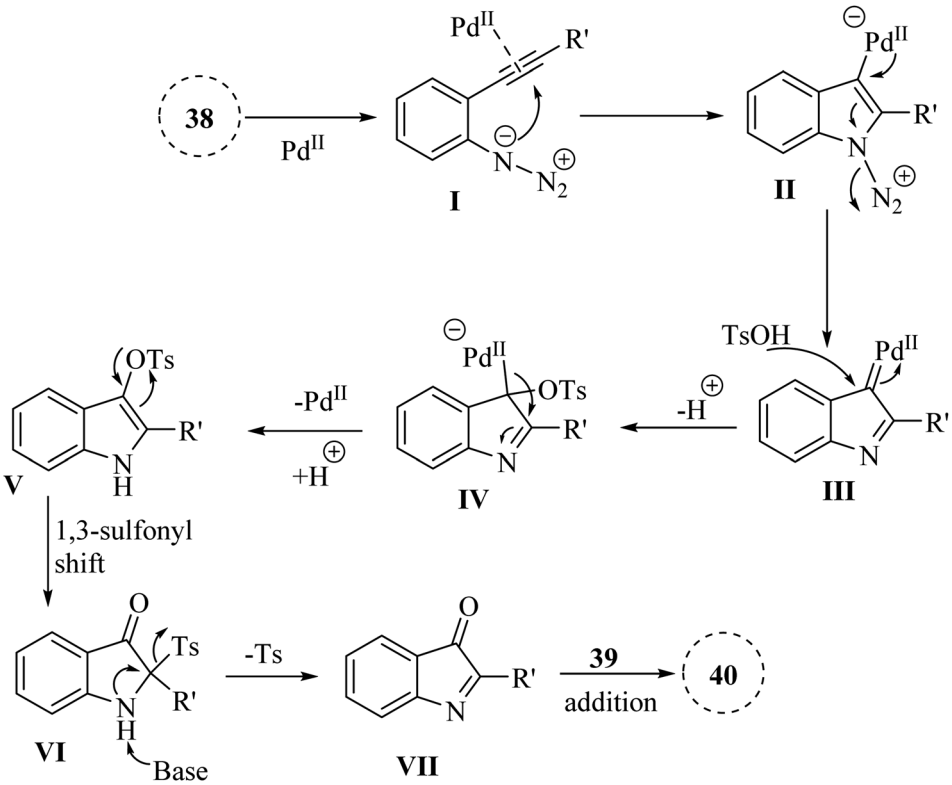


Scheme 19 Synthesis of pyrrolo-indole derivatives **37**.

2.1.2 Pd-catalyzed transformation. In 2017, Zhang and co-workers[130] introduced an innovative approach for the synthesis of C_2-quaternary indolin-3-one derivatives **40** through the use of Pd-catalyzed one-pot reactions involving 2-alkynyl arylazide derivatives **38** and sulfonic acid derivatives in the presence of 1,4-dioxane and Cs_2CO_3 (Scheme 20). The results demonstrated that this reaction can accommodate a broad array of structurally varied **38** (up to 90% yield), as well as enolates derived from commercially available ketone derivatives **39** (up to 95% yield) and malonate derivatives (up to 80% yield). In the case of **38** results, nevertheless, substituting R^2 with carbonyl groups resulted in the formation of a complex, as indicated by TLC and ^{1}H NMR analysis. When the reactions were performed without adding Cs_2CO_3 and acetophenone, the initial products **A** (61%) and **B** (35%) were generated. In addition, the reactions proceeded favourably using TsOH instead of MsOH, resulting in relatively high yields of the desired products within a short timeframe. The reaction yields were not remarkable when conducted at reflux, indicating a limitation in optimizing reaction conditions for higher yields. The utilize of certain substrates, such as acetophenone derivatives with specific substituents such as F, *meta*-NO_2, and OMe, resulted in relatively low product yields, highlighting the limitations in substrate compatibility. The formation of complex products was observed when switching substituents to carbonyl groups, suggesting challenges in achieving desired outcomes with certain modifications. It should be noted that the reaction without a base yielded only trace amounts of the corresponding



Scheme 20 Synthesis of indolin-3-one derivatives **40**.

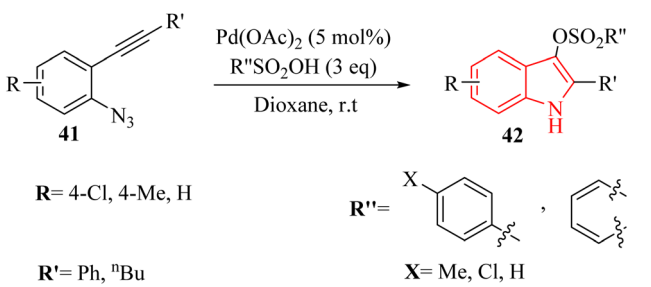


Scheme 21 A mechanism for the one-pot reactions catalyzed by palladium involving 2-alkynyl arylazide derivatives **38**.

product, emphasizing the necessity of base for effective transformation.

A mechanism underlying this transformation is depicted in Scheme 21. The activation process is produced intermediate **I**, coordinated with Pd. Subsequently, this intermediate undergoes cyclization, resulting in the formation of species **II**. Upon N_2 release, Pd-carbenes **III** is formed, and then TsOH trapped them to yield complex **IV**. Next, intermediate **V** is generated from **IV** *via* the protodemetalation process. When exposed to heat and under basic conditions, **V** can experience a 1,3-sulfonyl shift to generate **VI**. Subsequently, reductive desulfonation leads to the formation of intermediate **VII**. Ultimately, the Mannich-type reaction involving ketone is resulted in the **40** formations.[130]

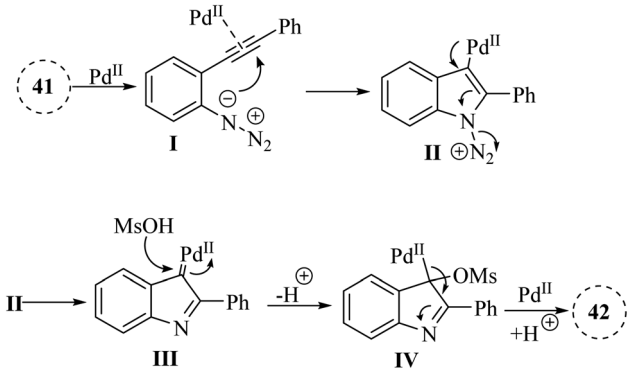
In 2024, Zhang *et al.*[131] reported a highly effective technique for producing 1*H*-indole-3-sulfonate derivatives **42** through a series of consecutive reactions involving 2-alkynyl arylazide derivatives **41** and sulfonic acid derivatives, catalysed by Pd(II) in 1,4-dioxane at 25 °C (Scheme 22). The reactions were observed to proceed rapidly, with the most completing them within a more 10 minutes. The desired products generated in 82–96% yields when used MsOH in the reaction, and 4-methylbenzenesulfonic acid produced the desired products in 70–97% yields. Also, benzenesulfonic acid, 4-chlorobenzenesulfonic acid and, naphthalene-1-sulfonic acid were tested and generated the desired products in 87–95% yields. Authors investigation revealed that the reaction involving **41** with a terminal alkyne group was not very efficient. The crude mixture produced a blend of decomposition products that remained unidentified despite analysis using ^{1}H NMR and TLC. The authors suggested that further investigation was needed to optimize the methodology for broader applications. These challenges underscored the need for a mild and efficient synthetic technique for 1*H*-indole-3-sulfonate derivatives.



Scheme 22 Synthesis of 1*H*-indole-3-sulfonate derivatives **42**.

A mechanism underlying this transformation is depicted in Scheme 23. Initially, compound **41** through coordination with a Pd catalyst at the triple bond, resulting in the formation of complex **I**. Then, complex **II** is formed through intramolecular amination of an N_3 group with an activated alkyne. Next, **IV** is formed by trapping alpha-imino palladium carbene species C14 after the release of N_2 using MsOH. Finally, the desired product **42** is formed through subsequent protodemetalation reactions.[131]

In 2018, Li *et al.*[132] synthesized polyfunctional indolin-3-one derivatives (**45**, **47** and **48**) through a Pd-catalysed one-pot

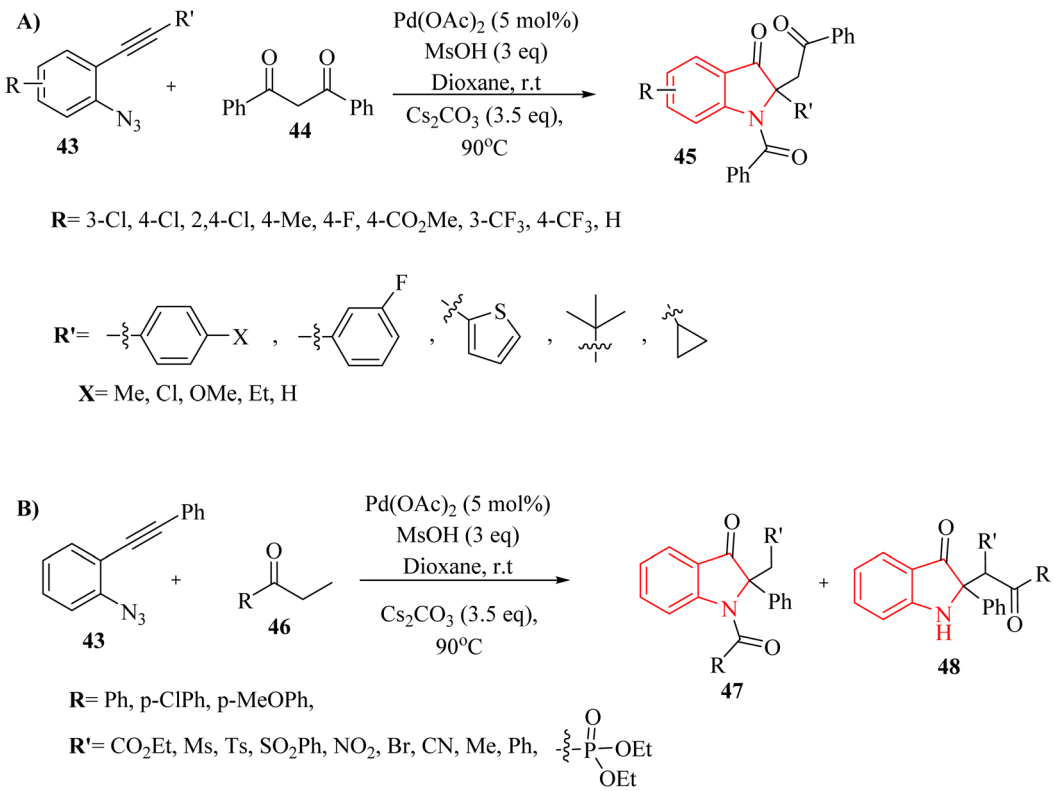


Scheme 23 A mechanism for the reactions catalyzed by palladium involving 2-alkynyl arylazide derivatives **41**.

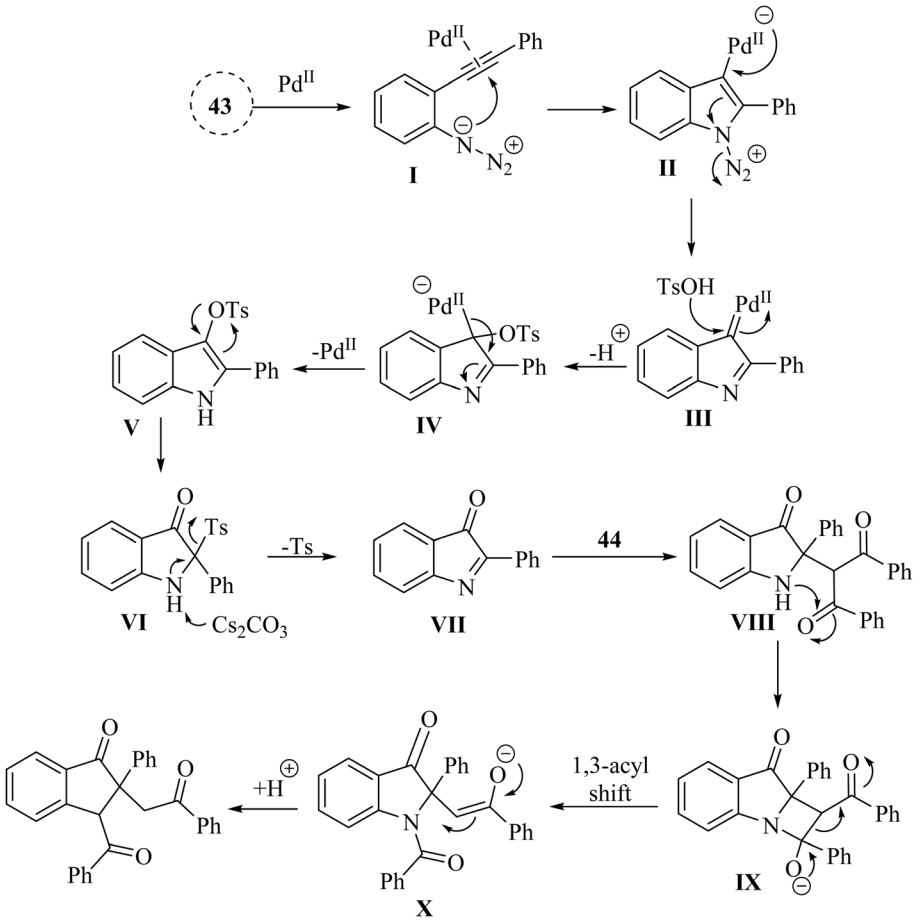
insertion reaction of cyclic C-acylimines into C–C s-bonds reactions in the presence of Cs_2CO_3 in 1,4-dioxane at 90 °C (Scheme 24A and B). In the case of 2-alkynyl arylazide derivatives **43**, it was found that the corresponding products were successfully obtained with yields of up to 96% (Scheme 24A). Furthermore, in the case of aryl ketone derivatives **46**, the synthesized products demonstrated excellent yields ranging from 80% to 95% when utilizing beta-ketoester and beta-ketosulfone derivatives (Scheme 24B). However, when alpha-nitrocarbonyl and beta-ketophosphonate were employed in the reactions, lower product yields of 28% to 68% were observed. When alpha-bromocarbonyl was evaluated, the resulting mixture contained decomposition products that remained unidentifiable despite analysis using ^{1}H NMR and TLC, indicating potential limitations in substrate compatibility. The study displayed that the yields of products could be affected by steric effects of the substrates. The research also noted that certain highly active carbon anions produced during the reaction may not led to insertion reactions due to insufficient stabilization.

A proposed mechanism underlying this transformation is depicted in Scheme 25. Compound **43** is activated by coordination of Pd catalyst with alkyne. This is formed a Pd-coordinated intermediate **I**. Then, species **II** is produced from **I** *via* an intramolecular cyclization. The alpha-imino Pd carbene **III** is formed by the release of N_2. In the following, **III** is attacked by TsOH and is formed the complex **IV**. Following protodemetalation, the aryl sulfonate **V** is generated. Next, **V** is converted into the active intermediate **VI** *via* a 1,3-Ts shift step. After that, key intermediate **VII** is formed after subsequent reductive desulfonation of **VI**. In the next step, alkylated compound **VIII** is produced when **VII** undergoes Mannich-like addition. Complex **IX** is generated *via* an intramolecular attacking of N to C. Next, complex **X** is formed from **IX** *via* 1,3-acyl shift. Lastly, the desired product is produced after protonation process.[132]

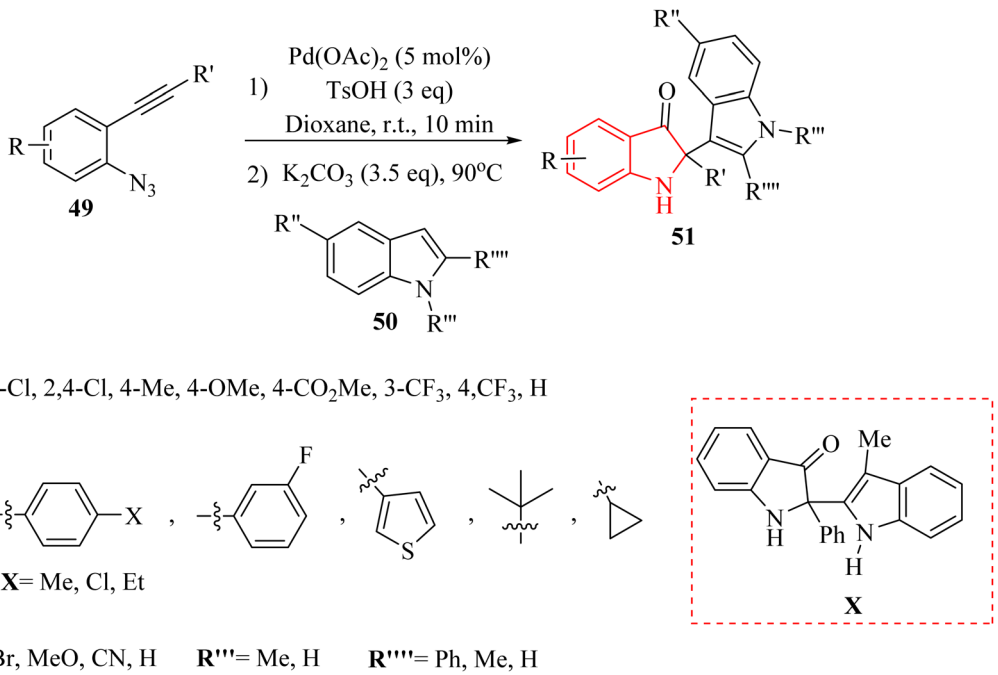
Yong *et al.*[133] introduced a Pd-catalyzed one-pot two-step reaction of 2-alkynyl arylazide derivatives **49** and indole derivatives **50**. The reactions involving **49**, TsOH and **50** in the presence K_2CO_3 in 1,4-dioxane at 90 °C. In the case of the



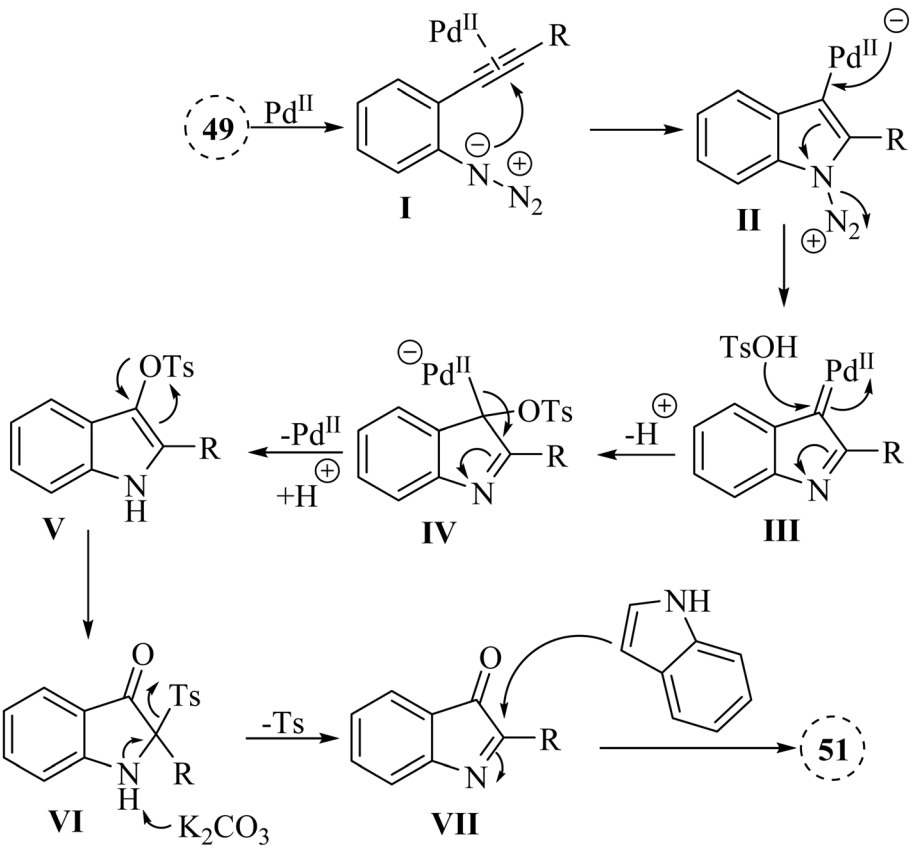
Scheme 24 (A) Scope of the 2-alkynyl arylazide derivatives **43**, (B) scope of the aryl ketone derivatives **46**.



Scheme 25 A mechanism for the Pd-catalyzed of **43**.



Scheme 26 Synthesis of phenylindolin-3-one derivatives **51** catalyzed by Pd.

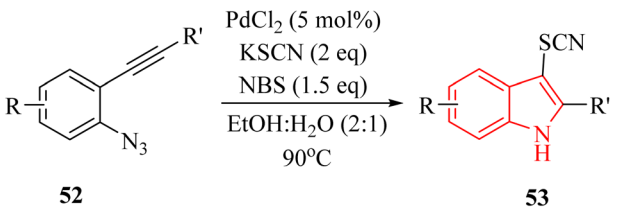


Scheme 27 A mechanism for the one-pot reactions of **49** catalyzed by Pd.

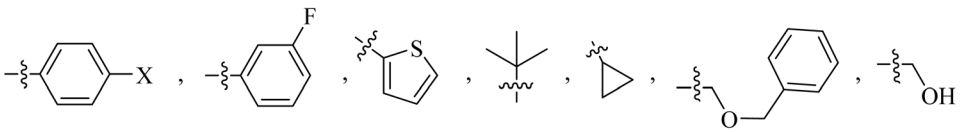
derivatives of **51**, the desired products obtained with yields of up to 97% (Scheme 26). Nevertheless, no desired product was identified when 3-methyl-1*H*-indole was examined for its reactivity as a nucleophile (Scheme 26 **X**).

A mechanism underlying this transformation is depicted in Scheme 27. Compound **49** is activated by coordination of Pd catalyst with alkyne. This is formed a Pd-coordinated **I**. Then, species **II** is produced from **I** *via* an intramolecular cyclization. The alpha-imino Pd carbene **III** is formed by the release of N_2. In the following, **III** is attacked by TsOH and is formed the complex **IV**. Following protodemetalation, the aryl sulfonate **V** is generated. After 1,3-Ts shift of **V** and reductive desulfonation of **VI**, compound **VII** is generated. Finally, desired product **50** is formed after subsequent reductive desulfonation of **VI** which it is trapped by **51**.[133]

In 2021, Hu and colleagues[134] developed an innovative and effective method to synthesize 3-thiocyanindole derivatives **53**. This process involved a Pd-catalyzed bromination and cross-

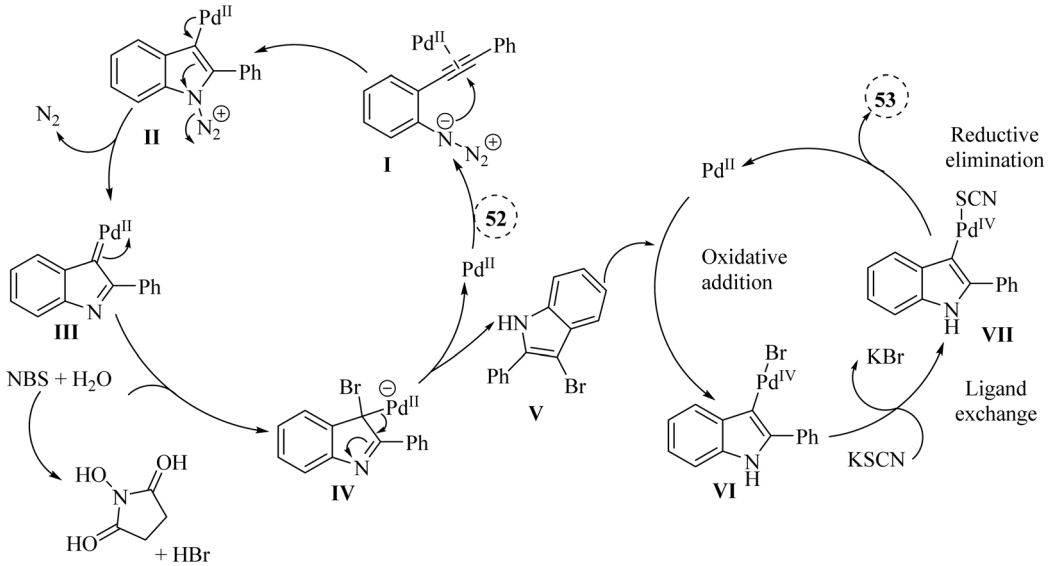


R= 3-Cl, 4-Cl, 3-F, 4-F, 3-Me, 4-Me, 4-F, 3-CF_3, 4-CF_3, H

R'= 

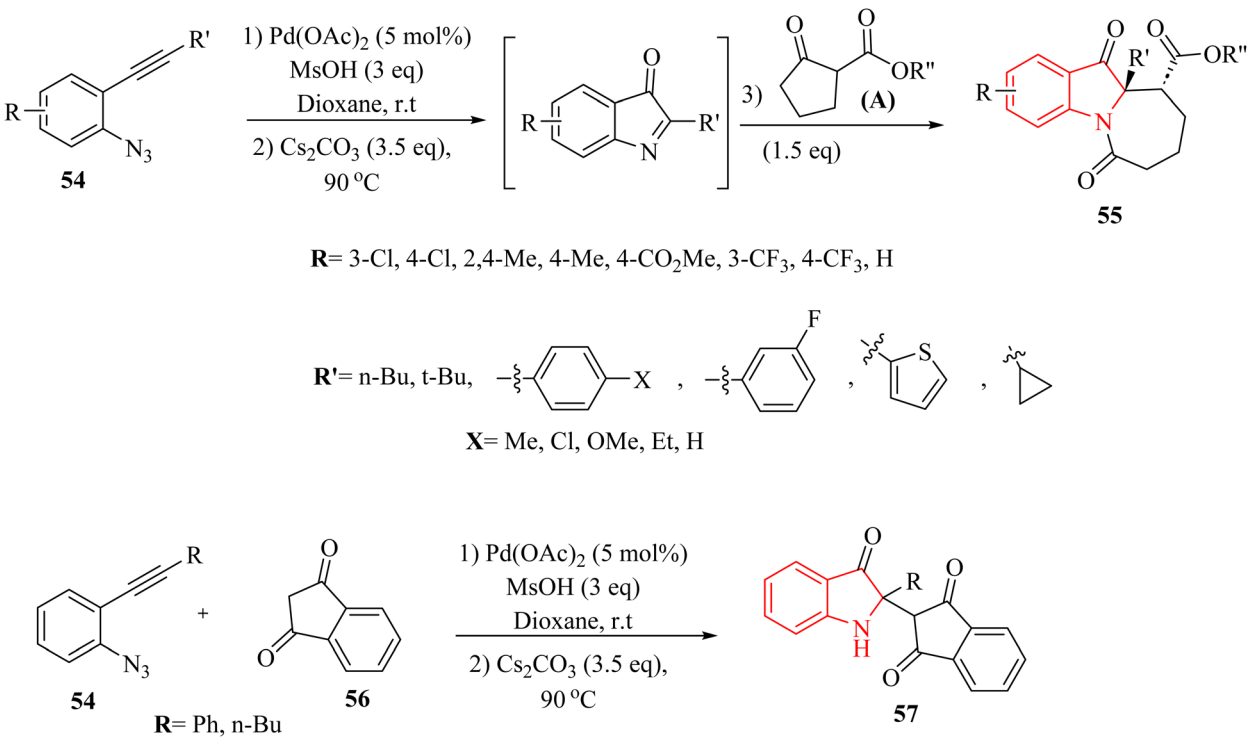
X= Me, Cl, Br, OMe, Et, n-C_5H_{11}, H

Scheme 28 Synthesis of 3-thiocyanindole derivatives **53**.



Scheme 29 A mechanism for the Pd-catalyzed reactions of **52**.

coupling reaction, assisted by NBS, of 2-alkynyl arylazide derivatives **52** with KSCN in a solvent mixture of EtOH and H_2O (2 : 1) at 90 °C (Scheme 28). The results demonstrated that this reaction can accommodate a wide range of structurally diverse **52** (up to 98% yield). A reaction involving a Br-containing substrate was conducted under standard conditions, yielding the corresponding product with a 71% yield after 4 hours. When authors extended the reaction time to 10 hours, they still obtained the desired product as the single product. The authors highlighted that existing thiocyanation reactions often face limitations such as harsh reaction conditions, which could be detrimental to sensitive substrates. It noted a narrow substrate scope, indicating that not all compounds could be effectively utilized in these reactions. Low product yields were also a concern, as many techniques did not generate adequate quantities of the corresponding thiocyanate products. These



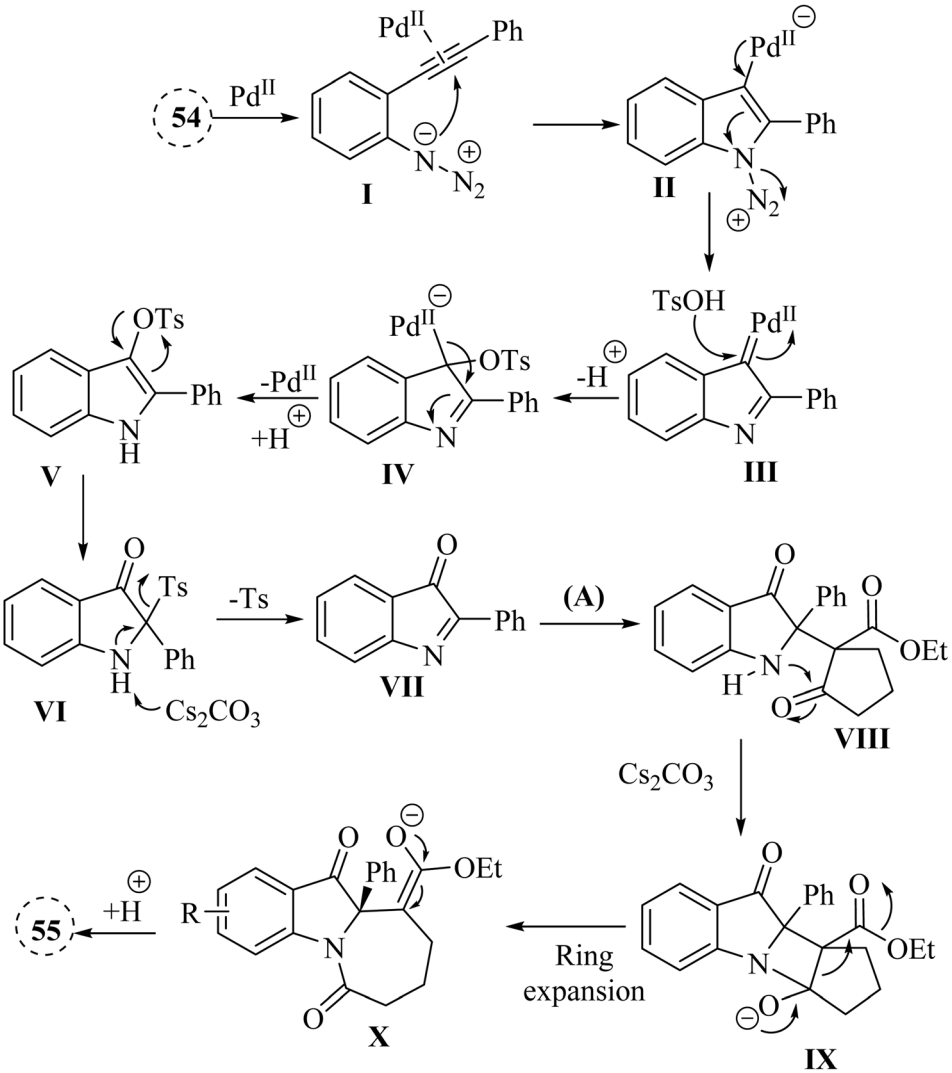
Scheme 30 Synthesis of indoline-3-one derivative derivatives **55** and 3*H*-indol-3-ones **57**.

challenges underscored the necessity for developing a highly efficient and general thiocyanation technique that can accommodate a broader range of substrates.

A mechanism underlying this transformation is depicted in Scheme 29. Initially, compound **52** through coordination with a Pd catalyst at the triple bond, resulting in the formation of complex **I**. Then, complex **II** is formed through intramolecular amination of an N_3 group with an activated alkyne. In the following, **III** is produced *via* a release of N_2. Next, complex **IV** is formed from **III** when it is trapped by HBr. After that, intermediate **V** is generated after demetalation and protonation of **IV**. In the next step, **VI** is produced *via* an oxidative addition of **V**. Next, complex **VII** is generated *via* a ligand exchange with KSCN. Lastly, the corresponding product is obtained *via* a reductive elimination of **VII**.[134]

In the year 2020, Li and colleagues[135] outlined a new approach for producing *N*-fused 7 membered multi-functional polycyclic indoline-3-one derivative derivatives **55** by introducing cyclic *C*-acylimines into cyclic beta-diketone derivatives (**56** or **A**) (Scheme 30). This process was carried out in the presence of Cs_2CO_3 at 90 °C. The reaction with the substrate containing an R′ = *tert*-butyl group was unsuccessful, and only the initial intermediate, 2-(*tert*-butyl)-1*H*-indol-3-yl 4-methylbenzenesulfonate, was able to be isolated. This likely occurred due to steric hindrance. Under standard reaction conditions, an attempt was made to carry out the insertion reaction with **56**. Unfortunately, the corresponding insertion product was not generated (Scheme 30).

A mechanism underlying this transformation is depicted in Scheme 31. The activation process is produced intermediate **I**. Subsequently, this intermediate undergoes intramolecular cyclization of azide group, resulting in the formation of species **II**. Upon N_2 release, Pd-carbene **III** is formed, and then TsOH is trapped them to yield complex **IV**. Next, intermediate **V** is generated from **IV** *via* the protodemetalation process. When exposed to heat and under basic conditions, **VII** is generated through a 1,3-sulfonyl shift of **V** and reductive desulfonation of **VI**. Subsequently, complex **VIII** is produced *via* a nucleophilic



Scheme 31 A mechanism for the reactions of 2-alkynyl arylazide derivatives **54** with cyclic beta-diketone derivatives (**56** or **A**) catalyzed by Pd.

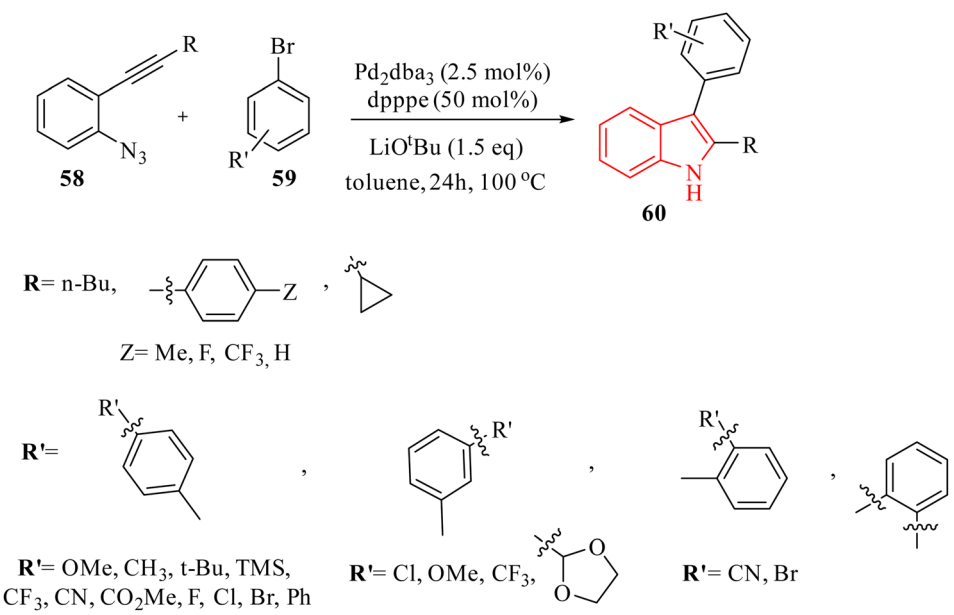
addition of **A** to **VIII.** Then, a four-membered ring complex **IX** is generated from **VII** *via* an intramolecular addition. Lastly, the corresponding product **55** is produced through protonation of complex **X.**[135]

Reactions 20, 24, and 30 are essentially similar but have differences that can be noted as follows. In the case of products, the reaction 20 focused on N-fused 7-membered rings, while the reaction 24 targeted polyfunctional indolin-3-one derivatives, and the reaction 30 emphasized C_2-quaternary indolin-3-one derivatives. In the case of reaction mechanisms, the reaction 20 involved a straightforward insertion into cyclic β-diketone derivatives, the reaction 24 emphasized the insertion into carbon–carbon σ-bonds, and the reaction 30 highlighted a rearrangement of sulfonate derivatives, showcasing different mechanistic pathways. In the case of functional group tolerance, each method had varying degrees of functional group tolerance, with the reaction 24 illustrating a broader scope of substrates and conditions compared to the reaction 20 and 30. This consolidation not only emphasized the progress made in this area but also set the stage for future research exploring further applications and optimizations of these methodologies.[130,132,135]

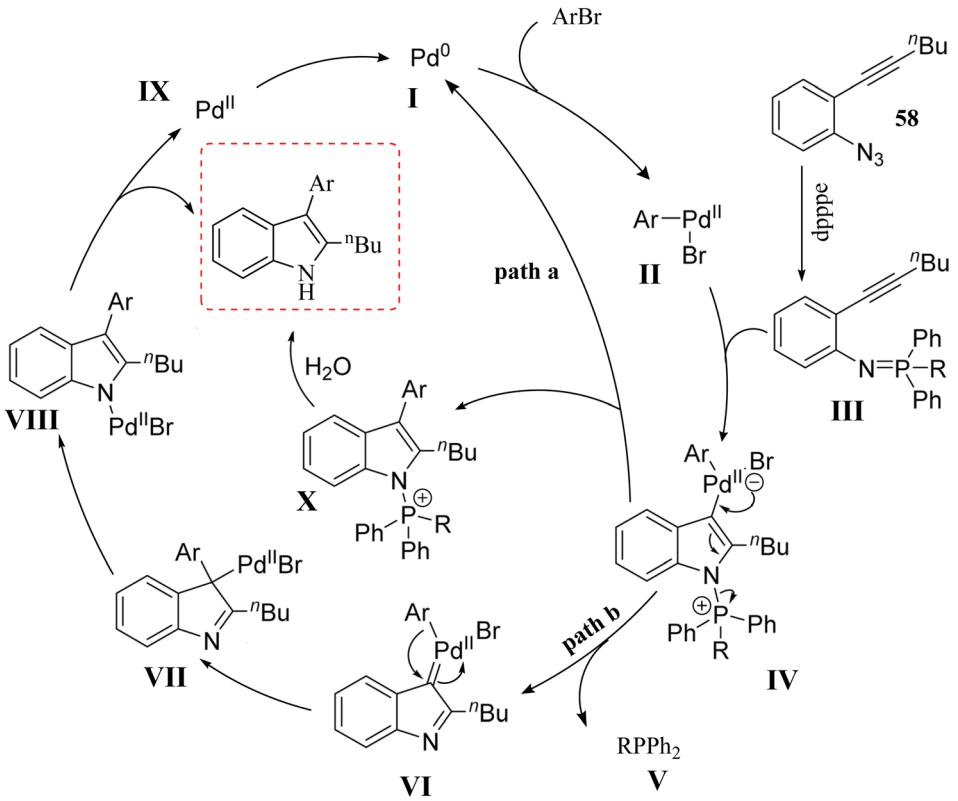
In 2016, Zhou *et al.*[136] reported the development of a Pd-catalyzed synthesis method for the production of poly-substituted indole derivatives **60**. This method involved the coupling of aryl bromide derivatives **59** with 2-alkynyl arylazide derivatives **58** (Scheme 32). The reaction was conducted in the presence of LiOtBu, Pd_2dba_3, and dpppe in toluene at 100 °C for generated **60**. The authors discussed challenges related to the low yields observed in the synthesis of indoles, particularly when using certain aryl bromide derivatives and azide derivatives as substrates. It should be noted that the reaction conditions need to be optimized, as variations in the loading of Pd catalysts and ligands significantly affect the yields.

A mechanism underlying this transformation is depicted in Scheme 33. Two possible pathways were reported. In pathway a, oxidative addition of **59** to a Pd(0) catalyst is generated **II.** Then, compound **58** is produced **III** *via in situ* by a Staudinger reaction. After that, intermediate **IV** (5-*endo*-dig) is formed when the nitrogen of the phosphinimine group is attacked the aryl Pd(II)-activated triple bond nucleophilically. **IV** undergoes reductive elimination to form intermediate **X**, which is then transformed into the final product through hydrolysis. In pathway B, **IV** is transformed into **VI** *via* back electron donation from Pd. Following migratory insertion, **VII** is formed and then isomerized into intermediate **VIII.** Lastly, protonation of intermediate **VIII** is produced final product **60** and a Pd(II) species, which is then reduced to the Pd(0) catalyst by **V.** The authors also noted that the reaction mechanism was complex, requiring further investigation to fully understand the pathways involved.[136]

In 2021, Li and colleagues[137] reported on the synthesis of functionalized pyrroloindoline derivatives **63** *via* a one-pot reaction catalysed by $Pd(OAc)_2$. This reaction involved the use of thioacetamide derivatives **62** and 3*H*-indol-3-one derivatives, which were produced *in situ* from 2-alkynyl arylazide derivatives **61** when accompanied by Cs_2CO_3 in 1,4-dioxane at 90 °C (Scheme 34). The derivatives of **63** were generated in yields ranging from 56% to 84%. However, when substrates with different alkyl groups on the alkyne carbon (R′ = *n*-C_6H_{13} or cyclohexane) were used, the desired products could not be obtained (**Z**). Instead, only the first-step product was observed. One challenge highlighted was the unstable properties of 3*H*-indol-3-one derivatives, which could have led to partial decomposition after column chromatography, complicating their use in further reactions. Also, existing synthetic techniques for pyrroloindoline derivatives often suffer from drawbacks such as the need for specific reagents, narrow substrate



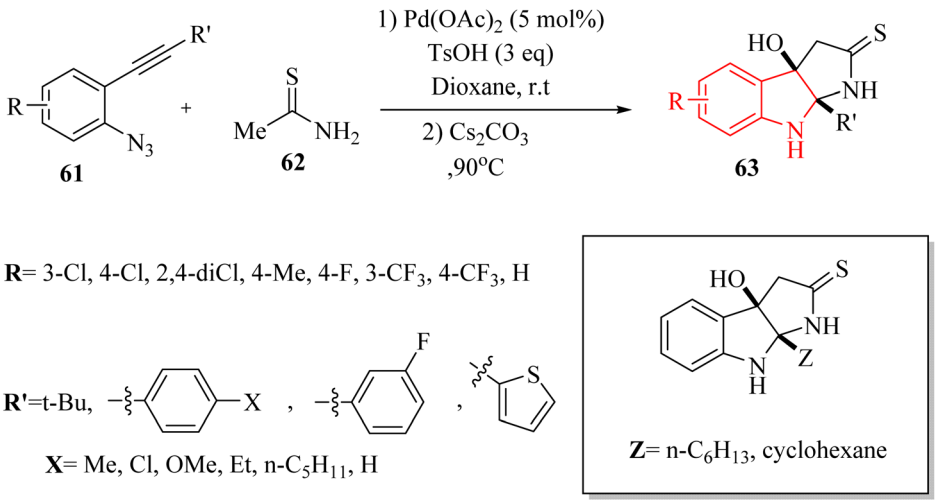
Scheme 32 Synthesis of indoles **60**.



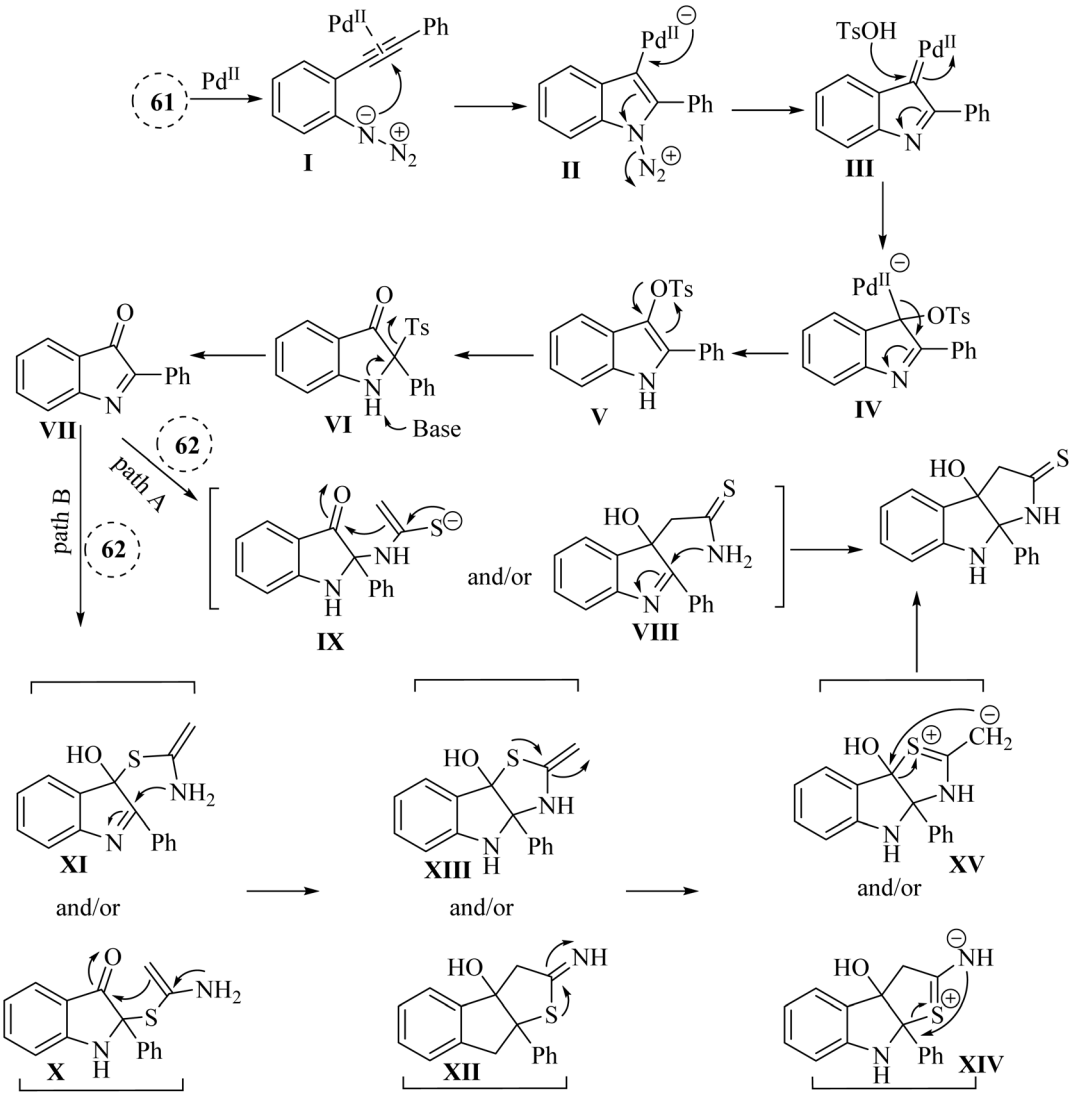
Scheme 33 A mechanism for the reactions of 2-alkynyl arylazide derivatives **59** with aryl bromide **60** catalyzed by Pd.

scope, and harsh reaction conditions, indicating a demand for more efficient synthetic strategies.

A mechanism underlying this transformation is depicted in Scheme 35. To activation of **61**, Pd-$(OAc)_2$ is coordinated with the alkyne to generated **I**. In the following, it is attacked by azido group to formed complex **III**. Next, **III** is formed when N_2 released from **II**. After that, **IV** is produced when **III** trapped by TsOH. Next, **V** is formed after demetalation and protonation of **IV**. Then, **VII** is produced following a 1,3-Ts shift of compound **V** and the desulfonation of compound **VI**, using Cs_2CO_3 at 90 °C. In the following, the carbon and/or nitrogen atom of 3 is attacked **VII**, resulting in the formation of **VIII** and/or **IX**, which then undergoes intramolecular cyclization to yield the **63** (pathway A). Next, **VII** is captured by the sulfur atom of three, resulting in the formation of **X** and/or **XI**, which subsequently cyclized to produce **XII** and/or **XIII** along with their resonance forms **XIV** and/or **XV**. Ultimately, a rearrangement of O and/or N yielded the **63** (pathway B).[137]



Scheme 34 Synthesis of pyrroloindoline derivatives **63**.

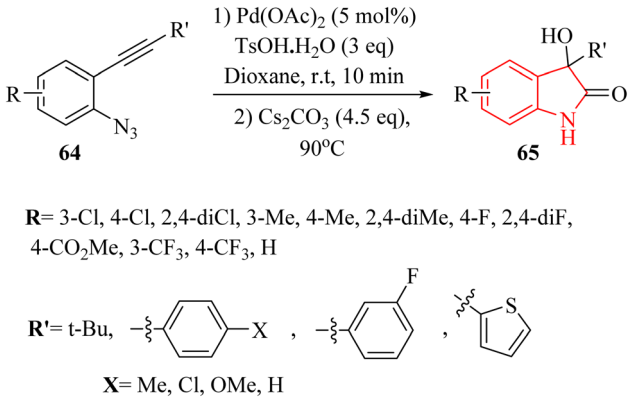


Scheme 35 A mechanism for the reactions catalyzed by palladium involving 2-alkynyl arylazide derivatives **61** and thioacetamide derivatives **63**.

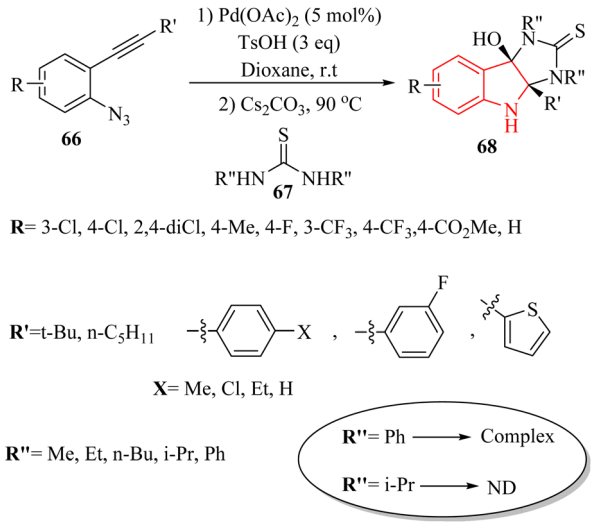
In 2020, Zhou and colleagues[138] developed Pd-catalysed one-pot approach for synthesizing 3-hydroxy-2-oxindole derivatives **65** from in situ-generated 2-hydroxyl-indoline-3-one derivatives, derived from 2-alkynyl arylazide derivatives **64** in the presence of Cs_2CO_3 in 1,4-dioxane at 90 °C (Scheme 36). It should be noted that various groups tolerated. The resulting products gave in yields ranging from 51% to 93%. An acyloin rearrangement process occurred during the reactions. The authors displayed that further studies on the application of acyloin rearrangements are underway, suggesting a gap in understanding the broader implications and potential applications of this reaction process.

A mechanism underlying this transformation is depicted in Scheme 37. Initially, activation of compound **64** is produced **III**, which could be captured by $TsOH \cdot H_2O$ to form **V**. Then, **VII** is generated following a 1,3-Ts shift of **V** and a subsequent reductive desulfonation. Subsequently, the hydroxylation of $TsOH \cdot H_2O$ crystal water or water is generated by acid-base neutralization to the C=N double bonds of **VII** leads to the formation of **VIII**. Ultimately, the corresponding product **65** is obtained *via* an acyloin rearrangement of **VIII**. The authors mentioned that the proposed mechanism for converting 1-azido-2-(phenylethynyl)benzene to 3-hydroxy-2-oxindole was speculative, indicating a need for more definitive mechanistic studies.[138]

In 2020, Li *et al.*[139] published a significant advancement in the synthesis of hybrid imidazo-indole derivatives **68** (Scheme 38). The study presented a pioneering approach for the rapid and effective production of these compounds through a Pd-catalysed one-pot annulation process. This process involved the reaction of thioureas **67** with 3*H*-indol-3-one derivatives, which were produced *in situ* from 2-alkynyl arylazide derivatives **66** in the presence of Cs_2CO_3 in 1,4-dioxane at 90 °C. The utilization of easily accessible starting materials further underscored the practical significance of this methodology. The study reported impressive product yields, with **66** products being obtained in the range of 56% to 97% yields, and **67** products achieved a remarkable 97% yield. However, it should



Scheme 36 Synthesis of 3-hydroxy-2-oxindole derivatives **65**.

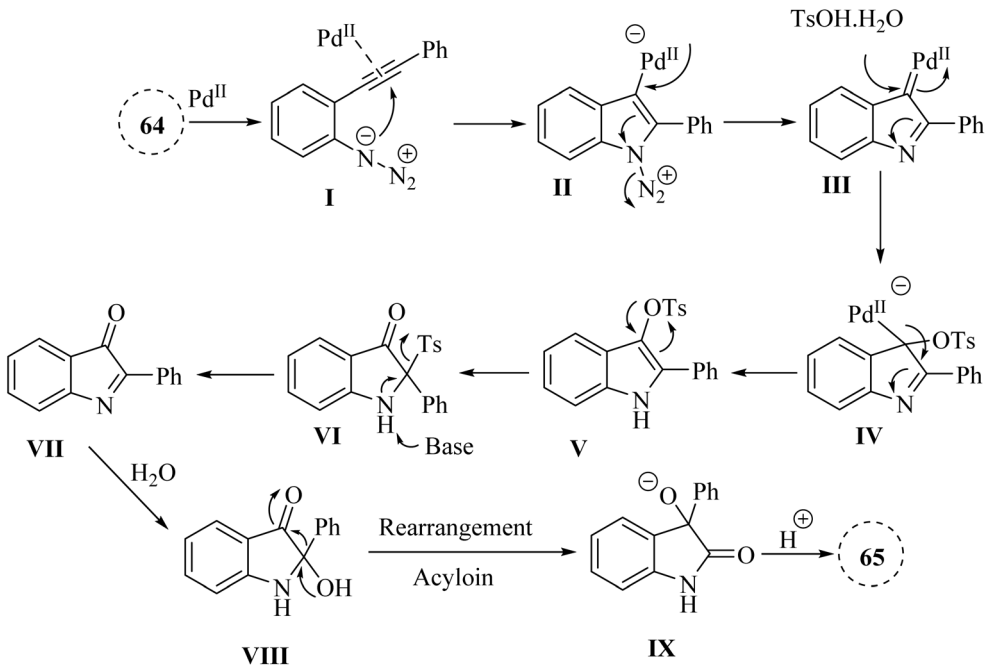


Scheme 38 Synthesis of indole-2-thione derivatives **68**.

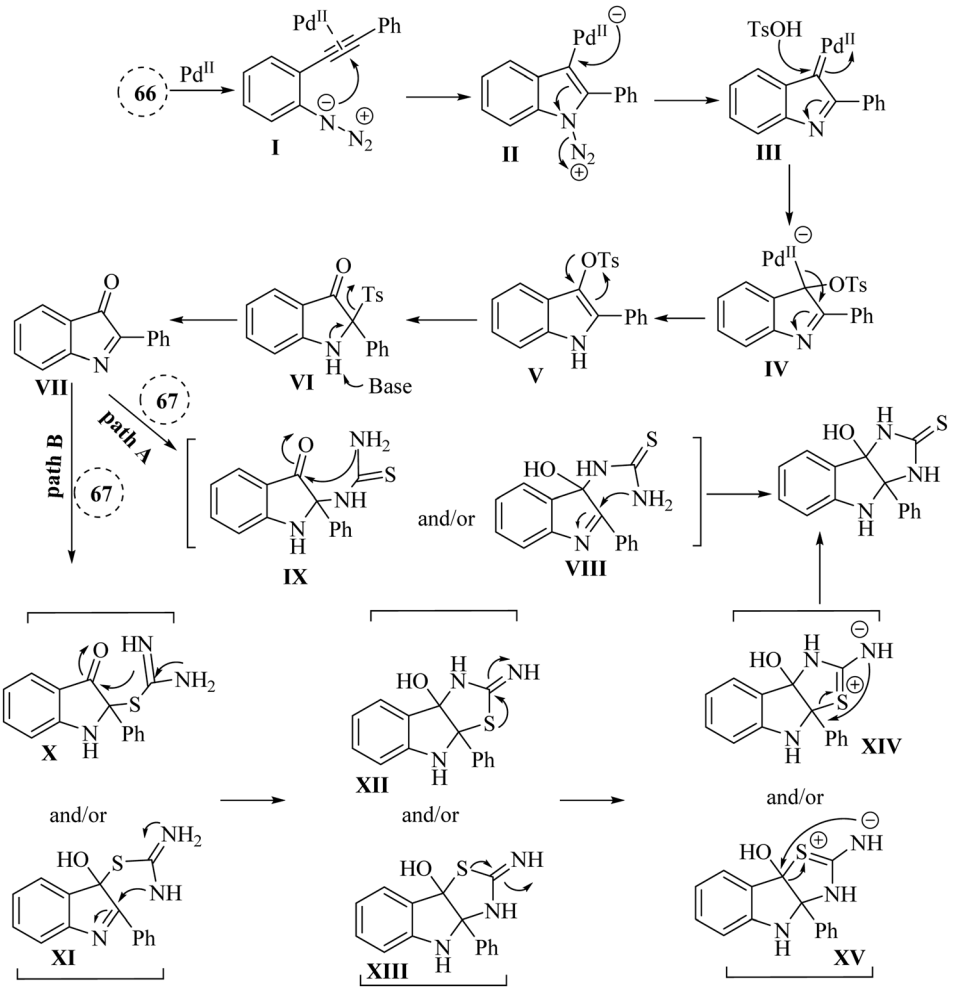
be noted that **67** with aryl or bulky substituted groups did not yield the desired products, possibly due to steric effects. The authors were emphasized the importance of developing practical techniques for synthesizing imidazoloindoline derivatives, which remains underexplored.

A mechanism underlying this transformation is depicted in Scheme 39. Compound **66** is transformed into **VII** through the capture of alpha-imino Pd carbene, followed by a 1,3-Ts shift and a reductive desulfonation sequence. Following this, intermediates **VIII** and/or **IX** is generated *via* the intermolecular amination of **67** with **VII**, which could then be further transformed into **68** through intramolecular amination cyclization (pathway A). Next, the sulfur atom of **67** is attacked the **VII**, resulting in the formation of **X** and/or **XI**. This is followed by an amination of intramolecular, producing **XII** and/or **XIII** and their resonance forms **XIV** and/or **XV**. Finally, the corresponding product is obtained through a final rearrangement step (pathway B).[139]

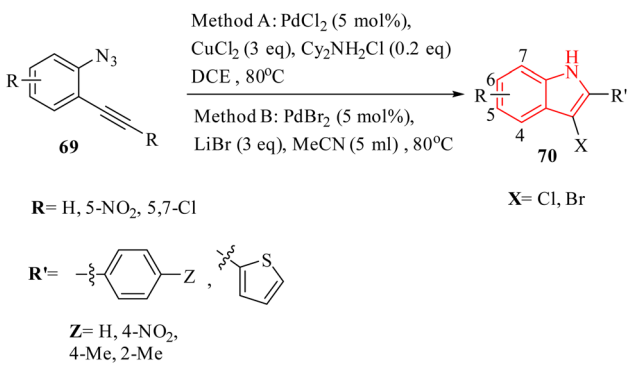
2.1.3 Bimetallic (Pd/Cu)-catalyzed transformation. A new and selective method for synthesizing 3-haloindole derivatives **70** was established *via* the halopalladation cyclization of alkyne derivatives with azide derivatives by Zhang *et al.*[140] (Scheme 40). By employing PdX_2 (X = Br or Cl) and halide sources, a range of 2-alkynyl aryl azide derivatives **69** effectively underwent the halopalladation cyclization reaction, yielding the derivatives of **70** with yields between 42% and 90%. The study could benefit from investigating the scalability and practical applications of the synthesized compounds in medicinal chemistry. The



Scheme 37 A mechanism for the reactions of 2-alkynyl arylazide derivatives **64** into **65** catalyzed by Pd.



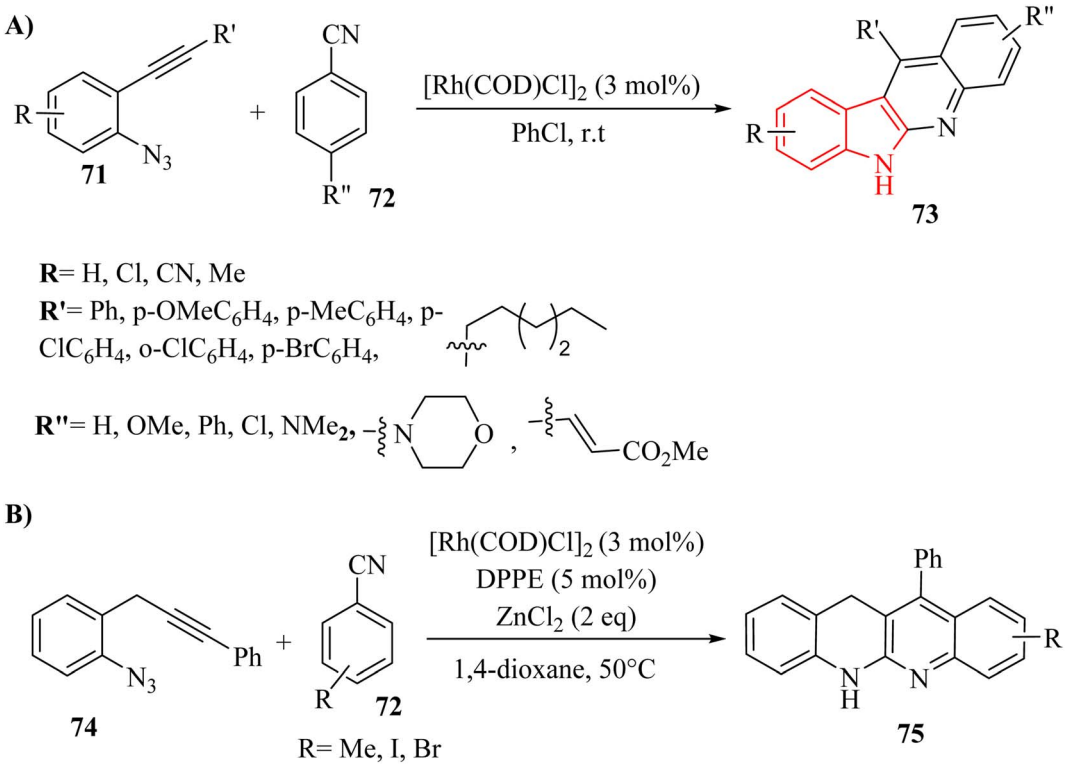
Scheme 39 A mechanism for reactions of 2-alkynyl arylazide derivatives **66** and transformed into **68** catalyzed by Pd.



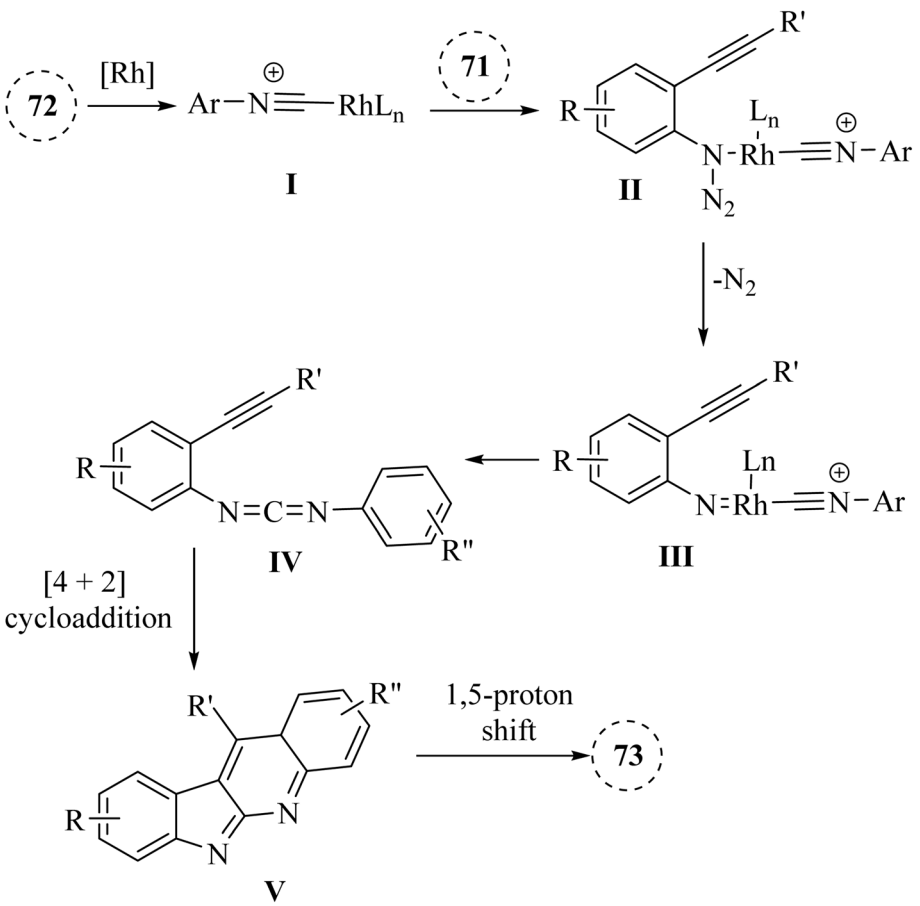
Scheme 40 Synthesis of 3-haloindole derivatives **70**.

authors illustrated that efforts to study the mechanism of the halopalladation cyclization process were underway, suggesting a gap in understanding the detailed reaction pathway and intermediates involved.

2.1.4 Rh-catalyzed transformations. A new Rh-catalyzed coupling-cyclization method for *o*-alkynyl **71**/propargyl arylazide derivatives **74** with arylisocyanide derivatives **72** were developed by Yang *et al.*[141] The study was highlighted a lack of extensive studies on the transition-metal-catalyzed coupling-cyclization reactions of *o*-alkynylpropargyl arylazide derivatives or *o*-azidoaryl acetylenic ketone derivatives with isocyanide derivatives, indicating that such reactions were considerably rare in the literature. This process generated reactive arylcarbodiimide intermediates, which then underwent an intramolecular [4 + 2] cycloaddition. This offered a straightforward approach to synthesize 6*H*-indolo[2,3-*b*]quinolone derivatives **73** (up to 87% yield) (Scheme 41A) and dibenzonaphthyridone derivatives **75** (up to 72% yield) (Scheme 41B) using readily available non-fused ring starting materials, the process yields the desired product in a single step, with N_2 as the sole by-product. In the case of the derivatives of **71**, when 1-isocyano-4-/nitrobenzene was used as the coupling partner, the desired product was not obtained. Also, the reaction efficacy was not significantly affected by the steric and electronic properties of the aryl groups. There was a need for further investigation of the generality of the reaction with various arylisocyanides and *o*-azidoarylalkynes to fully understand the scope and limitations of the methodology.



Scheme 41 (A) Synthesis of indolo-quinolone derivatives **73**, (B) synthesis of dibenzonaphthyridone derivatives **75**.



Scheme 42 A mechanism for the reactions of 2-alkynyl arylazide derivatives **71** with arylisocyanide derivatives **72** catalyzed by Rh.

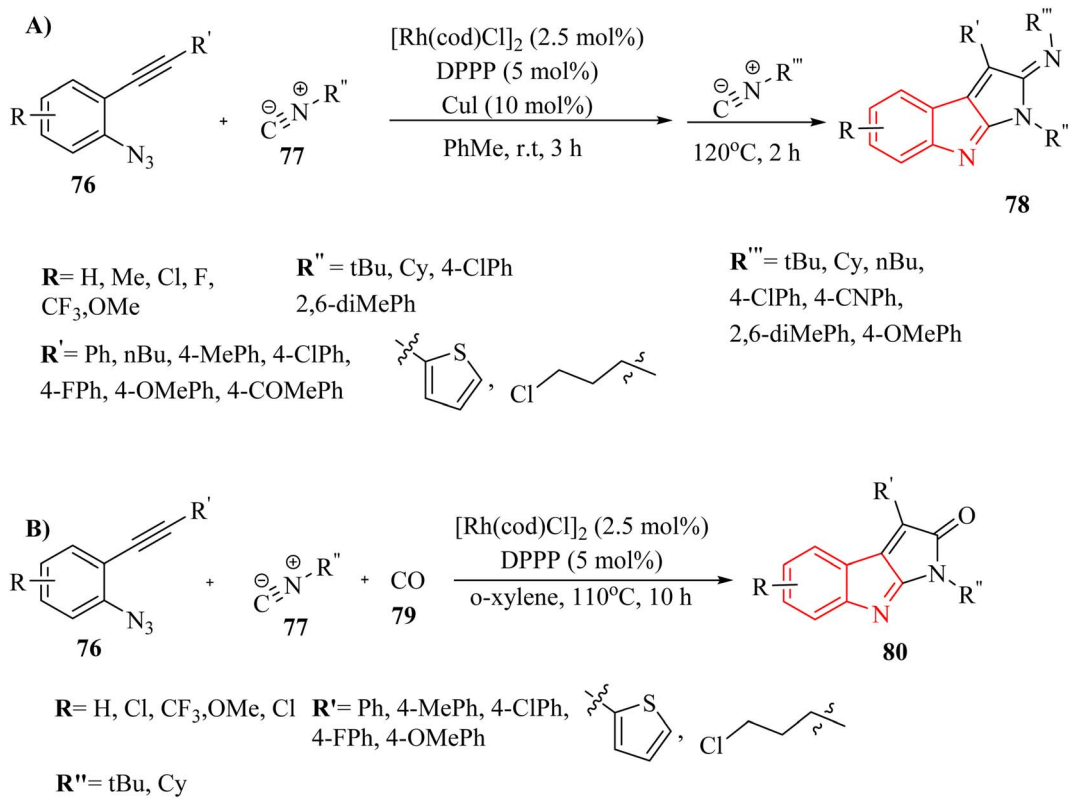
A mechanism underlying this transformation is depicted in Scheme 42. Firstly, intermediate **I** is formed *via* the coordination of compound **72** with $[Rh(COD)Cl]_2$, which then interacted with compound **71** to produced **II**. Then, intermediate **III** is generated *via* the release of N_2 in **II**. Next, **III** undergoes migratory insertion and the departure of rhodium and formed **IV**. Lastly, the desired product **73** is obtained from **IV** *via* an internal [4 + 2] cycloaddition reaction, followed by a 1,5-proton shift.[141]

Zhang and colleagues[142] detailed a self-relay Rh(I)-catalyzed cascade reaction that systematically constructs two different sigma-donor/pi-acceptor ligands. This process results in the synthesis of intricate fused heterocyclic systems through relay-catalyzed nitrene transformations and a series of cyclization steps. This approach provided a straightforward and efficient strategy for assembling the pyrrolo-indole framework (**78** and **80**), which was an essential structural element present in many valuable natural products and pharmaceuticals (Scheme 43A and B). Moreover, authors evaluated the reactivity of isonitrile derivatives **77** and CO **79** (Scheme 43B). The findings demonstrated that isonitrile derivatives **77** exhibit greater reactivity compared to their isoelectronic counterpart **79**, whether in coupling reactions with azide derivatives or in aza-Pauson–Khand-type cyclization. The introduction of two different s-donor/π-acceptor ligands resulted in relatively lower yields compared to using two isonitrile derivatives. Variation in the electronic nature or positions at the phenyl ring of aryl azide derivatives did not remarkably affect reactivity, indicating limited influence of substituents. Aliphatic substituents illustrated little reactivity in the transformation, suggesting a limitation in substrate scope. The presence of unexpected side reactions was common in late transition-metal-catalyzed nitrene transformations, which could complicate the reaction outcomes.

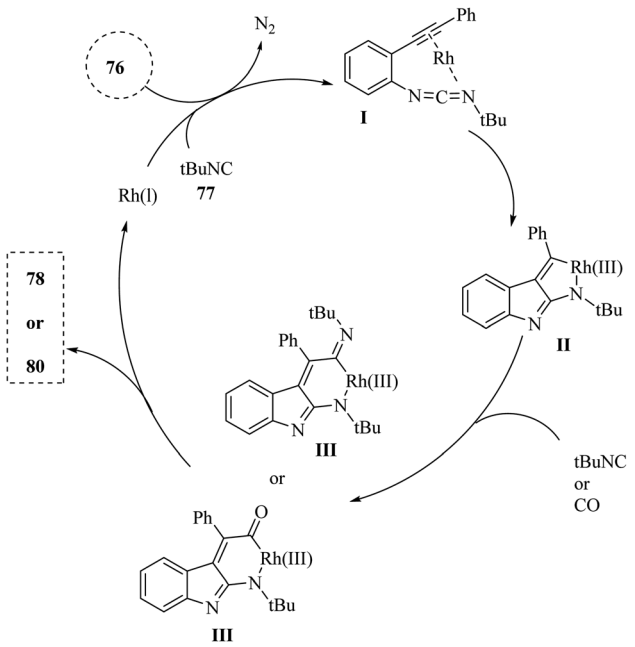
A mechanism underlying this transformation is depicted in Scheme 44. Initially, compound **76** and **77** are reacted and generated intermediate I along with release of N_2. Subsequently, Intermediate **I** has the capacity to generate a new intramolecular C–C bond, resulting in the formation of rhodacycle **II**. This is occurred through π-complexation with Rh(I) followed by an oxidative cyclometalation step. Subsequently, the introduction of an additional sigma-donor/pi-acceptor ligand, such as RCN or CO, into the Rh–C bond of **II** is facilitated the creation of rhodium complex **III**. Finally, the targeted derivatives (**78** and **80**) were synthesized *via* a reductive elimination process, which concurrently restored the active Rh(I) catalyst.[142]

2.2 Synthesis of quinolines

2.2.1 Au-catalyzed transformation. In 2013, Gronnier *et al.*[143] introduced a new synthetic procedure for the production of polysubstituted quinolone derivatives (**82**, **83**, and **83′**) from 2-alkynyl arylazide derivatives **81** (Scheme 45A and B). This innovative Au-catalysed transformation has proven to be highly efficient, demonstrating the ability to generate the desired products in CH_3CN at 80 °C while accommodating a diverse



Scheme 43 (A) Synthesis of pyrrolo-indole derivatives **78** with isonitriles **77**, (B) synthesis of pyrrolo-indoles **78** with isonitriles **77** and CO **79**.

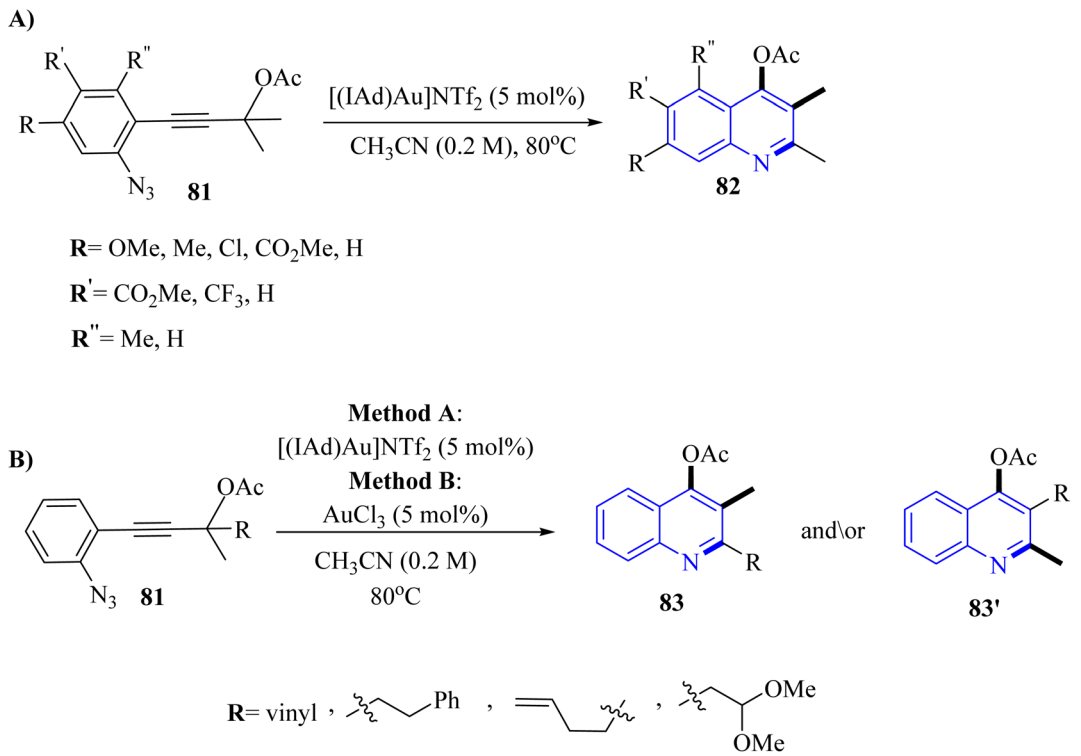


Scheme 44 A mechanism for the reactions of 2-alkynyl arylazide derivatives **76** with isonitrile derivatives **77** or CO **79** catalyzed by Rh.

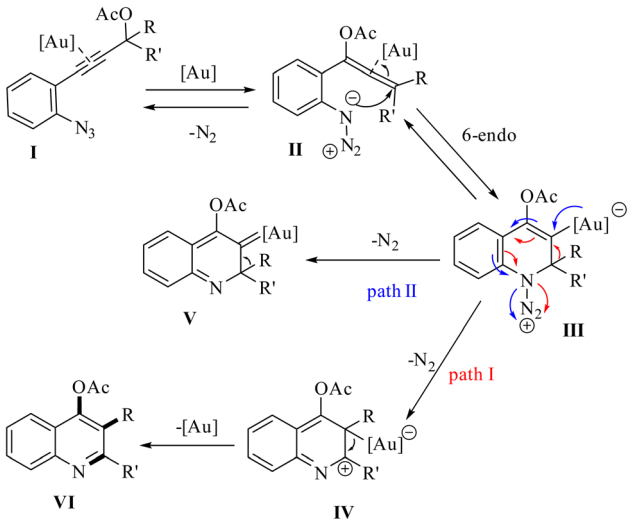
range of commonly employed functional groups. Remarkably, this process has yielded the desired products with yields of up to 99%. Two Au catalysts were investigated *via* the reaction namely $[(IAd)Au]NTf_2$ (A) and $AuCl_3$ (B). Initially, authors directed our attention toward derivatives of **81** (Scheme 45A), which featured a substitution on the aromatic nucleus. Regardless of the catalyst used (A and B), the reactions proceeded rapidly, yielding the corresponding quinolone derivatives. However, when a methyl group is positioned *ortho* to the alkynyl functionality, the reaction proceeds more slowly. In this specific case, the reaction can only be carried out using catalyst **A** (Scheme 45A). In these investigations concerning 1,2-group shift selectivity, one substituent remained consistently Me, while the other was subject to variation (Scheme 45B). Experimental evidence indicated that the Me group illustrated lower migratory aptitude compared to functionalized alkyl groups or a vinyl residue. Interestingly, more selective transformations occurred when **B** serves as the catalyst. Degradation of $AuCl_3$ was observed at high temperatures. No reaction was occurred at low temperatures with $AuCl_3$. Selectivity differences in reactions remained unexplained.

A mechanism underlying this transformation is depicted in Scheme 46. Initially, when compound **81** is treated with an Au catalyst, substrate **I** is anticipated to experience a more favorable 1,3-acetoxy shift, leading to the generation of allene **II**. Next, the azide's nucleophilic addition to the Au-activated species. This resulted in the formation of a cyclized intermediate (referred to as intermediate **III**). Subsequently, *via* a 1,2-shift of the R′ group and the catalyst's regeneration, this intermediate is evolved into quinoline **VI**. Finally, cationic intermediate **IV** could be generated *via* 2 pathways. Path I: could be generated from **III**, and path II: could be produced through an Au carbenoid of type **V** (path II).[143]

2.2.2 Cu-catalyzed transformation. Shen *et al.*[129] documented a Cu-catalysed oxidative cyclization of diyne derivatives, facilitating the direct synthesis of valuable derivatives of pyrrolo

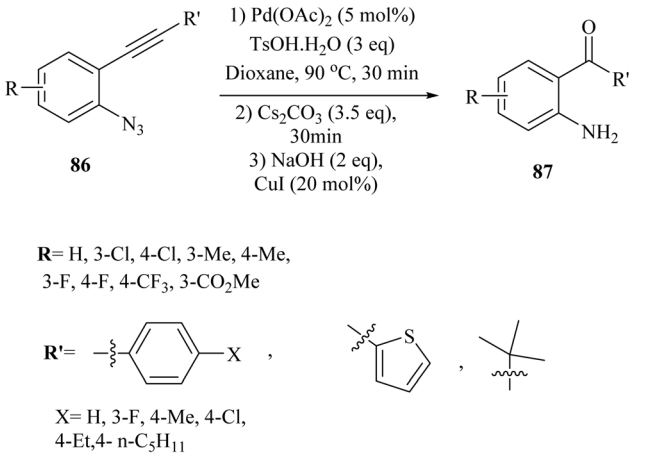


Scheme 45 (A) Scope of aryl substitution, (B) scope of 1,2-group shift selectivity.



Scheme 46 A mechanism for the gold-catalyzed transformation of **81** into polysubstituted quinolones.

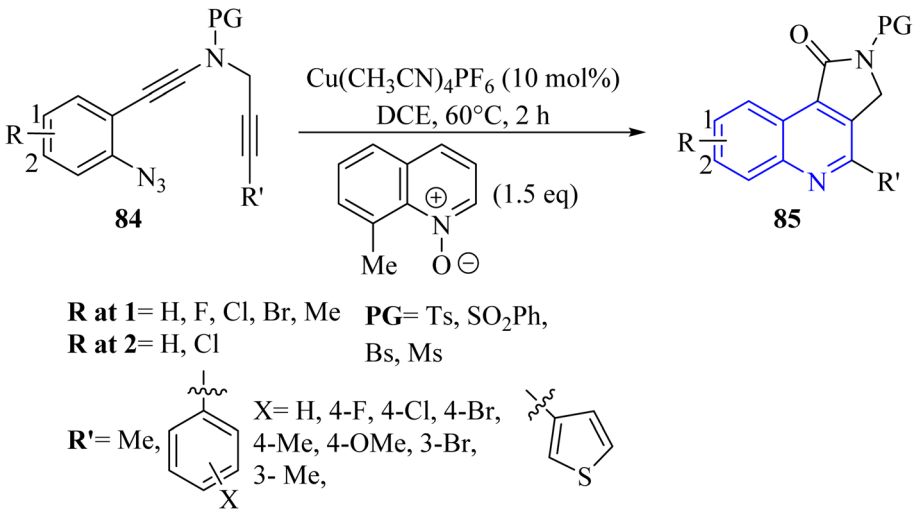
[3,4-*c*]quinolin-1-one **85** (up to 94% yield) (Scheme 47). The research was highlighted a lack of reported non-noble metal-catalyzed reactions for diyne oxidations, indicating a gap in the exploration of alternative catalysts beyond noble metals. In the case of **85**, the method demonstrated efficient performance for a range of aryl-substituted ynamide derivatives **84**, which carried both electron-donating and -withdrawing groups. However, no the corresponding product was detected when using alkyl-substituted ynamide. Significantly, there was no formation of diketone through dual oxidation using the same oxidant in any of the cases. One challenge was that the generated vinyl metal carbene was highly reactive and prone to overoxidation by the same oxidant, leading to side reactions. Another challenge arised from the azido group, which may directly attack the ynamide, initiating alkyne amination *via* a presumed α-imino metal carbene pathway. These competing reactions complicated the selective formation of the corresponding products in the Cu-catalyzed oxidative diyne cyclization.



Scheme 48 Synthesis of 2-aminobenzophenone derivatives **87**.

2.3 Synthesis of 2-aminobenzophenones (bimetallic (Pd/Cu)-catalyzed transformation)

In the year 2021, Yang *et al.*[144] presented a new and innovative process involving a single-step, three-part reaction of 2-alkynyl arylazide derivatives **86**. The study was discussed the partial hydrolysis of the ester group under basic reaction conditions as a limitation, which affected the yield of the corresponding product. This process entailed the Pd-catalysed generation of 3-hydroxy-3-phenylindolin-2-one derivatives, followed by the hydrolysis of amide bonds and Cu-catalysed decarboxylation, resulting in the production of 2-aminobenzophenone derivatives **87** (Scheme 48). The reaction done when accompanied by Cs_2CO_3 and NaOH in 1,4-dioxane at 90 °C. The findings from this study revealed that the reaction was capable of accommodating a wide variety of structurally diverse **86**, with yields of up to 90%. However, when the reaction was repeated using



Scheme 47 Synthesis of pyrrolo-quinolin-1-one derivatives **85**.

a substrate containing a steric hindered group (R′ = *t*-Bu), the desired product was not obtained, leading only to the formation of an acyloin rearrangement product with a yield of 76%. It should be noted that the reaction's yield was remarkably impacted by the use of a radical scavenger, indicating that a radical process might be involved, which complicates the reaction mechanism.

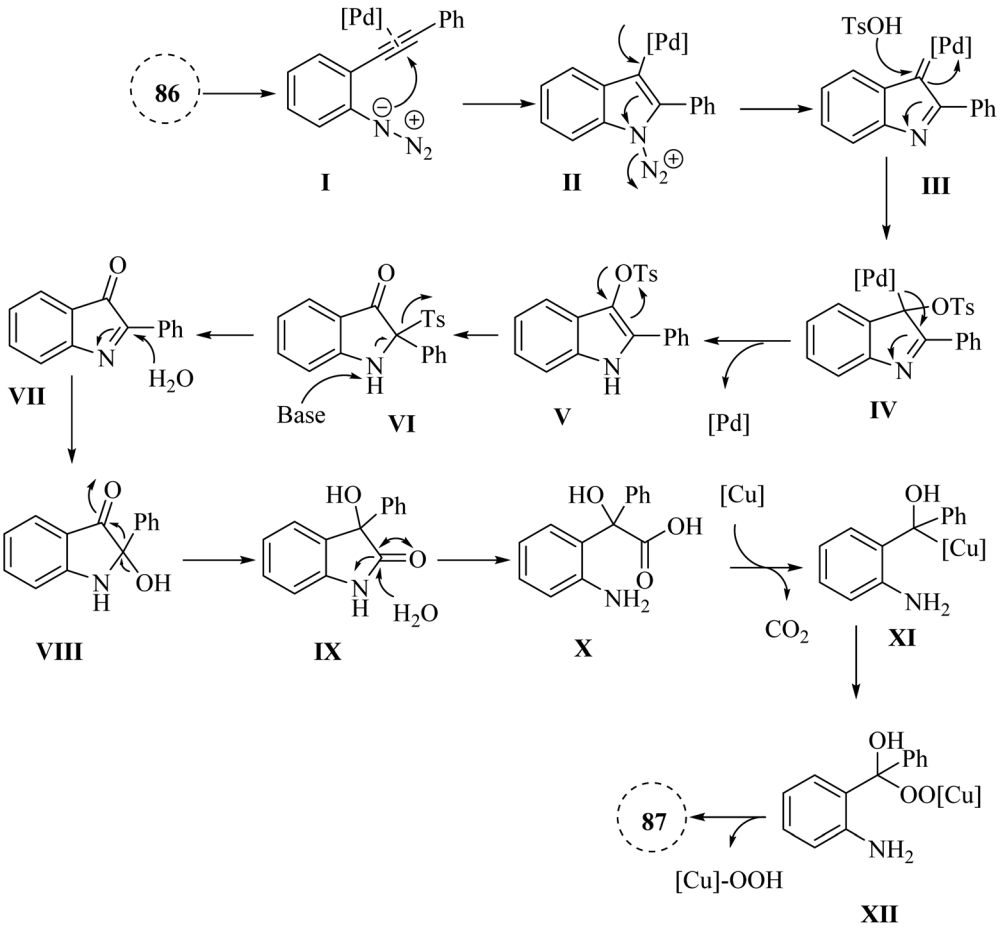
A mechanism underlying this transformation is depicted in Scheme 49. Initially, alpha-imino Pd carbene **III** is generated from **87** which is activated by Pd catalyst. Then, **III** is attacked by $TsOH \cdot H_2O$ and produced complex **IV**. Next, intermediate **V** is obtained from a rearrangement of **IV** and also Pd catalyst is regenerated. After a 1,3-Ts shift process, **VI** is formed from **V** in the presence of Cs_2CO_3. After that, **VII** is produced *via* a reductive desulfonation of **VI**. Then, **VIII** is formed *via* a hydrolysis of C=N bond of **VII**. In the following, an acyloin rearrangement to give **IX**. Next, **X** is formed *via* a hydrolysis of amide bond of **IX**. After that, **XI** is generated *via* a Cu-catalysed decarboxylation of **X**. Finally, it is oxidized to product **87**.[144]

3. 2-Alkynylbenzyl azides

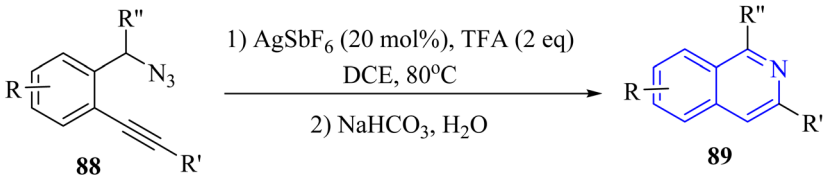
3.1 Synthesis of quinolines

3.1.1 Ag-catalyzed transformation. In 2009, Niu *et al.*[97] developed a new and effective technique for creating substituted isoquinoline derivatives **89** (Scheme 50). The authors indicated ongoing efforts to apply the Ag-catalyzed cyclization methodology for synthesizing natural alkaloids and pharmaceutical compounds, suggesting a gap in the exploration of these applications. This method involved an Ag-catalysed ($AgSbF_6$) cyclization of 2-alkynyl benzyl azide derivatives **88** using TFA, in the presence $NaHCO_3$ in DCE at 80 °C. The derivatives of **89** were produced in yields ranging from 31% to 85%. The yield of the products was only minimally affected by the position of the substituent on R′. Cyclization was continued to occur even when an alkyl group substitutes the end of the C–C triple bond. Only the six-membered-ring isoquinoline resulting from 6-*endo*-dig cyclization was produced, and TLC monitoring showed no presence of a 5-membered exocyclic product in the reaction mixture (Scheme 51 pathway B). Reduced yields were observed with lower catalyst loading. It should be noted that solvent coordination can decrease Ag catalyst activity. Required to further investigation into the role of TFA in the reaction, as its effect on yield was uncertain. The research highlighted that while Ag catalysts had potential, they were often considered less efficient than other late transition metals, indicating a gap in optimizing Ag catalysts for better performance.

A mechanism underlying this transformation is depicted in Scheme 51. The Ag catalyst is coordinated with the alkynyl



Scheme 49 A mechanism for the reactions of 2-alkynyl arylazide derivatives **86** and transformed into **87** catalyzed by Pd and Cu.



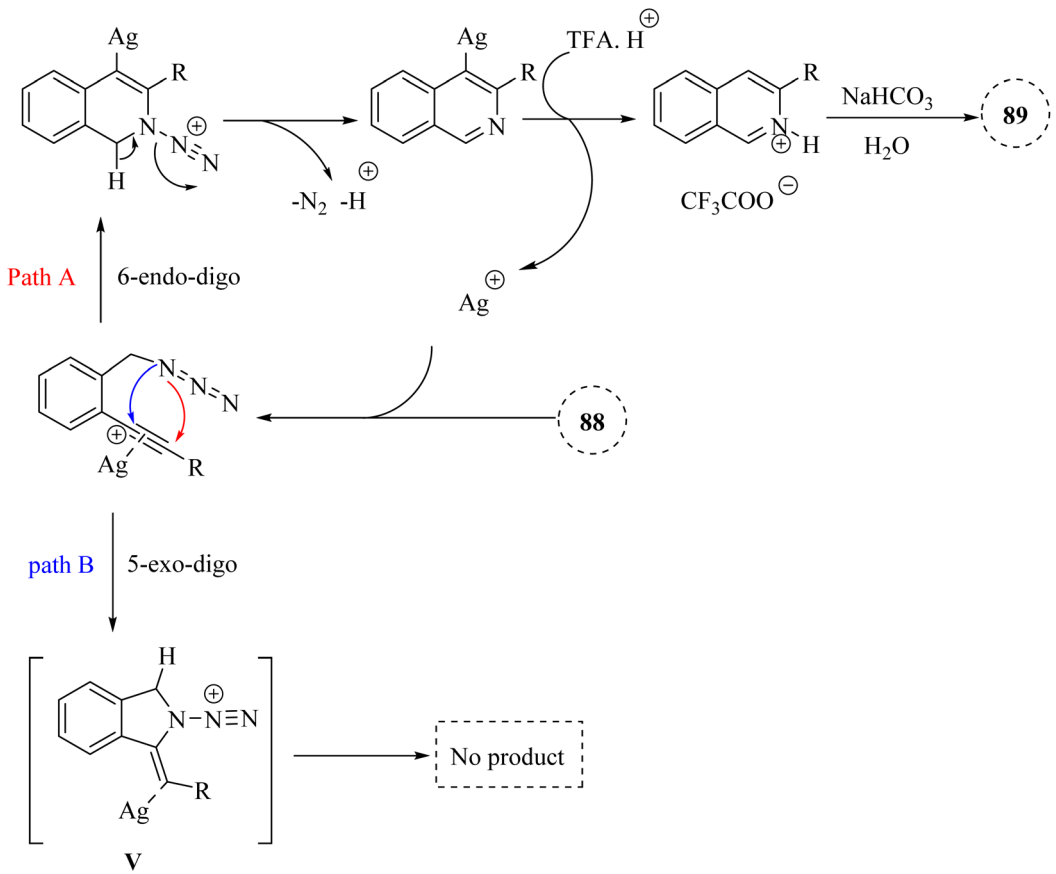
R= 3-Me, Cl, H **R'**= Et, Ph, Bu, H

R''= Ph, 4-$CH_3C_6H_4$, 3-$CH_3C_6H_4$, 2-$CH_3C_6H_4$, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-$CH_3COC_6H_4$, 4-$CH_3OOCC_6H_4$, pentyl

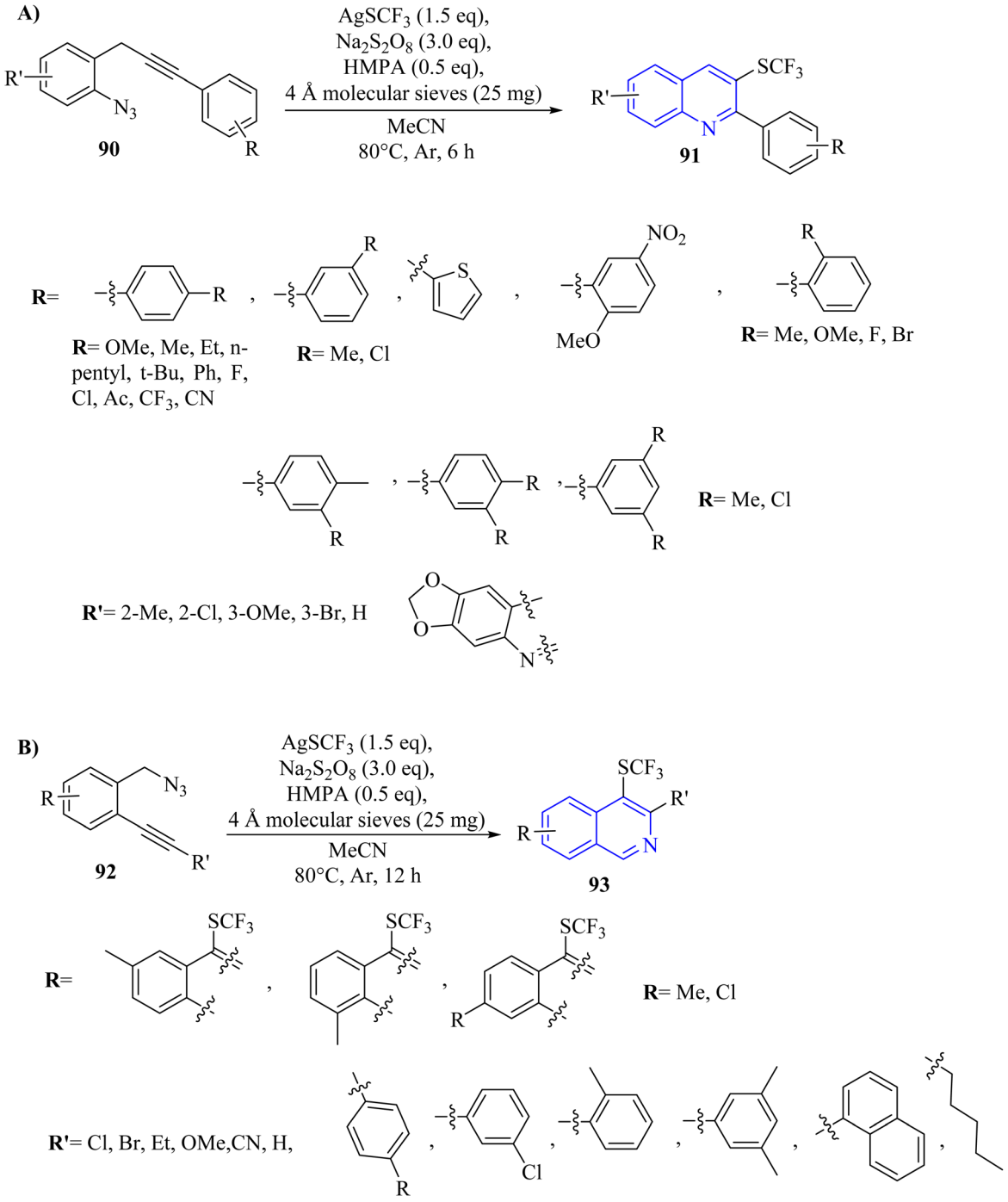
Scheme 50 Synthesis of isoquinoline derivatives **89**.

group of **88** to forms complex **I.** Then, the nitrogen atom selectively is targeted the electron-deficient triple bonds through a 6-endodig cyclization process, resulting in the formation of **II.** Next, **II** is released N_2 and H^+, resulting in the formation of **III.** After that, **III** is reacted with TFA and H^+, producing **IV** and regenerating the Ag catalyst for the next catalytic cycle. Lastly, the desired product **89** is obtained *via* the reaction between **IV** and saturated $NaHCO_3$. The research did not extensively cover the mechanistic details of the cyclization process, which could be explored further.[97]

A method involving $AgSCF_3$ and $Na_2S_2O_8$ promoted trifluoromethylthiolation and cascade cyclization of *ortho*-propargyl arylazide derivatives (or *ortho*-alkynyl benzylazide derivatives **90**) initiated by a C–C triple bond. This approach enabled the synthesis of valuable SCF_3-substituted quinolone **91** (Scheme 52A) and isoquinoline **93** (Scheme 52B) compounds by forming one C(sp^2)–SCF_3 bond and one C–N bond in a single process.[145] Trifluoromethylthio-substituted quinolone derivatives **91** were obtained in 47–89% yields from *o*-propargyl arylazide derivatives **90.** The steric effect at the *ortho* position had



Scheme 51 A mechanism for the reactions of 2-alkynyl benzyl azide derivatives **88** and their transformation into isoquinoline **89** catalyzed by Ag.



Scheme 52 (A) Synthesis of quinolone **91**, (B) synthesis of isoquinoline **93**.

minimal impact on this transformation. Overall, substituents with different electronic effects were well-compatible. The product with an *ortho*-Me group was detected in trace amounts due to the steric effect of the *ortho* substituent. Typically, this transformation illustrated comparable electronic and steric effects to those seen with opropargyl arylazide substrates. In this section, TLC analyses revealed an increase in byproducts, possibly resulting from the SCF_3 radical's insufficiently selective addition to the C–C triple bond of the substrate. The substrate containing an alkyl group failed to produce the desired product. There were some challenges and limitations about the reaction such as (1) poor solubility was affected NMR spectrum acquisition, (2) inadequate acquisition time led to doublet peak in NMR, and (3) reaction system scalability was posed challenges in product yield.

A mechanism underlying this transformation is depicted in Scheme 53. The SCF_3 radical is produced *via* the oxidation of $AgSCF_3$ by $Na_2S_2O_8$, which then added to the C–C triple bond of

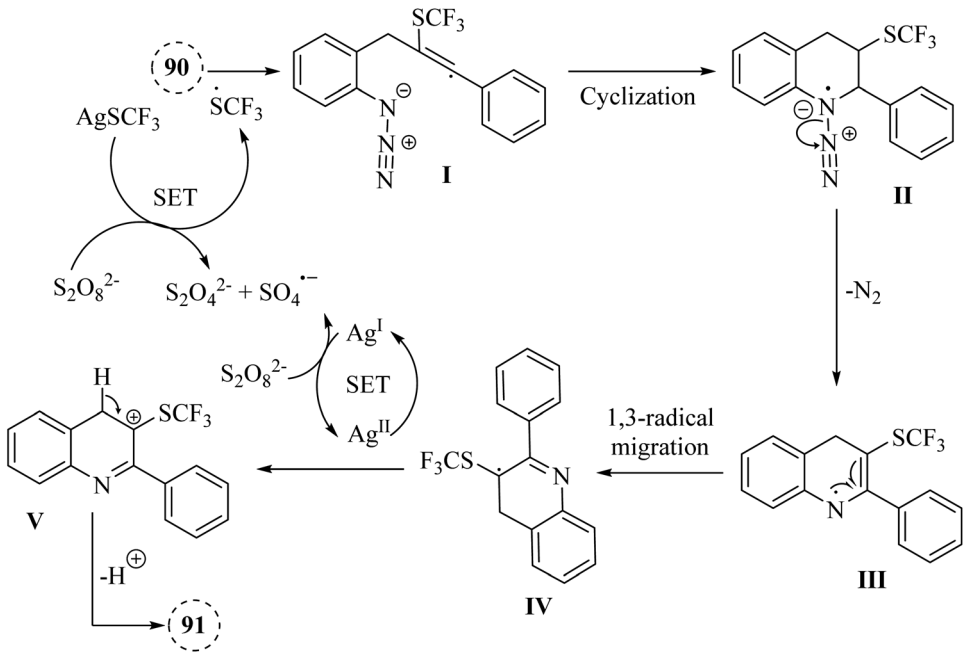
substrate **91**, forming **I**. Then, radical anion intermediate **II** is generated from **I** *via* the subsequent 6-*endo*-dig cyclization process. In the following, **II** is released N_2 and formed nitrogen radical intermediate **III**. Next, carbon radical intermediate **IV** is generated through a 1,3-radical migration of **III**, which is experienced an additional SET process, transitioning from **IV** to the Ag(II) species, resulting in the formation of the desired product **92**. There is a need for further exploration of the reaction mechanisms involved, particularly the radical pathways that govern these transformations, as indicated by control experiments showing inhibition with specific additive.[145]

3.1.2 Au-catalyzed transformation. In 2016, Pan and colleagues[146] devised a streamlined and pragmatic approach for synthesizing a variety of fused isoquinoline derivatives **95** through an alpha-imino Au carbene intermediate (Scheme 54). The study noted the challenges in extending the reaction to tandem alkyne amination-intramolecular N–H insertion, which resulted in a complicated mixture of products without obtaining the corresponding isoquinoline. This method was significant for its ability to construct fused six-membered rings in a singular step, showcasing the efficacy of the Au-catalysed tandem sequence. The reaction took place in DCE at 80 °C. The research highlighted the limitation of existing cyclization methods, which require quenching by an electrophile, restricting the position 4 of the produced isoquinoline to only hydrogen or halogen. This method was also characterized by its use of easily obtainable starting materials, its high adaptability, and its straightforward process. The derivatives of **95** were obtained in yields ranging from 68% to 95%. Efforts to synthesize ynamide derivatives **94** using Boc and Ac groups were unsuccessful, likely because these protecting groups are too unstable. It should be noted that triazole formation was not detected in any of the instances.

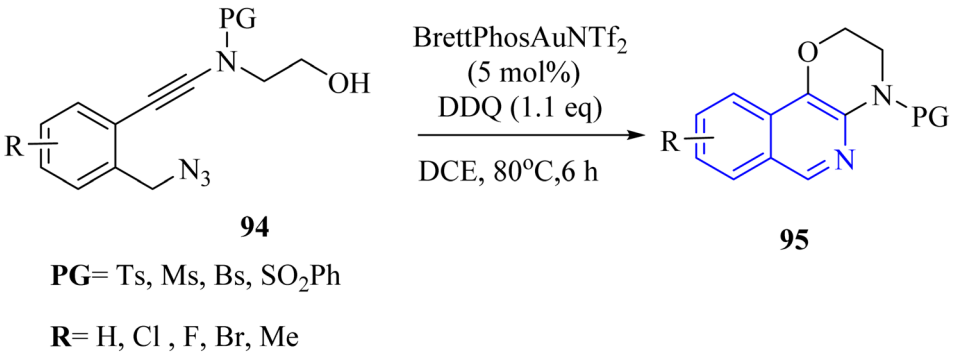
A mechanism underlying this transformation is depicted in Scheme 55. The process began with the Au-catalysed nucleophilic addition of the azide to the alkyne group, which is then followed by the release of N_2, resulting in the formation of the crucial alpha-imino Au carbene intermediate **II**. The next step is involved the OH group intramolecularly trapping the alpha-imino Au carbenoid, forming **III**. This intermediate then undergoes proton transfer, deauration, and dehydrogenative oxidation, ultimately producing the desired product **95**.[146]

3.1.3 Bimetallic (Au/Ag)-catalyzed transformation. 2-Alkynyl benzyl azide derivatives **96** underwent intramolecular cyclization with $AuCl_3$ and $AgSbF_6$ in THF at 100 °C in a pressurized vial, authors produced isoquinoline derivatives **97** up to 80% yields (Scheme 56).[147] The **97** yielded from secondary azide derivatives were lower compared to those from primary azide derivatives. The yields of the derivatives **97** were lower for five-membered heterocyclic derivatives compared to their six-membered counterparts. The authors also noted that secondary azide derivatives yield lower amounts of isoquinoline derivatives compared to primary azide derivatives, presenting a challenge in achieving corresponding product yields. The research indicated a need for the development of additional synthetic techniques for isoquinoline derivatives, as existing techniques have considerable drawbacks such as the use of strong acids and elevated temperatures.

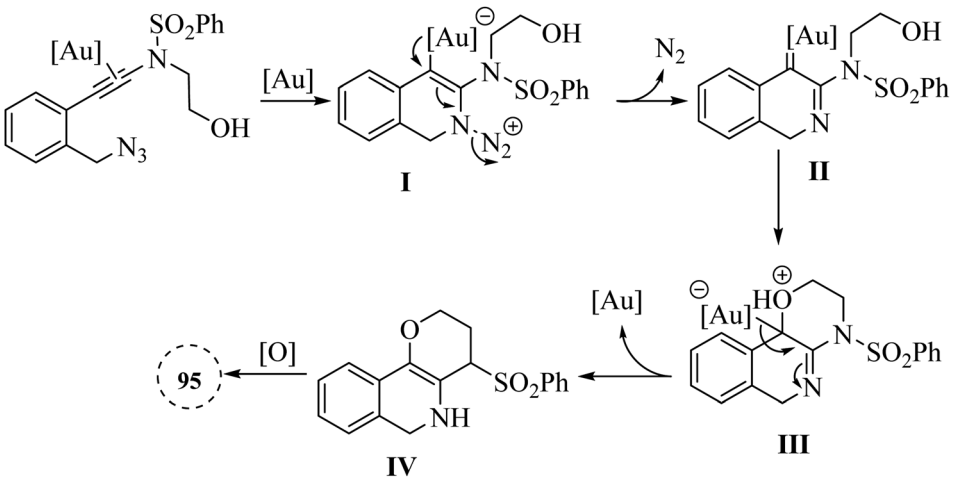
A mechanism underlying this transformation is depicted in Scheme 57. First, the triple bond of compound **96** is coordinated with the Au catalyst, increasing the alkyne's electrophilicity and forming intermediate **I**. Then, the nitrogen atom is performed a nucleophilic attack on the electron-deficient



Scheme 53 A mechanism for the $AgSCF_3$ and $Na_2S_2O_8$ promoted trifluoromethylthiolation and cascade cyclization of *ortho*-propargyl arylazide derivatives **90**.



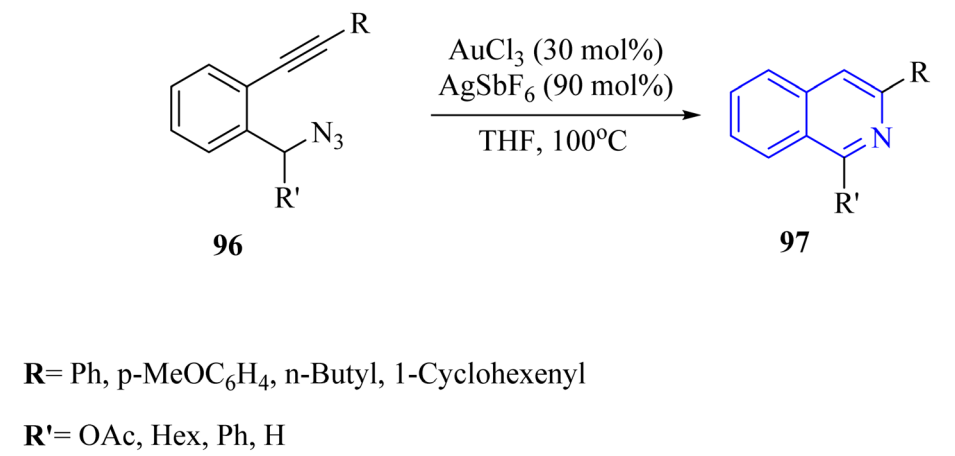
Scheme 54 Synthesis of fused isoquinoline derivatives **95**.



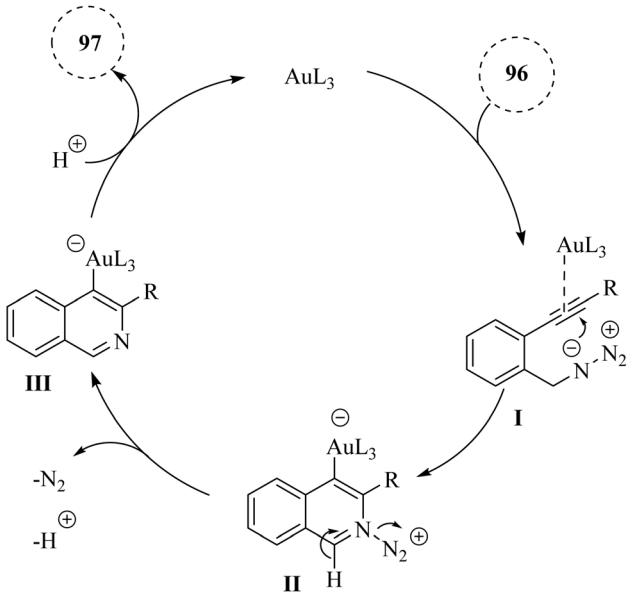
Scheme 55 A mechanism for the reaction of ynamide derivatives **94** and their transformation into **95** catalyzed by Au.

alkyne, resulting in the formation of intermediate **II**. Compound **III** is generated *via* the removal of N_2 and H^+. The protonolysis of **III** then leads to the creation of the corresponding product **97** and restored the desired catalyst.[147]

3.1.4 Pd-catalyzed transformation. 2-Alkynyl benzyl azide derivatives **98** underwent a palladium-catalysed electrocyclic reaction, selectively yielding either 4-bromoisoquinoline derivatives **99** and 4-bromoisoquinolone derivatives **101** under varying conditions (Scheme 58).[148] The authors noted the absence of efficient synthesis methods for 4-bromoisoquinoline derivatives and 4-bromoisoquinolin-1(2*H*)-one derivatives using 2-alkynyl benzyl azide derivatives, highlighting a need for



Scheme 56 Synthesis of isoquinoline derivatives **97**.

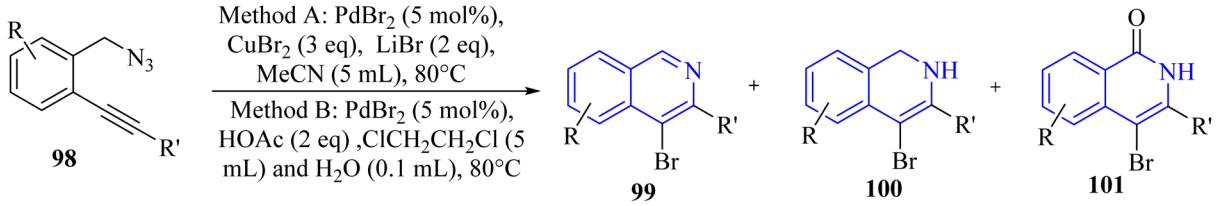


Scheme 57 A mechanism for the reaction of 2-alkynyl benzyl azide derivatives **96** and their transformation into **97** catalyzed by Au and Ag.

further exploration in this area. **99** was synthesized using $PdBr_2$/$CuBr_2$/LiBr in MeCN, while **101** was selectively produced with $PdBr_2$/$CuBr_2$/HOAc in CH_2ClCH_2Cl. It should be noted that effects of different substituents on reaction selectivity require more comprehensive investigation to optimize yields.

A novel and selective approach for synthesizing 4-haloisoquinoline derivatives **103** involved halopalladation cyclizations of alkyne derivatives with azide derivatives (Scheme 59).[140] Using PdX_2 (X = Cl or Br) and halide sources, various 2-alkynyl benzyl azide derivatives **102** efficiently underwent the halopalladation cyclization reaction, resulting in the formation of haloisoquinoline derivatives **103** (Scheme 59). Various derivatives of **102** were smoothly converted into the corresponding **103** derivatives (up to 77% yield) by treating them with $CuCl_2$, $PdCl_2$, and Cy_2NCl (method A). The authors discovered that substrates featuring an electron-donating aryl group at the terminal alkyne were favorably accepted, whereas those containing a NO_2 group were rendered inactive. The bromopalladation annulation of certain azide derivatives was performed under standard conditions B, which include $CuBr_2$, $PdBr_2$, and LiBr. There was a mention of ongoing efforts to extend the application of the developed protocol in organic synthesis, suggesting that its versatility and potential uses are not fully realized.

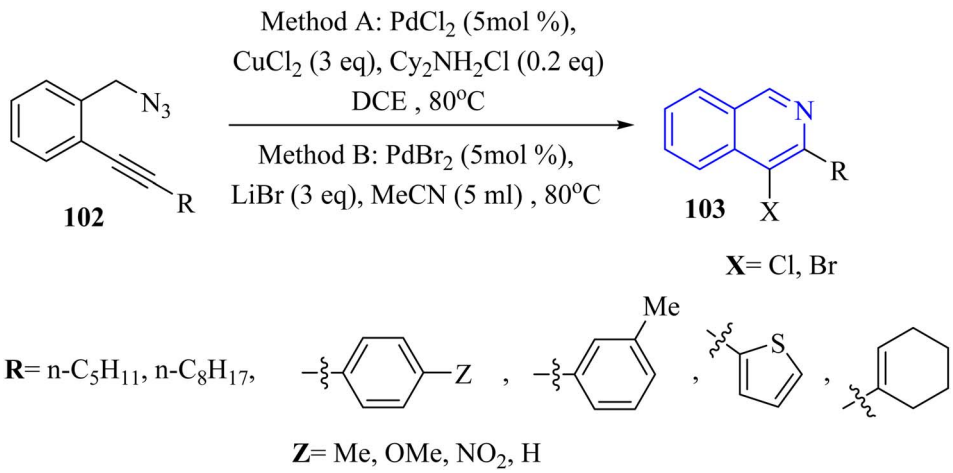
A mechanism underlying this transformation is depicted in Scheme 60. Initially, intermediate **I** is generated *via* the coordination of PdX_2 with an alkyne. Then, intermediate **II** is formed from **I** by halopalladation of alkyne. Next, intermediate



R= 3-MeO, 3,4-dimethoxy

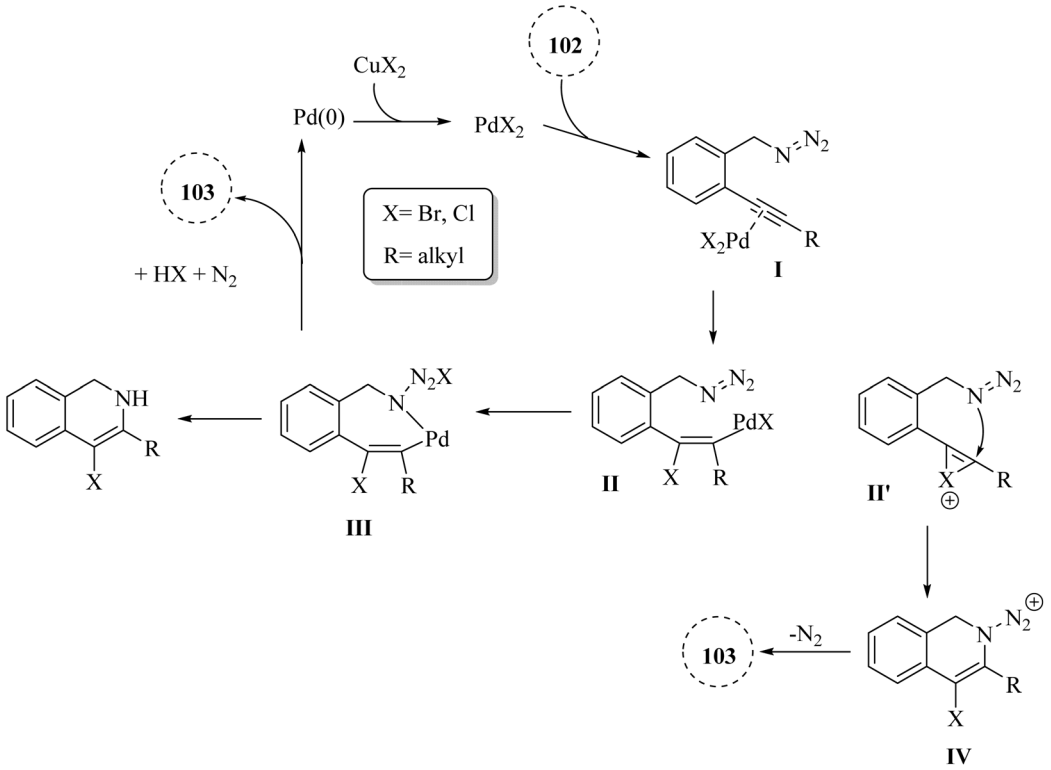
R'= o-MeC_6H_4, p-$MeOC_6H_4$, p-$NO_2C_6H_4$, 2-thiophene, C_6H_5, n-C_8H_{17}, n-C_5H_{11}, 1-cyclohexenyl

Scheme 58 Synthesis of bromoisoquinoline and bromoisoquinolone.



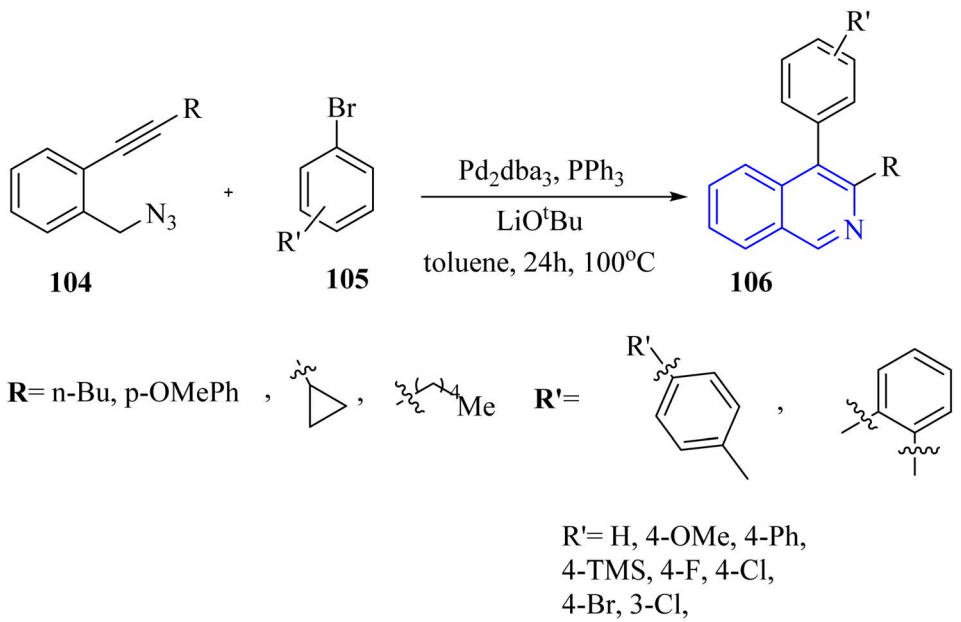
Z= Me, OMe, NO_2, H

Scheme 59 Synthesis of 4-haloisoquinoline derivatives **103**.



Scheme 60 A mechanism for the reaction of 2-alkynyl benzyl azide derivatives **102** and their transformation into **103** catalyzed by Pd.

III is produced *via* the reaction of the N–N double bond with Pd within the **II**. The corresponding product, along with N_2 and Pd(0) species, is formed through the reductive elimination and deprotonation of **III**. The active Pd(II)X_2 species are reformed by oxidizing Pd(0) with CuX_2, initiating a new catalytic cycle. It's also possible that the **103** is formed through a different mechanism: the halonium intermediate **II′** is swiftly generated from **I** with the assistance of a Pd catalyst, subsequently undergoing addition and elimination processes to produce compound **103**. The authors illustrated that further studies are needed to explore the mechanism of the halopalladation cyclization process, which remains an area of active investigation.[140]



Scheme 61 Synthesis of isoquinoline **106**.

In 2016, Zhou *et al.*[136] reported the development of a Pd-catalyzed synthesis method for the production of poly-substituted isoquinoline derivatives **106**. This method involved the coupling of aryl bromide derivatives **105** with 2-alkynyl benzylazide derivatives **104** (Scheme 61). The reaction was conducted in the presence of LiOtBu, Pd_2dba_3, and PPh_3 in toluene at 100 °C for generated **106**. The results of this process were significant, with the aryl bromide products being generated the **106** products yielding between 47% and 85%.

4 Conclusions

Advances in various metal-catalyzed transformations in the synthesis of quinoline and indole derivatives emphasize the efficiency and versatility of these methods in organic synthesis, especially those involving Pd and Au as well as their bimetallic compounds. 2-Alkynyl benzyl azide derivatives and 2-alkynyl aryl azide derivatives were innovative substrates that can facilitate complex molecules by imposing significant functional groups and high yields.

Reactions catalyzed by Au recognized for their ability to produce electrophilic intermediates and promote regioselective transformations, especially in the production of indole derivatives such as aryl-fused carbazole derivatives and indolinone derivatives. According to the explained mechanisms, it can be concluded that the Au carbene intermediates were very important and fundamental and showed the effect of the electronic properties of the substrate on the results.

On the other hand, the reactions catalyzed by Pd was showed high efficiency in the synthesis of polysubstituted isoquinoline derivatives and indole derivatives *via* electrocyclic processes. Also, the integration of two metals, Ag and Cu, has led to the development of the synthetic toolbox and thus the synthesis of complex heterocycles using the development of new methods.

By examining the studies, we can gain a better understanding of metal-catalyzed transformations and pave the way for future research aimed at synthesizing bioactive compounds and substances with various applications such as materials science and pharmaceuticals. It should be noted that the selectivity and efficiency of these synthetic strategies increases with the continuous exploration of reaction conditions, synthetic and mechanical pathways, and substrate Scope, and causes extensive innovations in the field of organic chemistry.

5 Future remarks

According to the studies and progress presented in this study on the synthesis of quinoline and indole derivatives vai metal-catalyzed transformations, several directions for further increase in the field of organic synthesis in the future can be imagined.

First of all, it is necessary to explore metal catalysts beyond gold and palladium, because it creates new reaction pathways. Meanwhile, other transition metals, particularly Co and Ni, may offer unique reactivity profiles that are effective in the synthesis of complex heterocycles. On the other hand, as shown in some studies, the use of bimetallic catalytic systems promises synergistic effects that can increase the selectivity and efficiency of reactions.

Secondly, it should be considered that the principles of green chemistry should be prioritized in this synthetic methodology, such as the use of green solvents, green synthetic techniques and reducing waste, which can greatly increase the stability of these reactions. Also, in terms of synthetic techniques, we can mention the use of microwaves or synthesis with the help of ultrasonic waves, which reduces reaction time and increases efficiency, and also makes these processes more practical for industrial applications. Due to the mechanistic insight obtained from the current studies, it has paved the way for the rational design of new catalysts and reaction conditions. Future research could focus on computational modeling of reaction mechanisms to obtain prediction of results as well as optimization of conditions before conducting experimental studies. This insight could reduce trial and error and enable the development of new synthetic routes.

In the last stage, the research should move towards the investigation and biological evaluation of the synthesized compounds, because the investigation of the medicinal properties of new quinoline and indole derivatives leads to the discovery of new drugs. It should be noted that interdisciplinary collaboration with medicinal, organic chemists and biologists is necessary to convert these synthetic advances into practical applications.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Author contributions

Seyedmohammad Hosseininezhad: project administration, conceptualization, idea maker, writing – original draft, writing – review & editing Sina Pirani Ahmad Abad: writing – review & editing Ali Ramazani: project administration, investigation, conceptualization.

Conflicts of interest

There are no conflicts to declare.

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