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Review

[RhCp*Cl_2]$_2$-Catalyzed Indole Functionalization: Synthesis of Bioinspired Indole-Fused Polycycles

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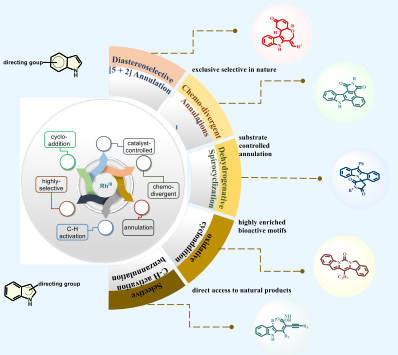
ABSTRACT: Polycyclic fused indoles are ubiquitous in natural products and pharmaceuticals due to their immense structural diversity and biological inference, making them suitable for charting broader chemical space. Indole-based polycycles continue to be fascinating as well as challenging targets for synthetic fabrication because of their characteristic structural frameworks possessing biologically intriguing compounds of both natural and synthetic origin. As a result, an assortment of new chemical processes and catalytic routes has been established to provide unified access to these skeletons in a very efficient and selective manner. Transition-metal-catalyzed processes, in particular from rhodium(III), are widely used in synthetic endeavors to increase molecular complexity efficiently. In recent years, this has resulted in significant progress in reaching molecular scaffolds with enormous biological activity based on core indole skeletons. Additionally, Rh(III)-catalyzed direct C−H functionalization and benzannulation protocols of indole moieties were one of the most alluring synthetic techniques to generate indole-fused polycyclic molecules efficiently. This review sheds light on recent developments toward synthesizing fused indoles by cascade annulation methods using Rh(III)-[RhCp*Cl_2]$_2$-catalyzed pathways, which align with the comprehensive and sophisticated developments in the field of Rh(III)-catalyzed indole functionalization. Here, we looked at a few intriguing cascade-based synthetic designs catalyzed by Rh(III) that produced elaborate frameworks inspired by indole bioactivity. The review also strongly emphasizes mechanistic insights for reaching 1−2, 2−3, and 3−4-fused indole systems, focusing on Rh(III)-catalyzed routes. With an emphasis on synthetic efficiency and product diversity, synthetic methods of chosen polycyclic carbocycles and heterocycles with at least three fused, bridged, or spiro cages are reviewed. The newly created synthesis concepts or toolkits for accessing diazepine, indol-ones, carbazoles, and benzo-indoles, as well as illustrative privileged synthetic techniques, are included in the featured collection.



1. INTRODUCTION

About 140 years ago, Adolf Baeyer discovered and elucidated the structure of a heteroaromatic molecule, "indole", giving it the trivial name benzo[*b*]pyrrole.[1,2] This discovery and elucidation revolutionized organic chemistry and synthetic endeavors enormously. Since then, indole and its derivatives have earned a coveted position among heterocycles in organic chemistry and the synthesis of natural products. So far, organic chemists have paid great attention to indole and the intriguing occurrence of indole derivatives, as well as polycyclic analogues in natural products and bioinspired moieties.[3,4] The prevalence of indoles in pharmaceuticals, agrochemicals, and functional materials is evidence of growing interest in developing safe and effective synthetic pathways to functionalize indole polycycles.[5,6] Additionally, when the indole alkaloid "reserpine" was initially identified as one of the first medicines for treating anxiety and mental illnesses in the middle of the 1950s, indole chemistry, in particular, attracted a lot of attention.[7,8] Indolyl-based anticancer "vincristine", which was proven helpful for various physiological actions, including anti-inflammatory and anti-hypertensive activities, was later identified in late 1960.[9−11] Although they are still being thoroughly researched, structurally related carbazoles, bridging carbocycles, oxepanes, and other compounds with widespread use in organic synthesis and materials, deserve to be mentioned.[12] Indoles are broadly distributed in preferred pharmacophores against a variety of targets with enormous activity, including anticancer (Panobinostat), antihypertensive (e.g., Pindolol), and anti-inflammatory (e.g., Indomethacin).[13−15] The most significant indole-embedded scaffolds, which are also functional cores for additional modifications and possible therapeutic possibilities, are presented in Figure 1.

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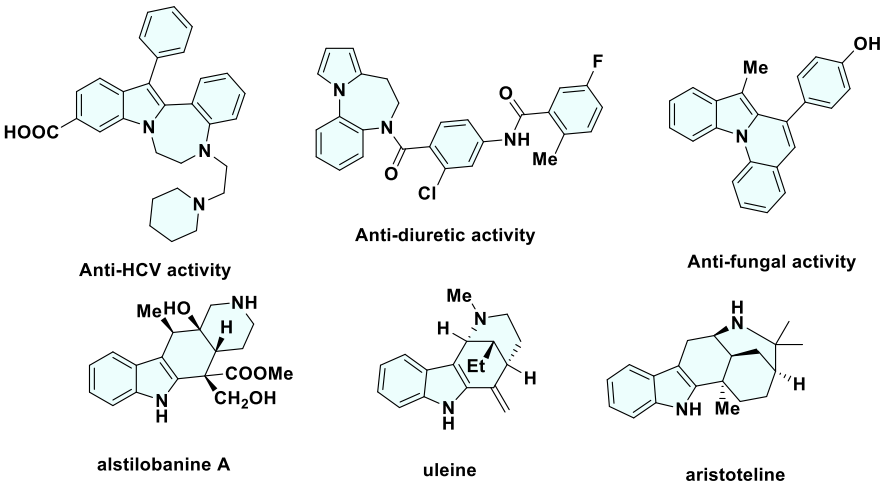

Figure 1. Biologically important indole core.

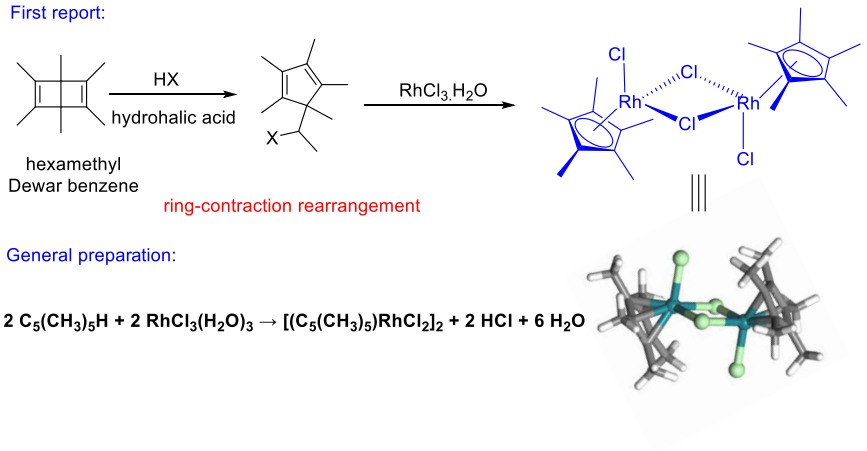

Figure 2. Synthesis and structural properties of $[Cp^*RhCl_2]_2$.

Indole has a distinctive electron-rich aromatic behavior compared to benzene, which leads to increased reactivity toward the electrophilic aromatic substitution reaction and the advantageous introduction of various functional group modifications in the core. Indole synthesis and functionalization have gained significant attention for over a century, and several methods for preparing them have been established.[16,17] The availability of promising starting materials and comprehensive and acceptable functional group tolerance are critical components of most synthetic techniques. As a result, synthesizing the indole core and its late-stage functionalization have shown exponential growth and extensive pioneering discoveries. By the end of 2023, several unique chemical alterations and late-stage functionalization of the pertinent indole core will be needed to accomplish these aims with sustainability and efficiency as the main priorities. Various innovative strategies, including homogeneous−heterogeneous catalysis, will be essential to achieving these goals. The enormous structural diversity and complexity of pharmacologically active indole-functionalized derivatives constitute a promising challenge for developing direct and selective synthesis.[18−20]

The functionalization of indole merely depends on the electron density and availability of the reactive site. In general, C-3 functionalization is quite straightforward, typically based on the Friedel−Craft reactions; conversely, the C-2 functionalization requires a feature assisted by either a group adjacent to the C-2 position or a protecting group present on the nitrogen (need of directing group in the pertinent core).[21−23] Additional functionalization of an adjacent benzene ring requires directing group assistance (directing group) or more promising C−H activation via transition metal catalysis pathways.[24,25] Recent studies are based on the refinements of transition metal catalysis pathways that allow rapid access to various positional selectivity.[26,27] Most recently discovered approaches depend on photoredox and transition-metal-catalyzed pathways to produce regio- and chemoselective transformations. After the discovery of the parent core, the initial studies revolved around synthesizing the core skeletal system; nevertheless, more recent progress focuses on functionalizing the parent core to create biologically pertinent scaffolds using advanced synthetic procedures, including photoredox/transition metal catalysis.[28] Recently, transition metals like Pd, Rh, Ru, and others have been used with a variety of directing group associations, such as carbonyls, sulfones, amides, etc.[29−31] The construction of a pyrrole ring and incorporation of a benzene ring in an existing pyrrole core fall under two major categories: synthesis and functionalization of indoles.[32] Numerous techniques exist for functionalizing indole, but the best-known synthetic approaches with the most significant contributions are Fischer−Jourdan, Madelung, Batcho−Leimgruber, and Gassman.[33−35] However, some exceptions render the prominent growth in the indole

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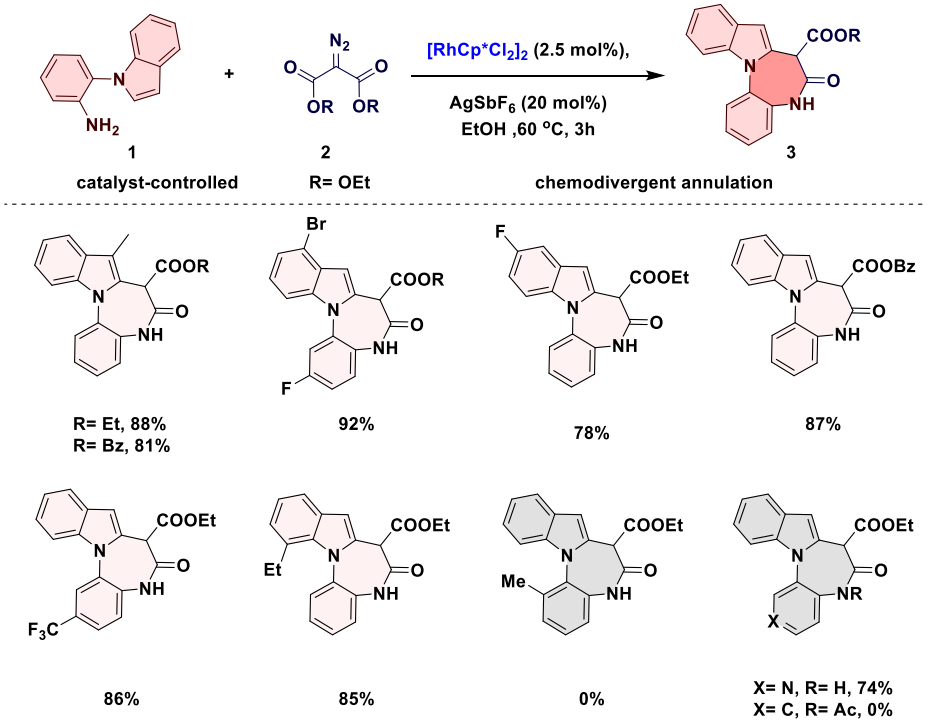
Scheme 1. Chemodivergent Annulation to Indolo-Fused Diazepine



functionalization, such as the need for prefunctionalization of the substrate, nonscalability of the protocol, and regio- and stereoselective concerns. Transition metal catalysis, especially incorporating Rh(III)-catalyzed pathways, is more substantial toward the functionalization of indoles in a rapid manner.[36] Along with that, as mentioned earlier, the limitations are also overcome by the typical use of Rh-benzannulation protocols.[37] The benzannulation term was originally adopted from the Latin word indicating the formation of two new bonds in the rapid "anellus method".[38] Gratifyingly, Rh-catalyzed benzannulations are promising and scalable techniques in modern organic synthesis pursuits in which new rings are formed over a pre-existing scaffold efficiently.[39−41] Additionally, Rh-catalyzed pathways are also known to foster many benefits, including no requirement of prefunctionalization, chemodivergent−convergent pathway, and straightforward and rapid access to molecular complexity in a one-shot manner. In this scenario, a significant breakthrough was the development of $[Cp^*RhCl_2]_2$ that is known for its broad applicability. The first ever synthetic report as well as general preparation are represented in Figure 2. The Rh(III) catalyst pentamethylcyclopentadienyl rhodium dichloride dimer ($[Cp^*RhCl_2]_2$) is an organometallic compound with the formula $[(C_5(CH_3)_5RhCl_2)]_2$, dark red in color. The catalyst is an air-stable diamagnetic solid, having idealized C_{2h} symmetry with each metal center having pseudo-octahedral geometry. The stated catalyst is prepared by the reaction of rhodium trichloride trihydrate and pentamethylcyclopentadiene in hot methanol (Figure 2). The first ever preparation of the catalyst was by the reaction of rhodium trichloride with hexamethyl dewar benzene.[42−44]

Among the several transition metal catalysis systems, Rh(III) catalysis pathways have drawn much interest from synthetic practitioners for their capacity to increase the molecular complexity of the indole nucleus through concurrent annulation protocols and regioselective C−H functionalization. Moreover, in addition to annulation strategies supported by Rh catalysis, C−H activation also efficiently allows for diversified access to the polycyclic-fused indole derivatives. The most common mechanistic insights for the catalytic cycles include secure coordination of functional groups, coordination of metal centers via binding sites, and generation of metal complexes of generally 5- or 6-membered metallacycles. Additional pathways incorporating the catalytic phase of Rh, including oxidative, reductive, eliminative, and additive protocols, are discussed at a suitable place in the pertinent review. Illustrating the significant advancements made and the improved comprehensive mechanistic insights of C−H activation, several researchers have already examined the transient existence of the directing group for C−H functionalization, which is relevant to this review.[45−50] Concluding from various aspects and reports published so far in the rapid access to generate molecular complexity, Rh is among the most efficient and distinguished catalysts, as explained.[51] Additionally, many synthetic accessible catalysts with varying oxidation states (0, 1, 2, and 3), such as $RhCl(PPh_3)_3$, $[Cp^*RhCl_2]_2$, $[Rh(OAc)_2]_2$, and $Rh_4(CO)_{12}$, have been extensively used in many synthetic transformations including inter- or intramolecular annulation, halogenations, arylation, alkylation, chalcogenation, and acylation.[52,53] In addition, several new and promising cycloadditions, hydroformylations, hydrogenations, and asymmetric functionalization offer a distinctive advantage over those which use Pd and Ru.[54−56] Therefore, inspired by the ground-breaking application of Rh(III) catalysis in organic synthesis protocols, numerous evaluations highlighting synthetic late-stage functionalization of indole scaffolds have been eloquently illustrated, defining the colossal achievements of these research areas based on promising techniques and broad applicability.

2. AIM AND SCOPE OF REVIEW

The selected topic is encouraging because functionalization has received less attention than the synthesis of indole, especially in

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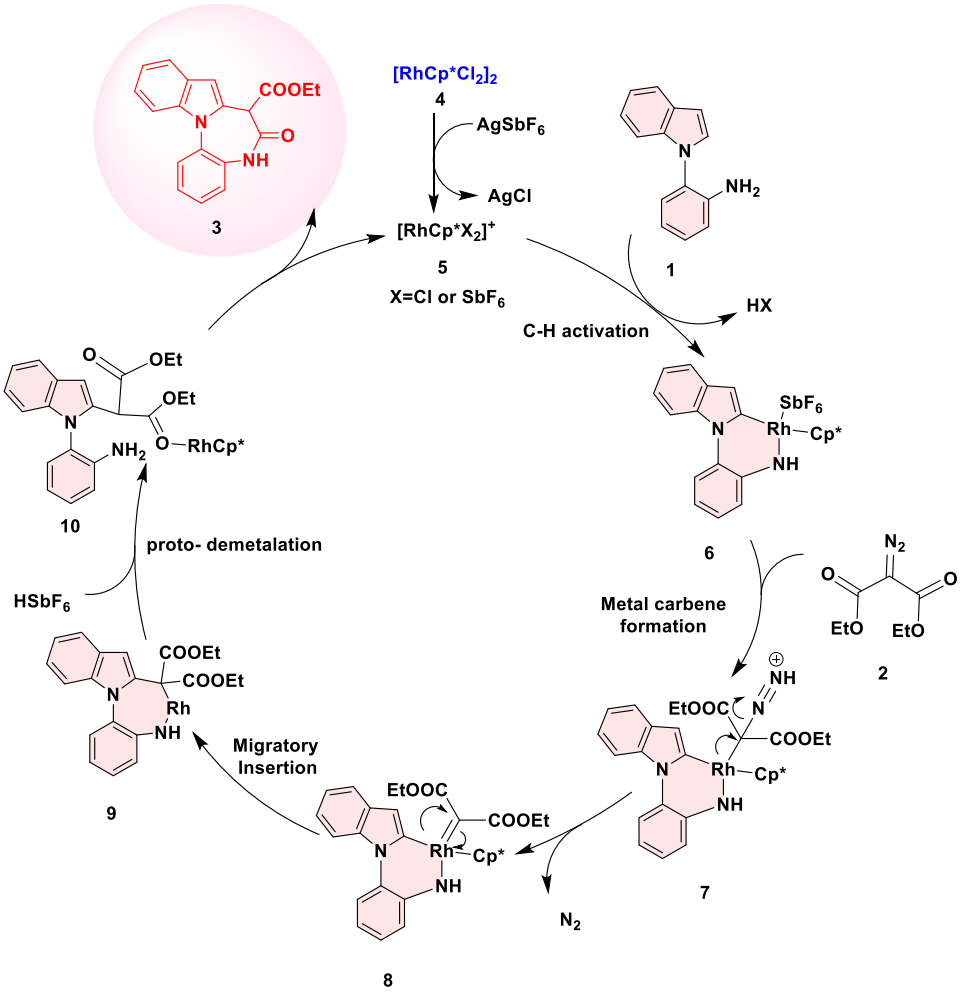
Scheme 2. Mechanistic Approach for Chemodivergent Annulation to Indolo-Fused Diazepine



terms of catalytic conversions, and a huge number of compilations have been devoted to it. This work aims to highlight recent advancements, focusing on creating unique, stable carbon−carbon and carbon−hetero bonds (based on our expertise in assembling C−C bonds) to create scaffolds inspired by polycyclic indoles.[57−60] The most effective ways to functionalize indoles are through catalyst-controlled chemo-divergent synthesis, oxidative cascade annulations, oxidative [4 + 2] annulations, reductive aromatization, and dearomatization via cross-coupling reaction over preactivated indole derivatives. These methods are well-illustrated using Rh(III) catalysis pathways. We were able to thoroughly discuss the current selective C−H functionalization of indole units based on $[RhCp^*Cl_2]_2$ by employing state-of-the-art synthetic techniques like dehydrogenative annulation, spirocyclization, chemo-divergent annulation, or reaction medium controlled pathways. To convey a degree of knowledge, particular focus is being paid to the substrate scope, applications of the established technique, detailed catalytic systems with comparative studies, and reaction protocols. This review also covers quinoxalines, indolo-pyrrolo-fused diazepines, other alkaloid analogues, and polycyclized indole derivatives. The synthetic chemistry community is anticipated to be inspired by the further classification of reviews based on indole-fused cores such as 1,2,3,4- or 4,5-fused indoles and their compilations to find novel reactivity paradigms for the creation of C−hetero/N−hetero bonds in this cutting-edge research field. The sectional review is segregated based on the analysis of positional selectivity and the kind of reaction pursuits to functionalize the required core effectively. The mechanistic discoveries highlight $[RhCp^*Cl_2]_2$-catalyzed pathways encouraging catalyst-controlled chemo-divergent synthesis approaches and distant C−H functionalization, which are the leading progressive objectives of the review and justify this differentiation. The main goal is to offer possible information on chemical reactions that could be catalyzed to functionalize indole rings.

2.1. Diazo Compounds As Reacting Partners to Access Fused Indole Scaffolds. *2.1.1. Synthesis of 1,2-Fused Indole Compounds.* Indole/pyrrole-tethered heterocycles are of substantial importance in natural products due to their widespread bioactivity. Most notably are diazepines, in the process of drug discovery and natural product synthesis, namely, Lixivaptan(II) (antidiuretic activity), benzo[1,4]diazepino[1,7-*a*]indole (anti-HCV activity), and other exciting diazepines with widespread applications in pharmacology.[61−63] Inline, certain attempts were tried, most notably by Ohta, who investigated methods to cyclize indole-fused benzo-1,4-diazepines utilizing the Cu(I) catalysis system.[64] A similar attempt was made by Mangette to synthesize indolo/pyrrolodiazepines by intramolecular N-arylation.[65]

Recently, Dhole et al. in 2019 disclosed the synthesis of indole-fused diazepine using a catalyst-controlled chemo-

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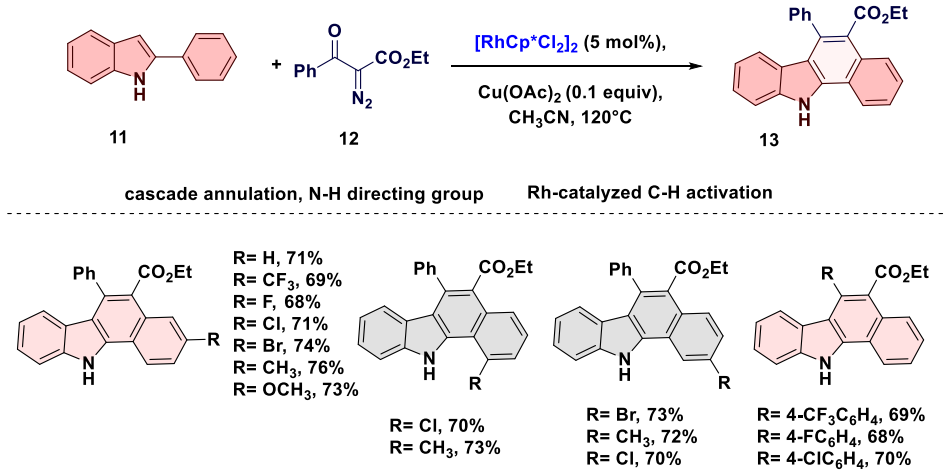
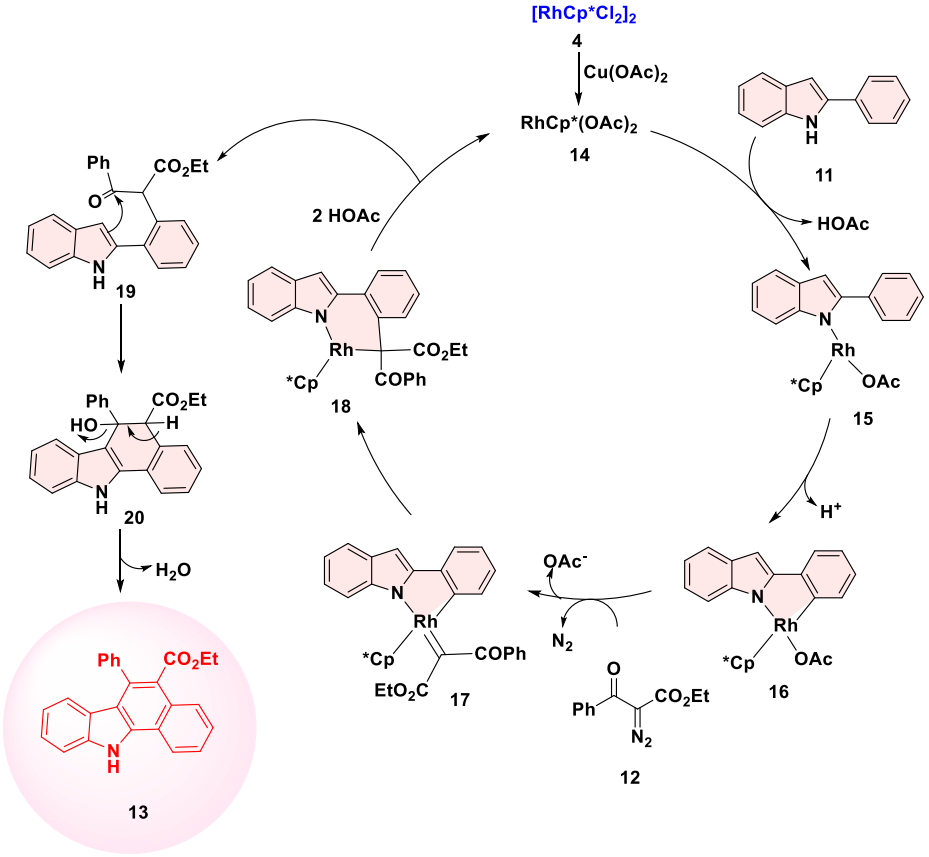
Scheme 3. Regioselective Annulation of 2-Arylindoles to Carbazoles



Scheme 4. Mechanistic Approach for Regioselective Annulation of 2-Arylindoles to Carbazoles



divergent annulation method between *o*-indolo anilines **1** and diazo compounds **2** to access fused diazepine **3** (Scheme 1).[66] Here, Rh(III) catalysis systems, which are particularly appealing from a synthetic standpoint because of their high efficiency, operational simplicity, selectivity, and efficiency, are employed to synthesize functional groups compatible with indole and indole-fused systems. The reaction underwent a highly selective phase of free amine-assisted C2−H activation, amidation, and diazepino production while catalyzing with Rh(III). To create diazepine **3**, 2-(1*H*-indol-1-yl) aniline **1** and diethyl diazomalonate **2** were combined in the presence of $[Cp^*RhCl_2]_2$ **4** and $AgSbF_6$. The reaction was initiated by forming the active dicationic Rh(III) species $[RhCp^*X_2]$ (X = Cl, SbF_6) **5** from $[RhCp^*Cl_2]_2$ and $AgSbF_6$. A six-membered rhodacycle intermediate **6** was produced by the coordination of a free amine group from the *o*-indolyl aniline **1** to $[RhCp^*X_2]$ **5** species and selective C2−H cleavage. The metal carbene species **7** was then produced by coordination of the entering diazo ester **2** to Rh(III) species **6**, and subsequent nitrogen extrusion generated intermediate **8**. Seven-membered rhodacycle **9** is produced by the later migration of the Rh−C bond into the carbene moiety; this intermediate would then undergo protodemetalation to produce C2-alkylated intermediate **10**. The free amine group finally attacked the carbonyl group in ester

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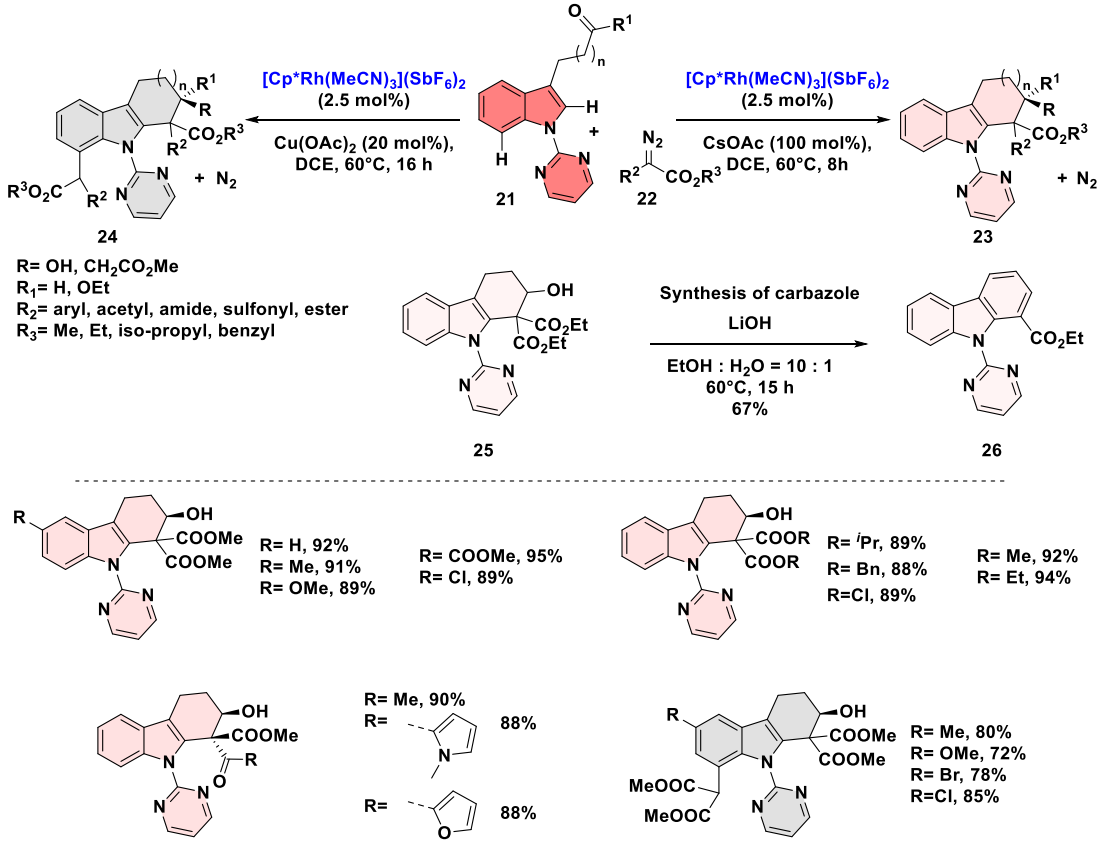
Scheme 5. Functionalization of Indoles to Access Diversified Carbazoles



moiety **10** through a nucleophilic attack, where $[RhCp^*]^{2+}$ served as a Lewis acid to activate the carbonyl group and produce the desired product **3** with the regeneration of the active catalyst **5** (Scheme 2). The substrates containing an electron-withdrawing/-donating group on the aniline or indole ring gave the desired product with maximum yield. Similar results were obtained in indoles with methyl groups at the C-3 position and electron-donating or -withdrawing groups on anilines. Rotamers were not seen in these cases, most likely because of the −Me group's steric hindrance, which hindered the rotation of the ester group. Both free-amine-protected and *ortho*-methyl-substituted *o*-indolyl anilines failed to provide the necessary core effectively. Notably, the method is extremely selective for diazepino-indole and utilizes a free amine-aided C2−H activation and amidation via a Rh(III)-catalyzed pathway in excellent yields. However, with the Ru-catalyzed pathway, the indolo-fused quinoxaline was afforded through the insertion of the N−H bond to ruthenium carbene followed by cyclization through a metallo-ene type reaction. Product formation depends entirely on the choice of transition metal catalyst.

2.1.2. Synthesis of 2,3-Fused Indole Compounds. To synthesize the 2,3- and 3,4-fused indole polycyclic compounds and align natural products, mainly containing benzo[*a*]-carbazoles and their functional derivatives possessing biological activities, numerous synthetic techniques have been developed so far based on diverse annulation strategies and transition-metal-assisted C−H activation.[67,68] While these simple methods are typically effective and reliable, recent research has focused on finding novel synthetic processes starting from readily available substrates. Using cascade reactions of 2-arylindoles **11** with diazo carbonyl compounds **12**, Zhang and Fan, in 2017, discovered a unique synthetic method for benzo[*a*]carbazoles **13** with an unprotected NH unit (Scheme 3).[69] The stated reaction commenced with the formation of an active catalyst $RhCp^*(OAc)_2$ **14** by anion exchange between $[RhCp^*Cl_2]_2$ **4** and $Cu(OAc)_2$, which then combined with **11** to form intermediate **15**. A five-membered rhodacycle **16** was then produced by the subsequent breakage of the C−H bond in **15**, which interacts with **12** to produce rhodium-carbene **17** after excluding N_2. Next, **18** was generated by the migratory insertion of a carbene into the rhodium−carbon bond in intermediate **17**. Finally, intermediate **18** was protonated to give **19**, which enabled the rhodium complex to begin a new catalytic cycle. Intermediate **19** underwent an intramolecular condensation via intermediate **20** to generate the desired product **13** in the second stage of this cascade mechanism (Scheme 4). To efficiently produce the necessary carbazoles, yields are often unaffected by the electronic properties of substituents on the indole or phenyl ring, whether electron donating or withdrawing. Notably, halogenated aromatic substrates are also suitable for the reaction under the given conditions, and for 2-phenyl moieties that have been meta-substituted, the reaction happened regioselectively on the less hindered site (there are two reactive sites accessible for meta substitutions). This strategy offers advantages, including simple substrates, robust functional group tolerance, high efficiency, and atom economy, in addition to the capability of synthesizing benzo[*a*]carbazoles with a range of substitution patterns. Also, it constitutes the first instance of the Rh-catalyzed process in which the functionalization of an intramolecular $C(sp^2)$−H bond to produce benzo[*a*]carbazole derivatives uses the NH unit of indole as a steering group.

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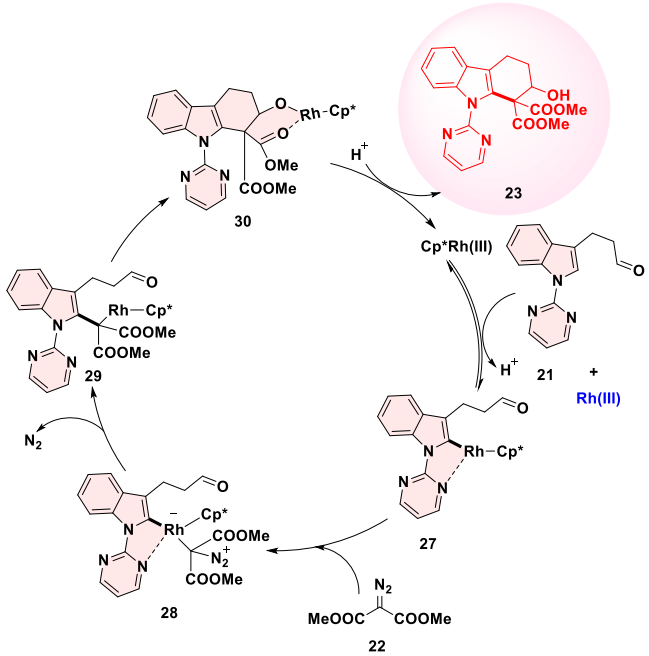
Polycyclic scaffolds, mainly carbazole derivatives, are widely found in a range of natural products, medications, and luminous materials. Because of their extended and planar conjugated systems, polycyclic carbazole derivatives have displayed exceptional photochemical characteristics.[70−72] As an example, 4CzIPN (1,2,3,5- tetrakis(carbazol-9-yl)-4,6-dicyanobenzene) has been extensively developed as an organic photocatalyst in visible-light-driven chemical transformations, and some carbazole derivatives displayed clear room-temperature ultralong phosphorescence.[73] As a result, numerous procedures for polycyclic carbazole compounds have been documented over the years. In line, Gao et al., in 2018, described an approach for C2−H activation of N-substituted indole **21** with diazomalonate **22** catalyzed by $[Cp^*Rh(MeCN)_3](SbF_6)_2$ and CsOAc as additives.[74] N_2 was the only byproduct of the process in which the resulting $C(sp^3)$−Rh intermediate underwent an intramolecular addition reaction to the C═O or C═C bonds to afford a variety of desirable 2,3-fused indoles **23** in good to exceptional yields. Interestingly, when $Cu(OAc)_2$ was used as an additive along with diazomalonate (4.0 equiv), the formation of 7-substituted 2,3-fused indoles **24** took place. In addition, 2,3-fused indole **25** was treated with LiOH in EtOH and H_2O at 60 °C to yield carbazole **26**, demonstrating the synthetic viability of the described approach (Scheme 5). Initially, an Rh(III)-catalyzed $C(sp^2)$−H bond cleavage generated a five-membered cyclometalated Rh(III) complex **27** from indole derivative **21** upon interation of the Rh(III) catalyst. Coordination of diazo compound **22** with so formed Rh(III) complex **27** yielded intermediate **28**, which then underwent intramolecular 1,2-migratory insertion of the aryl group to furnish intermediate **29**. Subsequent intramolecular nucleophilic addition of aldehyde within intermediate **29** resulted in the formation of rhodium alkoxide **30**, which underwent protonation to produce product **23** and regenerate the rhodium catalyst (Scheme 6). The described approach is promising for the synthesis of 2,3-fused indole scaffolds (applied extensively to carbazole synthesis) under an environmentally safe process that yields only dinitrogen as a byproduct and is suitable for indoles containing both electron-donating and -withdrawing groups that were coupled with diazamalonate to access corresponding products in excellent yields. Due to its strong compatibility with halogens and esters, synthetic transformation opens up a wide range of possibilities.

Scheme 6. Mechanistic Approach for Functionalization of Indoles to Access Diversified Carbazoles



One of the widely used essential scaffolds in bioactive natural products and medicines is isochromenone or quinonlinone.[75,76] They are also regarded as valuable building blocks for synthesizing various pharmaceuticals and useful functional materials.[77,78] Additionally, isochromenones with a six-membered lactone ring exhibit potent bioactivity, including anticancer, antibacterial, and anti-HIV properties.[79−81] In 2019, Rok Lee disclosed a simple and effective Rh(III)-catalyzed annulation of indole **31** with 3-diazoquinolinediones **32** for the construction of various and highly functionalized isochromenoquinolinediones **33** (Scheme 7).[82] The Rh-initiated protocol commenced with the formation of activated $[RhCp^*(OAc)_2]$ **14**, which then reacted with indole derivative **31** to generate rhodacycle **34** by the loss of acetic acid. The so formed rhodacycle intermediate **34**, then coupled with **32**, with the extrusion of nitrogen gas afforded **35**. Further, migratory insertion of intermediate **35** leads to the formation of cyclic eight-membered rhodacycle intermediate **36**. Subsequently, protonation of intermediate **36** afforded intermediate **37**, which finally underwent lactonization to produce desired product **33** (Scheme 7). The developed strategy has the potential to be used to transport a variety of pertinent compounds, including indolopyranoquinolinone, thienopyranoquinolinone, and pyridopyranoquinolindiones. Some of the noteworthy characteristics of this reaction are high atom economy, strong functional group tolerance, and high regioselectivity; the formed substance can also function as a powerful fluorescence sensor for the Fe^{3+} ion.[82] It was observed in the previous year that Rh(III) was the influencing catalyst for the annulation of benzamides with diazo compounds, though there is not a single example of the direct formation of highly functionalized isochromenoquinolinediones from the Rh(III)-catalyzed annulation of indole with 3-diazoquinolinediones.

2.2. Alkynes as Reacting Partners to Access Fused Indole Scaffolds. *2.2.1. Synthesis of 1,2-Fused Indole Compounds.* Furthermore, considering the diverse biological properties of pyrimido[1,6-*a*]indolone and its derivatives, such as inhibitors of topoisomerase II, fluorescent nucleosides, antagonists of the 5-HT3 receptor, etc. along with their common use in material chemistry, considerable work has been accomplished by creating novel motifs and revisiting their photophysical characteristics.[83−87] Among the most promising well-known tactics, [4 + 2] annulations and strategic coupling are the most used to access the desired core.[88,89] Moreover, the *N*-pivaloyloxy group, which functions as an internal oxidant, has been widely used to construct a range of heterocycles rewarded with the most significant contributions.[90] In 2011, Chada Reddy et al. published the results of a rhodium-catalyzed cascade annulation of *N*-(pivaloyloxy) benzamides with 2-alkynyl aldehydes to provide aminal functionality,[91,92] whereas *N*-carboxamide was identified as a directing group for the C-2 functionalization of indoles by the Cui research team in 2014.[88] In their further investigation, Reddy et al. in 2021 suggested a new technique for the synthesis of fused pyrimido[1,6-*a*]-indolone derivatives[93] where a domino [4 + 2] annulation/aza-Michael addition reaction was developed using C−H activation

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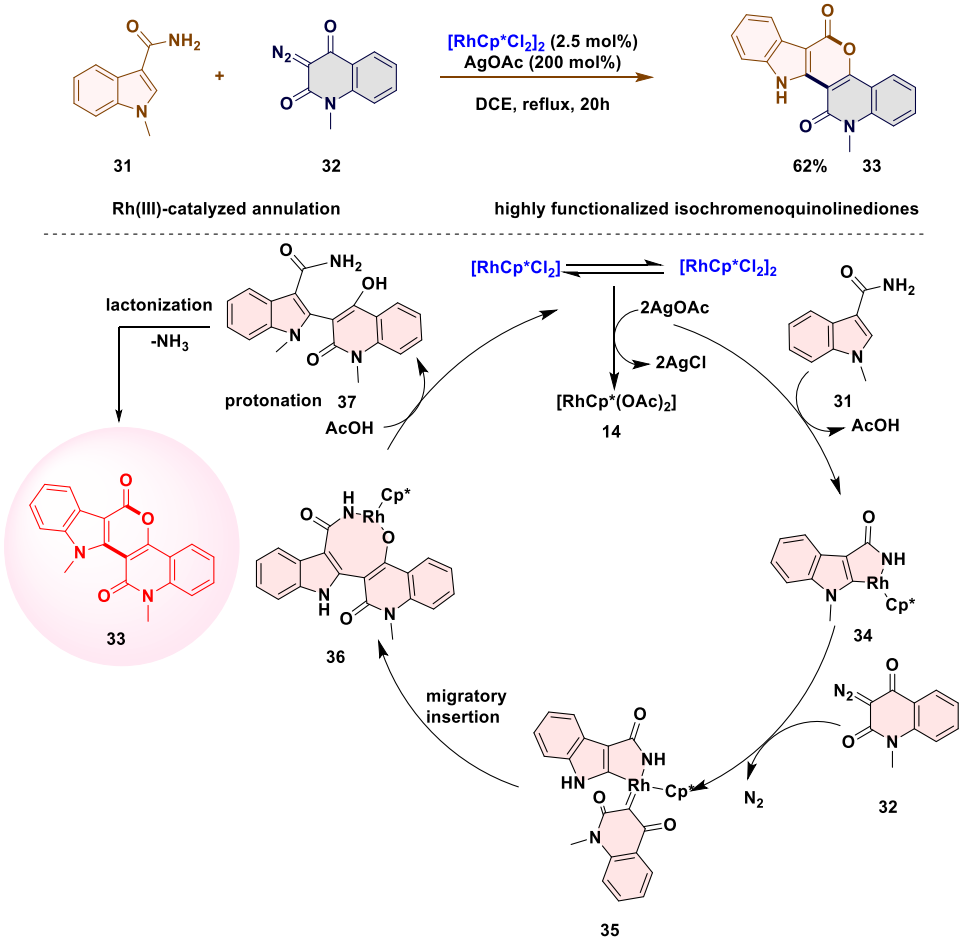
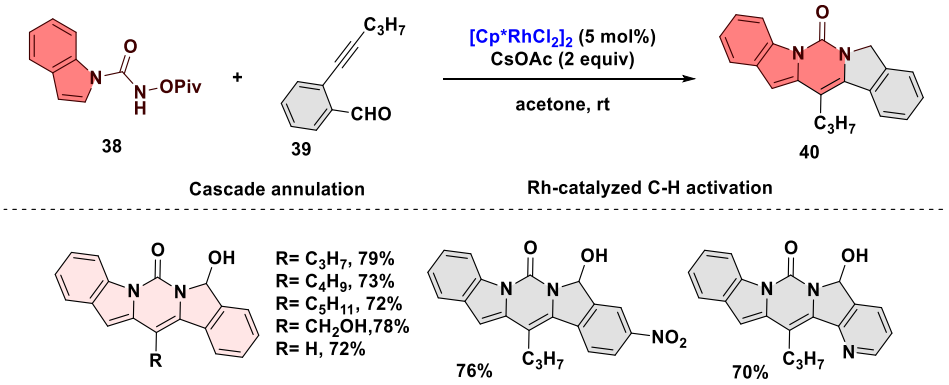
Scheme 7. Annulation of Unprotected Arylamides with 3-Diazoquinolinediones



Scheme 8. Cascade Annulations to Access Pyrimido[1,6-*a*]indolones



by annulating *N*-(pivaloyloxy)-1*H*-indole-1-carboxamide **38** with 2-alkynylaryl aldehydes **39** under the influence of the Rh(III) catalyst (Scheme 8). The catalytic cycle demonstrates the generation of the activated complex of Rh, followed by the addition of substituted indole **38** to access rhodacycle **41**. The generated cyclic intermediate **41** then couples with the substituted alkyne framework **39** to afford the intermediate adduct **42**. The intermediate **42** subsequently underwent reductive elimination and oxidative addition to afford **43** and **44**, respectively. Further base-promoted intramolecular attack by amide NH to aldehyde in **44** afforded **40** as the desired product (Scheme 9). The method has been proven to be efficient for producing annulated products in good yields with a range of alkyne substituents which proceed via a C−H activation-based annulation with an alkyne moiety, followed by the addition of nitrogen to the aldehyde/activated alkene. The strategy works well with alkynyl aldehydes with varying alkyl chains on alkynes; notably, alkynyl aldehydes bearing a nitro group on the phenyl ring were also effective in cascade annulation. Moreover, replacing a phenyl ring with hetero-aromatic rings like pyridine underwent annulation smoothly to afford the desired core efficiently. Moreover, the new technique allows further, exceptionally luminous dipyrrinone analogue synthesis.

Pyrrolo[1,2-*a*]indol-3-one motifs are highly preferred candidates for inclusion in various therapeutic compounds.[94] Over

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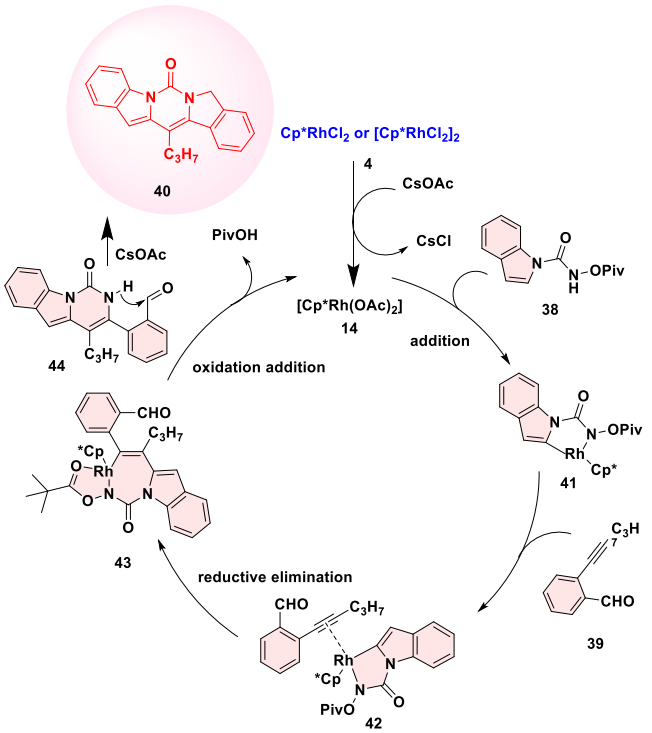
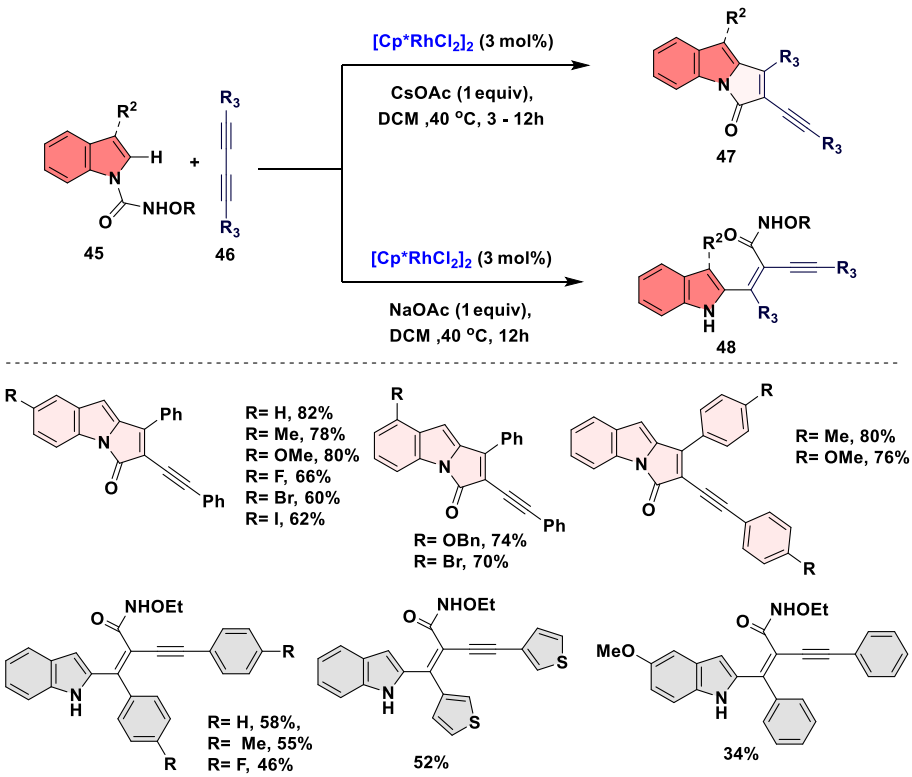
Scheme 9. Mechanistic Approach for Cascade Annulations to Access Pyrimido[1,6-*a*]indolones



the past few decades, numerous methodologies have been discovered for the synthesis of these essential scaffolds, including Mn(I)-catalyzed dehydrocyanative transannulation followed by hydrolysis, Co(III)-catalyzed redox-neutral annulation, and Pd(II)-catalyzed aerobic intramolecular cyclization.[95,96] The harsh reaction conditions and limitations in generating highly functionalized substrates are the main restrictions of the aforementioned methods. Therefore, to have more effective access to pyrrolo[1,2-*a*]indol-3-one from widely available starting materials, Vinaykumar Kanchupalli in 2021 described an effective approach to the [3 + 2] annulations and C2 alkenylations of indoles **45** with 1,3-diynes **46** catalyzed by a Rh(III) catalyst.[97] These reactions produced synthetically significant indol-3-ones and highly functionalized tetrasubstituted olefin derivatives **47** and **48**, respectively (Scheme 10). Previously, the groups of Tanaka and Cui independently described [4 + 2] annulations of *N*-alkoxycarbamoyl indoles with monoalkynes catalyzed by Rh(III).[26] Moreover, the Zhao group recently devised a strategy for synthesizing tetrasubstituted alkenes through an Rh(III)-catalyzed C−H alkenylation/directing group migration cascade between indoles and alkynes.[98] Recently, a noteworthy example by Zhang and colleagues demonstrated the formation of tetrasubstituted 1,3-enynes and alkylated 3*H*-pyrrolo[1,2-*a*]indol-3-one derivatives from indoles and 1,3-diynes using a Rh(III) catalyst.[99] So far, the developed approaches revealed a constrained range of dialkynes, and the majority of the products was made from 1,3-diyne precursors with alkyl substitutions. The stated strategy was initiated with the production of active catalyst **14** by ligand exchange with CsOAc.

Furthermore, coordination and subsequent regioselective migratory insertion of **45** resulted in the formation of a rhodacycle intermediate **49** with the aid of a carboxylate. The intermediate **50** was then created from intermediate **49** and 1,3-diynes **46** by intramolecular nucleophilic addition of the C−Rh bond to the carbonyl. The annulated product **47** was finally released by protonolysis of the *in situ* generated intermediate **51**, after path- b cleavage (alkoxy amine C−N bond cleavage),

Scheme 10. [3 + 2] Annulation and C−H Alkenylation of Indoles



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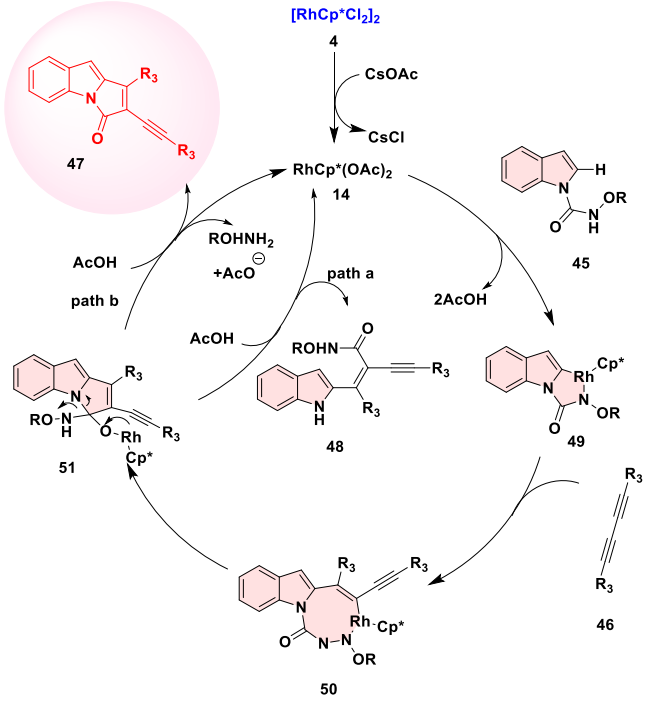
which also regenerated the active catalyst species **14**. In contrast, indole C2-alkenyated product **48** was delivered via path a cleavage (indole C−N bond cleavage) and protonolysis, which also regenerated the active catalyst species **14** (Scheme 11).

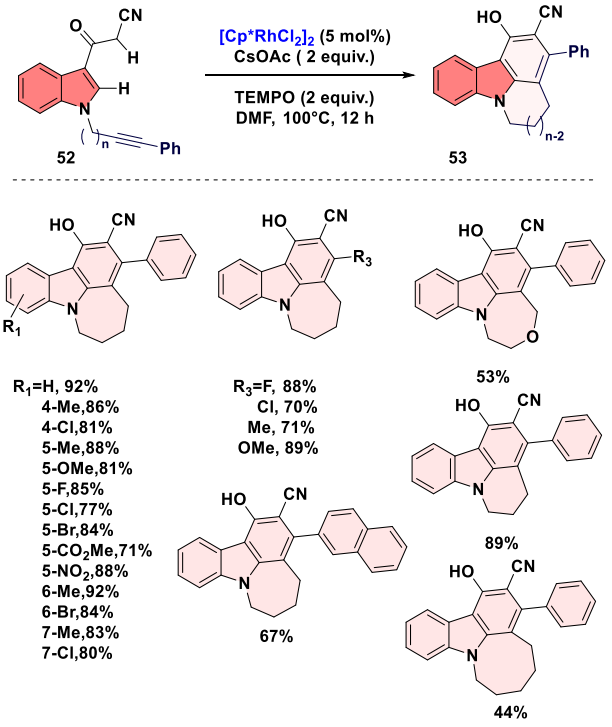
Scheme 11. Mechanistic Approach for [3 + 2] Annulation and C−H Alkenylation of Indoles



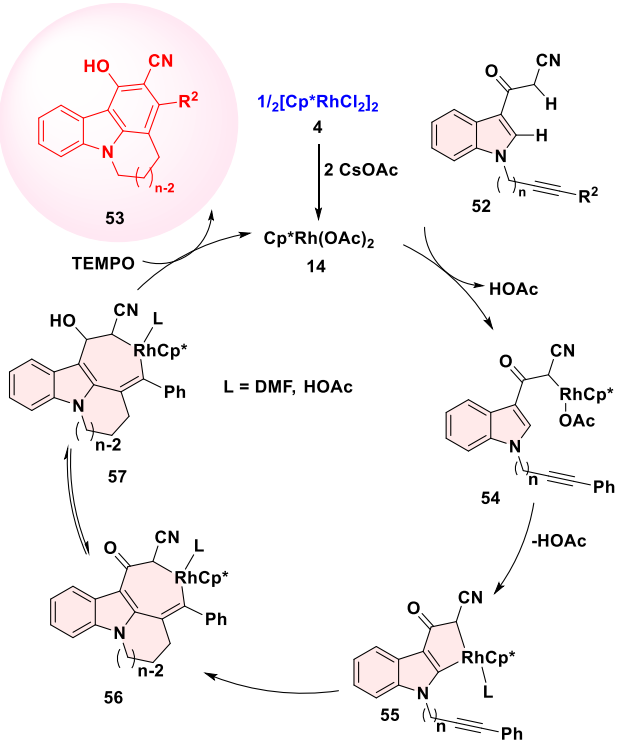
Indole carboxamides containing neutral, electron-donating, and σ-electron-withdrawing groups respond favorably to the approach. Additionally, hindered and largely substituted indoles and indoles bearing π-electron-withdrawing groups did not prevent the annulation. Unsymmetrical 1,3-diynes were also compatible and provided desired products, while symmetrical and unsymmetrical alkynes functioned well under the reaction conditions. Electron-withdrawing substituents such as NO_2-bearing 1,3-diynes failed to produce the desired products. It showed that the less-hindered carbon of the alkyne unit was where the indole C2 position was mostly functionalized, with the regioselectivity favoring only the activation of the side that was less hindered. A crucial aspect of this procedure was the additive-controlled selective creation of desired scaffolds under the Rh(III)-catalyzed system. Additionally, the synthesis of tri- and bisannulated alkenes has been effectively added to this method. The method is also utilized to quickly synthesize the core structures of protein kinase C inhibitors and analogues of melatonin.

2.2.2. Synthesis of 2,3- and 4,5-Fused Indole Compounds. Wang et al. described a mild and efficient method for the reaction of indole **52** in the presence of $[Cp^*RhCl_2]_2$ and TEMPO as an oxidant in DMF at 100 °C to produce fused carbazoles **53** (Scheme 12).[100] The reaction proceeded via C2−H bond activation followed by intramolecular oxidative cyclization steps (Scheme 13). Mechanistically, the first step of the transformation is the activation of the C(sp^3)−H bond by the activated form of catalyst **14** (formed via interaction of $[RhCp^*Cl_2]_2$ **4** with CsOAc) to afford the intermediate **54**. Then the indole's C(sp^2−H) bond was activated, affording the

Scheme 12. Intramolecular Cascade Sequence for the Formation of Fused Carbazole



Scheme 13. Mechanistic Approach for the Intramolecular Cascade Sequence for the Formation of Fused Carbazole



five-membered rhodacycle **55**. Further, the insertion of an alkyne derivative afforded six-, seven-, or eight-membered intermediates as shown in rhodacycle **56**. Finally, after the keto−enolization step to **56**, **57** was generated which further underwent reductive elimination to afford **53** as shown in the catalytic cycle in Scheme 13. The method involves the

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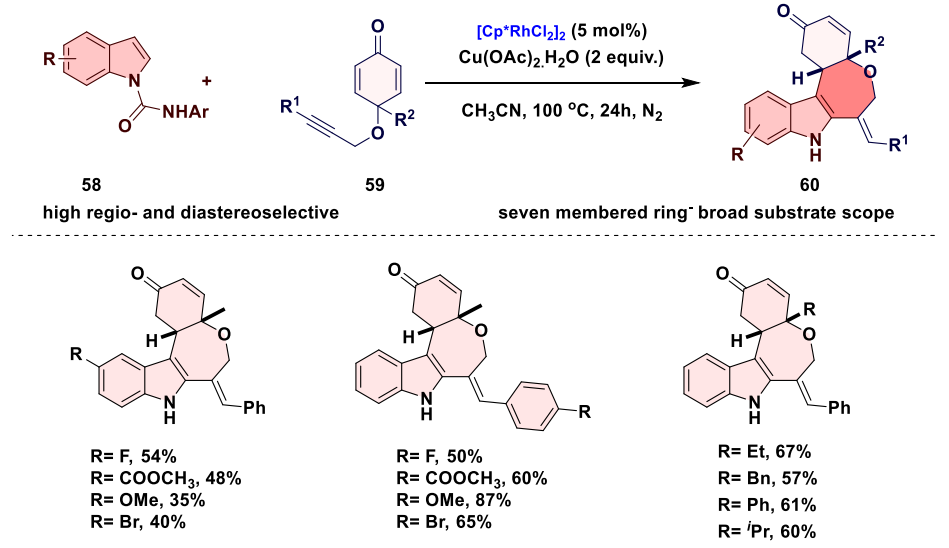
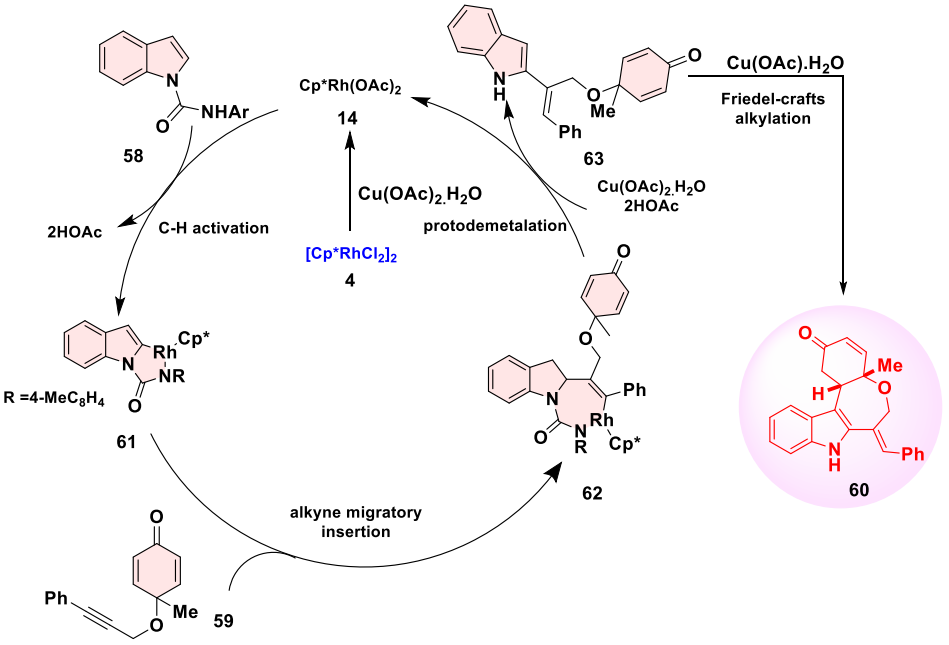
Scheme 14. Diastereoselective [5 + 2] Annulation of Indoles with 1,6-Enynes to Access Indole-Fused Oxepines



Scheme 15. Mechanistic Approach for Diastereoselective [5 + 2] Annulation of Indoles



intramolecular C−H activation of alkyne-tethered 3-(indol-3-yl)-3-oxopropanenitriles to produce fused carbazole scaffolds and entails annulation with the tethered alkyne and the sequential cleavage of $C(sp^2)$−H/$C(sp^3)$−H bonds to produce a succession of hydroazepino[3,2,1-*jk*]-carbazoles with six, seven, and eight members. By examining the substrate scope, it can be established that when n = 4 and electron-donating/-withdrawing groups are present at any location (4, 5, or 6) a series of fused carbazoles are produced in good to outstanding yields. In addition, the aryl groups attached to the alkynes possess advantageous electrical properties that encourage the production of the corresponding products, which are responsible for intramolecular annulation in high yields.

Seven-membered cyclic indole-fused ethers, namely, oxepanes and oxepines, are among the versatile structural motifs of biologically active natural products, especially in marine polycyclic ethers.[101,102] Notable examples of indole fused at the 2,3-position are distinctive frameworks that are embedded in many alkaloids including alstilobanine E, angustilodine, and dichotine.[103,104] Previously, gold-catalyzed intramolecular hydroarylation of indole with alkene and allenes was considerably impacted. Additionally, the [5 + 2] annulation alternative method was quite successful in producing indole-fused oxepines.[105] In particular, it has recently been shown that enone-tethered cyclohexadienones may be quickly assembled into highly strained polycyclic oxepine-fused indoles via a Lewis-acid-driven formal [5+ 2] annulation.[106−108] Hence, in 2021, Li reported a diastereoselective formal [5 + 3] annulation methodology between indoles **58** and 1,6-enynes containing cyclohexadienone **59** for the synthesis of indole-fused oxepines **60** (Scheme 14).[109] Under the influence of the Rh(III) catalyst, the reaction went through tandem indole C2−H alkenylation and intramolecular Friedel−Crafts alkylation. The stated reaction uses the Rh(III) catalyst system and was initiated by

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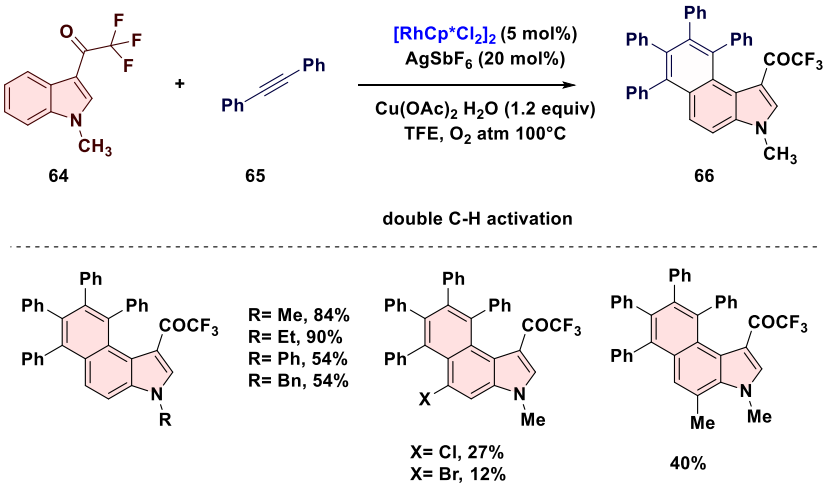
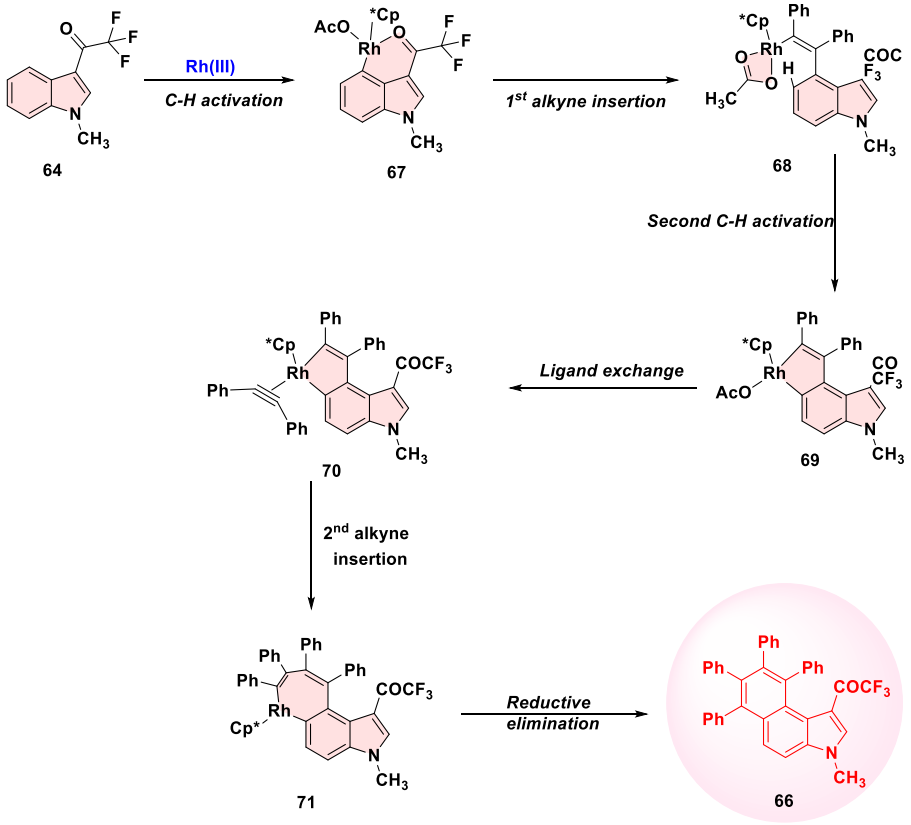
Scheme 16. Formal Oxidative [2 + 2 + 2] Cyclization for Selective Benzannulation of Indoles



Scheme 17. Mechanistic Approach for Formal Oxidative [2 + 2 + 2] Cyclization



the coordination of indole substrate **58** to the *in situ* produced Cp*Rh(OAc)$_2$ **14** species, which subsequently caused the indole C2−H bond activation, resulting in the creation of the intermediate **61**, which underwent regioselective alkyne migratory insertion to produce intermediate **62**. This intermediate then underwent protodemetalation to produce the alkenylation product **63**. Finally, the formal [5 + 2] annulation product **60** was obtained from the uncyclized indole intermediate **63** by intramolecular Friedel−Crafts alkylation (Scheme 15). Alkynes are well tolerated and regioselectively gave the appropriate products in good to excellent yields, but the reaction was shown to be particularly sensitive for indoles bearing electron-rich or -deficient groups on different locations. Typically, steric hindrance controls the formation of the product, particularly in the case of bulky 1,6-enynes with 3-position-substituted cyclohexadienones that are challenging to undergo [5 + 2] annulation product. The stated strategy enables rapid construction of indole-fused oxepines via indole 2,3-difunctionalizations in good to excellent yields with a broad substrate scope, via a diastereoselective formal [5 + 2] annulation of indoles with cyclohexadienone-containing 1,6-enynes through a rhodium-catalyzed regioselective indole C2−H alkenylation and intramolecular Friedel−Crafts alkylation relay. The *cis*-hydrobenzo[*b*]oxepine scaffold, discovered in various natural compounds with significant biological activity, is effectively approached using this methodology.

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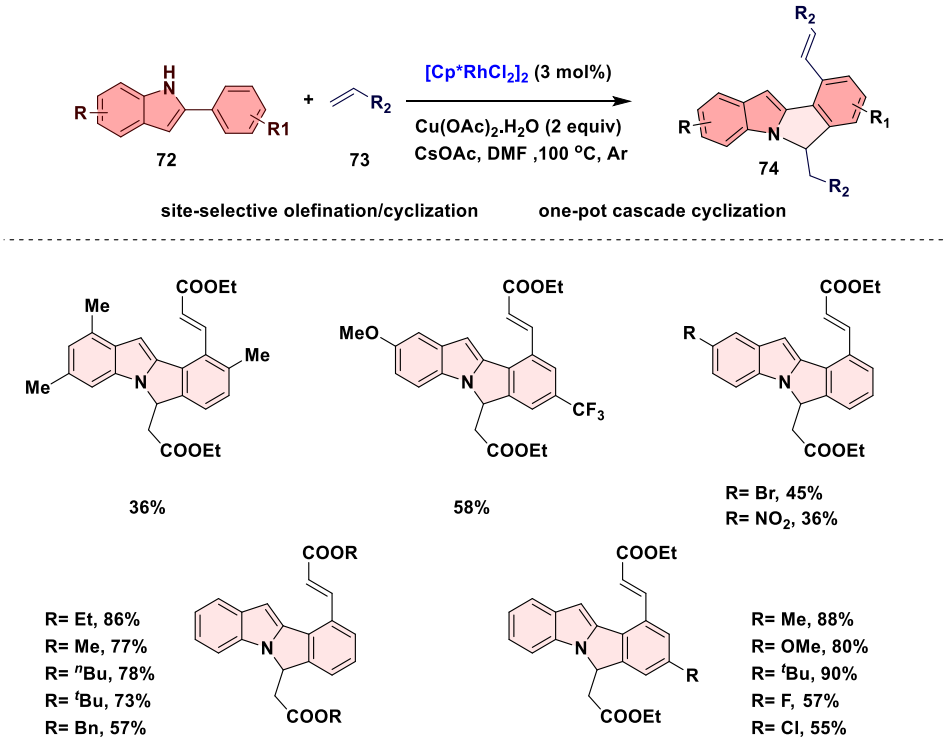
Scheme 18. Annulation Cascade for Rapid Access to 6*H*-Isoindolo[2,1-*a*]indole



Benzo[*e*]indoles are among the selective indole frameworks found in natural products, a class of hasubanan alkaloids and several analogues of anticancer agents, and considering the importance, several unique and distinct methodologies have been reported to this end.[110,111] Thus, Prabhu and team developed a double C−H activation and double insertion mechanism to create benzo[*e*]indole frameworks in 2018.[112] The synthetic approach to access the desired framework illustrates the weak directing group assistance for C-4 functionalization of indole, as shown in Scheme 16. The trifluoromethyl ketone moiety acts as a directing group and controlling factor for the benzannulation protocol. In the presence of a Rh(III) catalyst, alkynes **65** undergo oxidative cyclization with indole **64** at the C4−C5 position, resulting in benzannulated indole derivative **66**. The stated mechanistic route commenced with the C−H activation via a Rh catalyst directed by $COCF_3$, a group attached at the C-3 position of indole derivative **64**; this resulted in the formation of intermediate **67**. Further, the formed intermediate underwent an alkyne insertion, resulting in another intermediate, **68**. Again, the generated intermediate underwent a consequent second C−H activation to afford **69**, which experienced another ligand exchange and second alkyne insertion to afford **70** and **71**, respectively. Finally, reductive elimination from final intermediate **71** afforded **66** as the desired product (Scheme 17). The strategy works exclusively with symmetrical alkynes, while heterocyclic derivatives of symmetrical alkynes remain unreactive. The annulated product was not seen with ortho-substituted alkynes, perhaps due to the steric influences the ortho-substituents had. The benzannulated compounds are produced using this method, which accepts a number of para- and meta-substituted alkynes. However, the ortho-substituted alkynes only generate a modest amount of alkenylated molecules. Since annulated compounds containing heterocyclic sections are generally challenging, the current synthetic approach is favorable even though yields are typically moderate to good.

2.3. Alkenes as Reacting Partners to Access Fused Indole Scaffolds. *2.3.1. Synthesis of 1,2-Fused Indole Compounds.* The direct synthesis of 6*H*-isoindolo[2,1-*a*]indole with high bioactivity has attracted promising attention because direct manipulation and alteration of the indole unit by the Rh-catalyzed route through C−H activation are of substantial interest.[113] The necessary functionality can be accessed using a variety of synthetic transformations, including notable work by Gaunt et al. in 2005[67] for selectively alkenylating indoles with a Pd-catalyzed method, followed by work by Miura et al. using carboxylic acids as guiding groups.[114] Using excess alkenes and a Pd(II) catalyst, Carretero and associates studied using *N*-pyridylsulfonyl as a directing group to functionalize indole at the C-2 position.[115] To manage selectivity, some earlier approaches needed preactivation of groups and substantial catalyst loading. Thus, to address any inefficiencies in the protocol for organic synthesis, a detailed study of the selective transformation utilizing Rh as a possible catalyst was required. In line, an effective process for producing 6*H*-isoindolo[2,1-*a*]indole **74** from aryl indole **72** and alkene **73** by an intramolecular cascade cyclization process following an N−H-free indole-directed dialkenylation was presented by Wang et al. in 2021.[116] This method displayed exceptional regioselectivity and a high level of functional group tolerance (Scheme 18). The stated protocol was initiated by the formation of the active Rh catalytic species **14**, which underwent insertion with indole **72** to afford **75**. The subsequent introduction of activated ethyl acrylate **73** gave access to monomeric adduct **76**. Monomeric **76** and dialkylated **78** products were obtained without a base, whereas cyclized product **74** was obtained in excess CsOAc (Scheme 19). The methodology effectively provides the required skeleton for electron-rich substituted indoles and the phenyl ring. Halogens and CF_3 derivatives can be tolerated well during the reaction.

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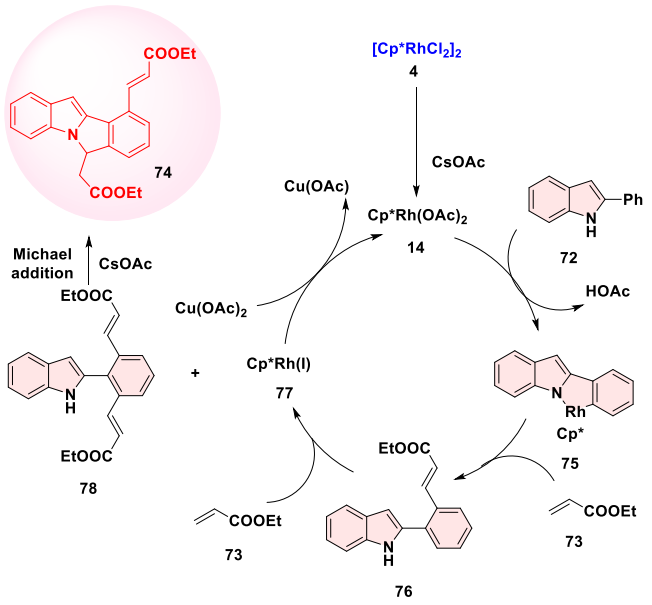
Scheme 19. Mechanistic Approach for Rapid Access to 6*H*-Isoindolo[2,1-*a*]indole

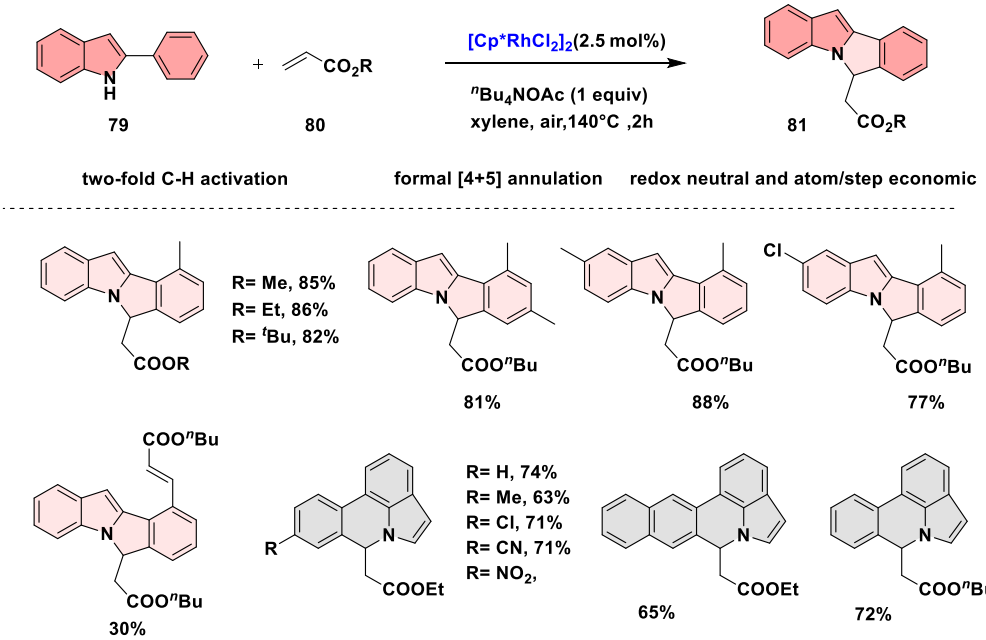


This approach offers a wide functionalization pathway for the efficient synthesis of 6*H*-isoindolo[2,1-*a*]indoles from a 2-aryl indole with substrates having an amide-directing group.

In conjunction with the prior study, Huang in 2021 showed a powerful catalytic system that utilizes molecular oxygen as the oxidant for cross-dehydrogenative coupling catalyzed by rhodium.[117] Here, rhodium was used to catalyze the oxidative annulation of aryl indoles **79** with alkenes **80** to create the beneficial isoindolo-indole **81** (Scheme 20). The mechanistic study shows that five-membered rhodacycle **82** was created by coordinating the phenylindole **79** nitrogen atom to Rh(III) **4** and the subsequent *ortho*-C−H activation. Then, rhodacycle **82** was inserted into ethyl acrylate **80** to produce intermediate **83**, and the ensuing H-elimination created Rh(I) sandwich complex **84**. The active Rh(III) species was then restored by oxygen, oxidizing **84**, which produced the appropriate product **86**. The C−H olefinated product **86** further easily converted into the aza-Michael product **81**, and the addition of quaternary ammonium salts significantly sped up the molecular oxygen oxidation phase (Scheme 21). It is interesting to note that when two ortho C−H bonds are present the reaction initiates disubstitution; in addition, when one of the ortho C−H links is blocked, the process yields monoalkenylation. To obtain the necessary compounds, methyl, ethyl, and butyl substituents were all thoroughly investigated. Surprisingly, when *n*-Bu_4NOAc was replaced by Me_4NOAc, just one C−H bond was broken, demonstrating strong chemoselectivity (see substrate scope, Scheme 20). Acrylates bearing different substituents, such as Cl, CN, and NO_2, were also successfully utilized, exhibiting remarkable functional group tolerance. The outcomes of subsequent experiments were not influenced by the electronic characteristics affecting reaction pursuits. The proposed methodology, which uses molecular oxygen as the only source, is promising for the regulated monoalkylated product and its conversion into annulated products compared to the uncontrolled annulation reported in Scheme 19.

2.3.2. Synthesis of 2,3-Fused Indole Compounds. Direct benzannulation reactions are effective tools in organic chemistry to construct polyaromatic compounds via direct metal-catalyzed C−H bond activation.[118] Thus, in 2018, Zhou et al. and Wang et al. disclosed the strategy for synthesizing carbazole scaffolds using a Rh catalyst.[119] Zhou et al. described the benzannulation reaction of N-substituted indole **87** with 1,3-dienes **88** in the presence of Rh(III) catalyst and $Cu(OAc)_2 \cdot H_2O$ as an additive in MeOH under O_2 at 40 °C, which resulted in various carbazole derivatives **89** including quinolin-2(1*H*)-ones, acridin-9(10*H*)-ones, and phenanthridin-6(5*H*)-ones. The reaction is governed by the π-allyl metal complex, which is generated from C−H activation followed by 1,3-diene insertion and the intramolecular nucleophilic allylic substitution reaction (Scheme 22). The procedure is undoubtedly one of the crucial techniques for producing carbazoles successfully because various often

Scheme 20. Regioselective C−H Activation and Dialkenylation/Annulation Cascade



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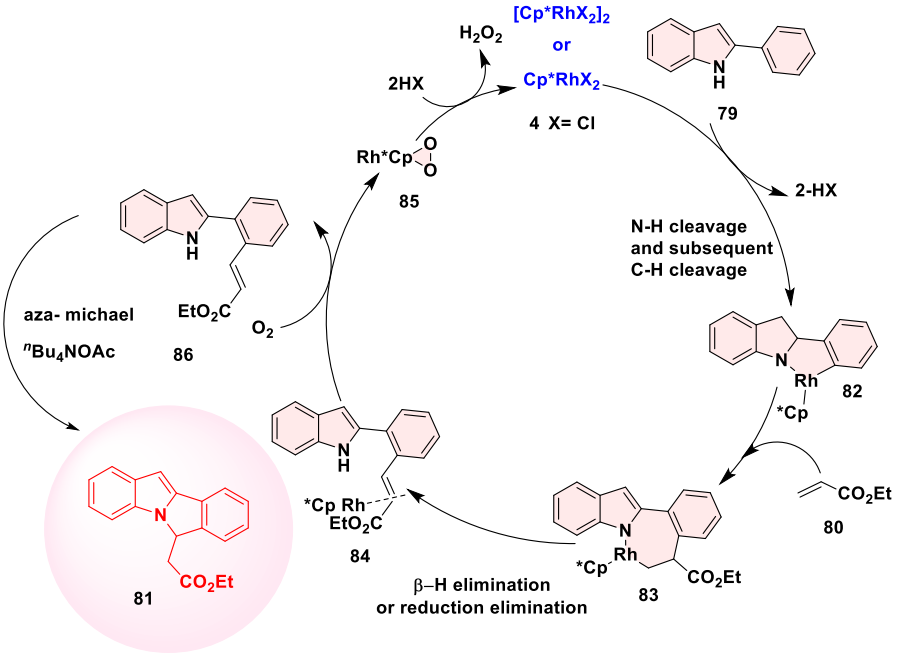
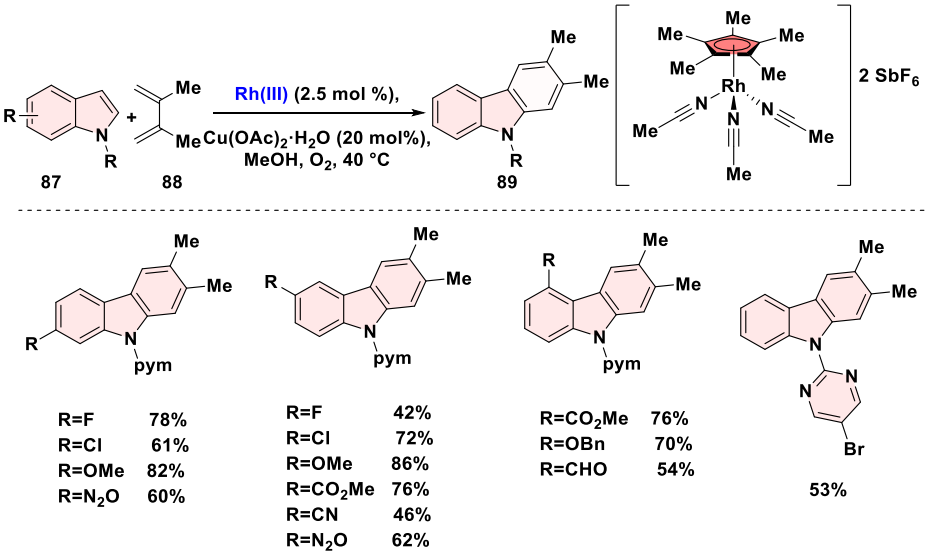
Scheme 21. Mechanistic Approach for Regioselective C−H Activation and Dialkenylation/Annulation Cascade



Scheme 22. Synthesis of Benzo-Fused *N*-Heterocycles via Direct Benzannulation with 1,3-Dienes



encountered functional groups (F, Cl, ether, etc.) were well tolerated. Other N-containing heterocycles, such as pyridines and thiazoles, may also function well as directing groups in the synthetic strategy. Wide-ranging substitution options are one of the methods' advantages over the conventional synthetic approach, which focuses on producing an N-heterocyclic ring. The introduction of patterns is simple with the newly formed benzene ring, and it was also proposed that the strong nucleophilicity of the corresponding N-heterocycle site had a significant impact on the observed reactivity.

2.4. Maleimides as Reacting Partners to Access Fused Indole Scaffolds. *2.4.1. Synthesis of 2,3-Fused Indole Compounds.* Maleimide-fused polyheterocycles are among the often-existing primary motifs in naturally occurring products and synthetic compounds with a wide range of biological and pharmacological activity.[41−43] Due to their widespread presence in pharmaceutical components and bioactive molecules, such as rebeccamycin, arcyriaflavin-A, granulatimide, angiogenesis inhibitors, anticancer drugs, and antiproliferative agents, maleimide-fused carbazoles are highly desirable candidates in organic synthesis.[120−124] Despite their significant contributions, there are still very few reliable ways to make maleimide-fused carbazoles or imidazo[1,2-*a*]pyridines. In 2017, Sheykhan et al. described a pseudo-Diels−Alder reaction using external alkenes and maleimides that used palladium as the catalyst to produce benzo isoindole-diones by successive C−H bond activation and dehydrogenative annulation.[125] Later, Bao et al. published a gentle and effective technique for synthesizing pyrrolo indole-diones by oxidizing 2-acetyl phenylhydrazines with maleimides under the guidance of rhodium.[126] The successful synthesis of maleimide-fused polyheterocycles using tetrasubstituted 1,3-enynes and alkylated 3*H*-pyrrolo[1,2-*a*]indol-3-one derivatives

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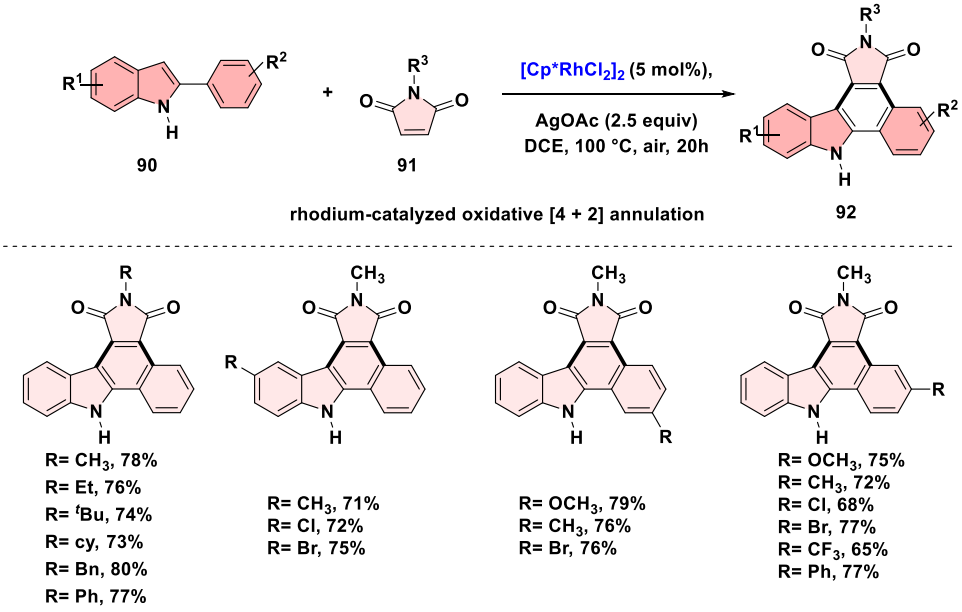
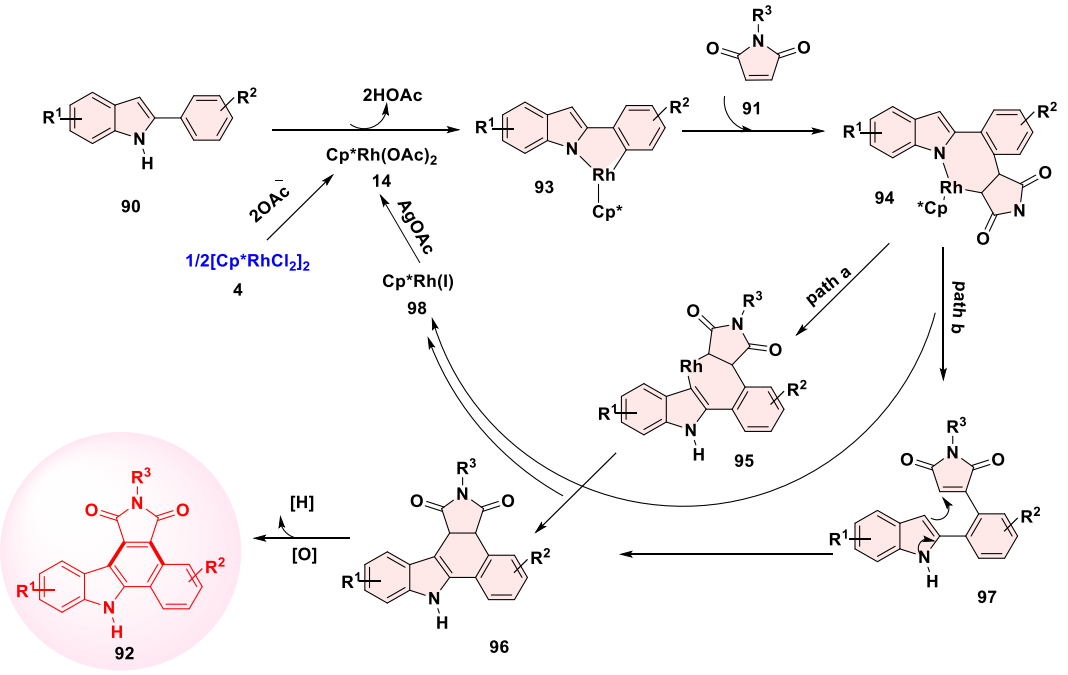
Scheme 23. Synthesis of Maleimide-Fused Benzocarbazoles via [4 + 2] Oxidative Cycloaddition



Scheme 24. Mechanistic Approach for the Synthesis of Maleimide-Fused Benzocarbazoles



of indoles and 1,3-diynes was recently demonstrated by Zhang and co-workers using an Rh-based catalyst system.[126,127] In contrast to prior work, Fan et al. in 2020 presented an effective and sustainable method for producing the pharmaceutically and synthetically important maleimide-fused benzocarbazoles **92** by oxidative [4 + 2] annulation of 2-arylindoles **90** with maleimides **91** (Scheme 23).[128]

Initially, the *in situ* generated active catalyst, $Cp^*Rh(OAc)_2$ **14**, interacts with **90**, followed by N−H and C−H cleavage, producing a five-membered rhodacyclic intermediate **93**. Next, the so-formed rhodacyclic intermediate **93** endured coordination and migratory insertion with **91** which resulted in a seven-membered rhodacyclic intermediate **94**. After the subsequent rollover of cyclometalation of **94**, intermediate **95** was produced, which further underwent reductive elimination that resulted in the intermediate **96** with the regeneration of the Rh(I) species (see path a, Scheme 24). On the other hand, intermediate **94** proceeded through a hydride elimination to produce intermediate **96** via intramolecular cyclization in intermediate **97**. Finally, intermediate **96** turned into the desired carbazole **92** by an oxidative aromatization step (Scheme 24). AgOAc was also found to oxidize the Rh(I) species to produce active Rh(III) for the subsequent catalytic cycle. The findings demonstrated that various maleimide substituents, including Et, Bu, and Bn, were compatible under normal circumstances. The desired product was available in moderate to good yields when the indole and benzene rings were halogenated or substituted differently. Notably, using this method, significant yields were obtained for

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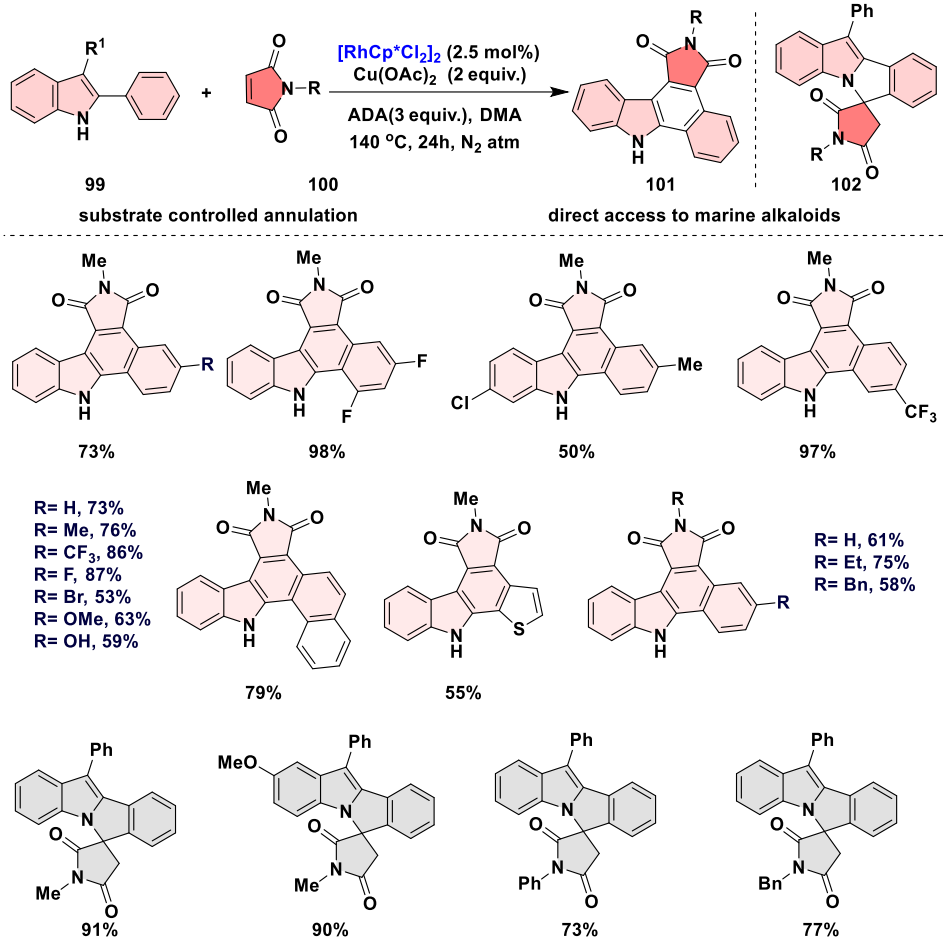
Scheme 25. Dehydrogenative Annulation and Spirocyclization of 2-Arylindoles



the seamless synthesis of a bioactive molecule. The method showed a limited range of dialkynes, and most of the products were produced from 1,3-diyne precursors with alkyl substitutions. Nevertheless, some of these well-known methods involve lengthy, multistep synthetic processes, challenging reaction conditions, and substantial waste production. Strong functional group tolerance, the use of widely accessible substrates, and high atom efficiency are all advantages of this method.

The effective conversion of readily available starting materials into lucrative carbo- and heterocycles was made possible by spirocyclization and annulation methods.[129,130] Therefore, considering the immense biological activity and substantial growth of Rh(III) catalysts to promote the synthesis of highly functionalized carbazoles, Kumar et al. in 2021 explored the synthesis of highly functionalized carbazole **101** and pyrrolidine **102** utilizing a Rh(III)-catalyzed cascade approach.[131] The dehydrogenation of maleimides **100** by Rh(III) followed by spirocyclization with 2-aryl indoles **99** was explored under the most benign reaction conditions (Scheme 25). The stated cascade annulation was initiated by coordinating activated Rh species **14** (generated after ligand exchange) with the nitrogen atom of indole **99**. Then a coordinated metalation−deprotonation route offered the rhodacycle **103** (via cleavage of the aryl group O−C−H bond) (Scheme 26). Subsequently, the formed rhodacycle **103** coordinated with maleimide **100** to afford intermediate **104**. The formed intermediate **104** underwent migratory insertion to access the key intermediate **105**, followed by intermediate **106**, and rollover of the indole backbone (if the C-3 position is unsubstituted) offered the substrate-controlled annulation intermediate **107** along with Rh(I) species utilizing C−H activation. Further, the so-formed generated intermediate **107** underwent oxidation to afford annulated substrate **101**.

On the other hand, reductive elimination offered by rhodacycle **105** produced substituted C-3 indole derivative **108**. Finally, intermediate **108** underwent instantaneous aza-Michael addition to develop the spiro-product **102**, followed by the regeneration of the Rh(III) catalyst assisted by $Cu(OAc)_2$ (Scheme 26). The highlighted method provided a large number of spirocyclic and annulated indole compounds with good yields. The aforementioned method provided remarkable functional group tolerance with a wide range of substrate applicability, stability, and scope. Maleimides were successfully used to annulate a variety of 2-arylindoles with various functionalities, including CF_3, OMe, Br, and F, to produce the required product in good to outstanding yields. The fact that 2-arylindoles had better yields of the annulated products when electron-withdrawing groups were attached to the C-2 aryl ring is noteworthy. In 79% and 53% of the reactions, respectively, naphthalen-1-yl-1*H*-indole and 2-(thiophen-2-yl)-1*H*-indole offer the required core alone. Similar outcomes, up to 90% of the target yield, were found for spiro products (see substrate scope in Scheme 25).

2.5. Iodonium Yields and Quinone As Reacting Partners to Access Indole-Fused Scaffolds. *2.5.1. Synthesis of 1,2- and 2,3-Fused Indole Compounds.* Intriguingly, pyrrolo[1,2-*c*]pyrimidin-1(2*H*)-ones, pyrimido[1,6-*a*]indol-

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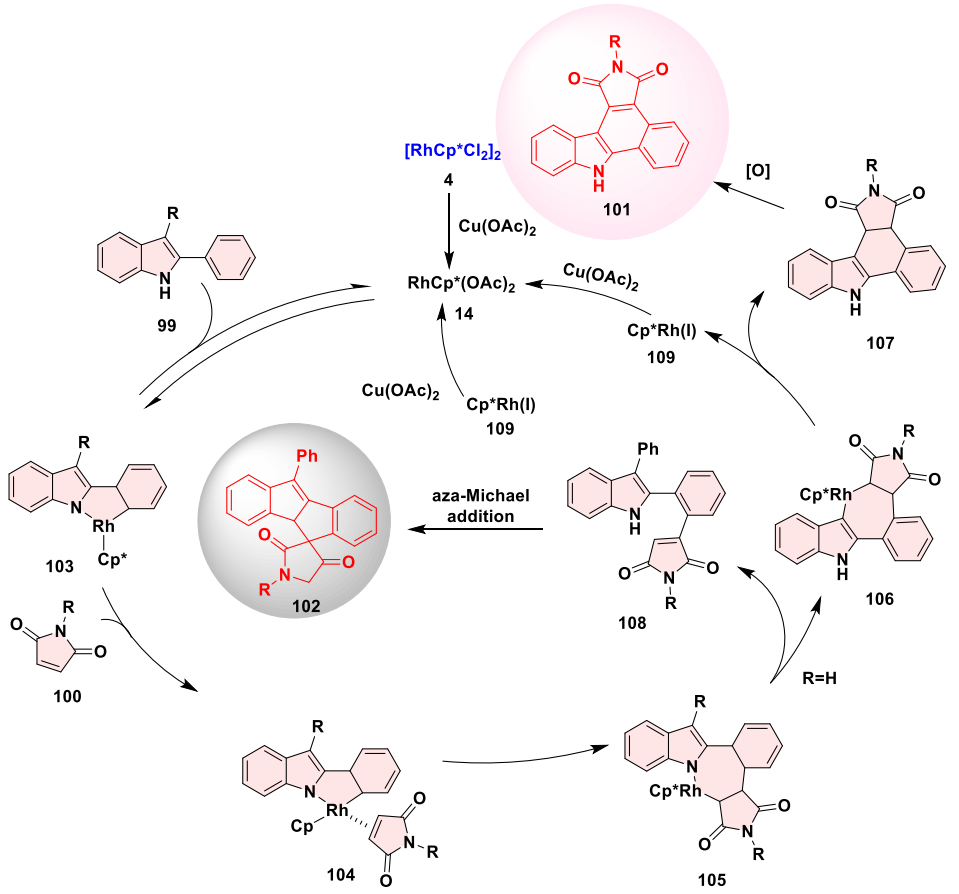
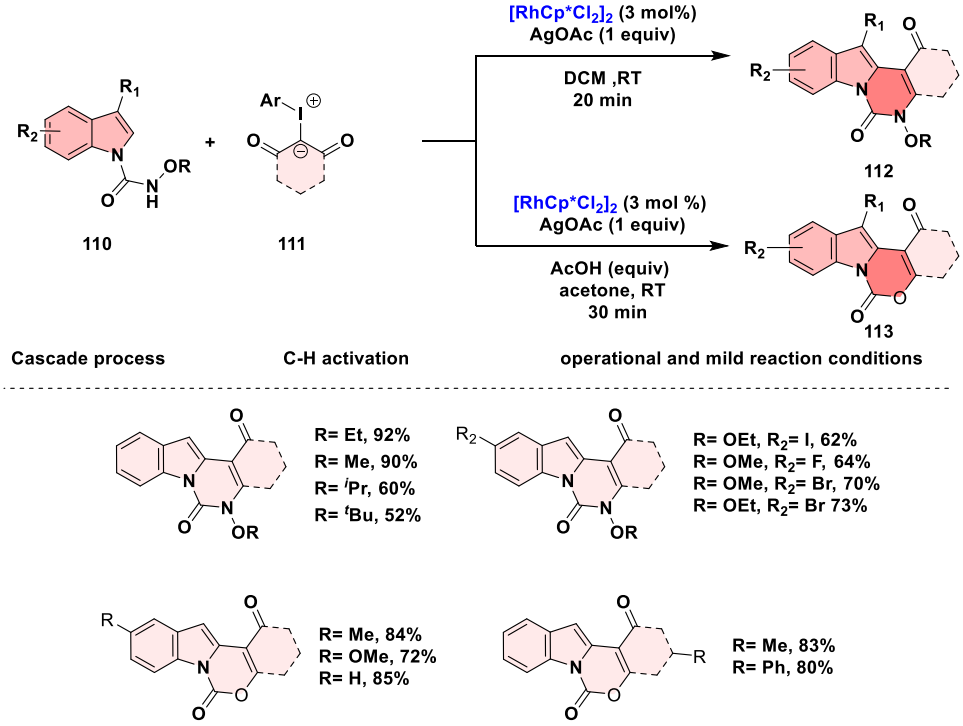
Scheme 26. Mechanistic Approach for Dehydrogenative Annulation and Spirocyclization



Scheme 27. Chemodivergent Annulations between Indoles and Iodonium Carbenes



1(2*H*)-ones, 1*H*-[1,3]oxazino[3,4-*a*]indol-1-one, etc., scaffolds are the among integral parts of fluorescent materials and with diverse biological activity.[132,133] As a result, both natural products and medicinal chemistry paid close attention to synthesizing these compounds.[134] In order to quickly fabricate 2*H*-pyrimido[1,6-*a*]indol-1-one derivatives, Chen and co-work-

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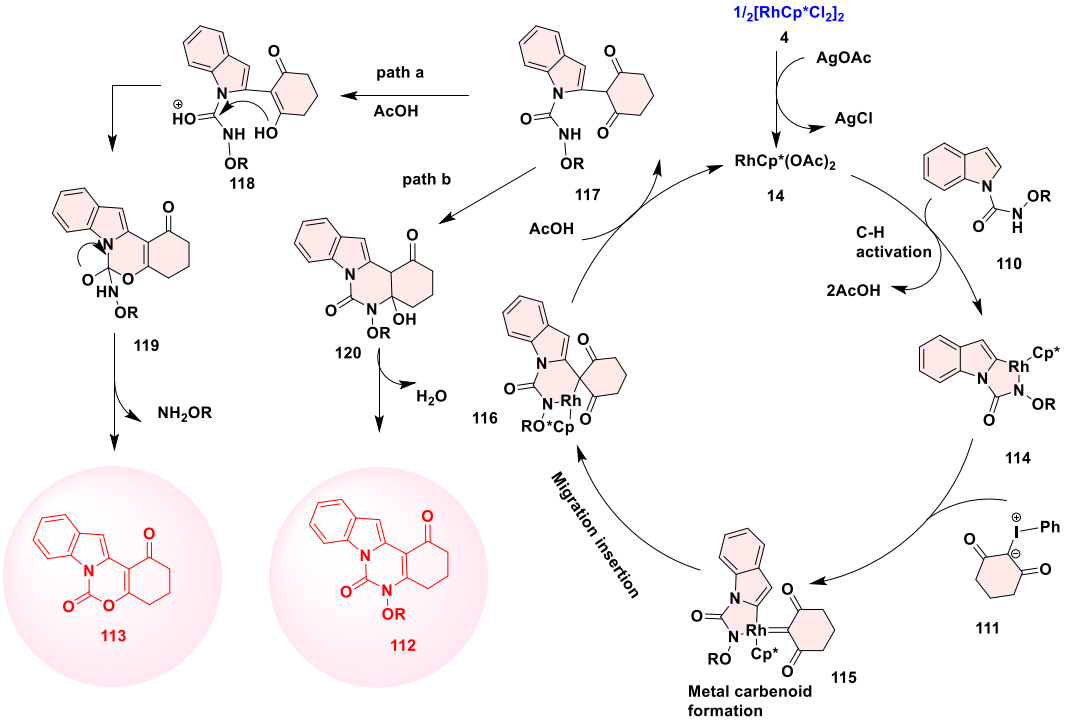
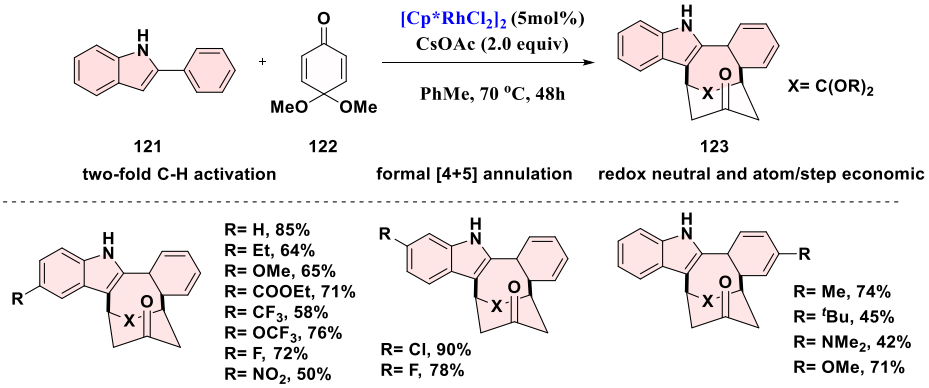
Scheme 28. Mechanistic Approach for Chemodivergent Annulations between Indoles and Iodonium Carbenes



Scheme 29. C−H Activation of 2-Arylindoles and Annulation with Quinone Monoacetals to Access Bridged Carbocycles



ers previously developed the Rh(III)-catalyzed [4 + 2] annulation of *N*-alkylaminocarbonyl indole with acyl diazo compounds.[135] For the synthesis of fused oxazinones, Zhang and colleagues developed the [3 + 3] annulation of *N*-carboxamide indoles and diazonaphthalen-2(1*H*)-ones in Rh-(III).[116] The Chen group recently generated dihydropyrimidoindolone and tricyclic [1,3]oxazino[3,4-*a*]indol-1-one derivatives via cascade [4 + 2]/[3 + 3] annulations of *N*-carbamoyl indoles with sulfoxonium ylides.[136] These reactions are less attractive due to their limited nature, although providing a tempting route to indole C−H annulation. In 2021, Kanchupalli et al. presented [4 + 2] and [3 + 3] annulations of *N*-carboxamide indoles **110** with iodonium ylides **111** to produce synthetically significant N-heterocycles **112** and **113**, using iodonium ylide as a precursor to a carbene (Scheme 27).[137] This technique offered new tri- and tetracyclic scaffolds with a wide range of functional group tolerance and moderate to good yields. The stated reaction strategy commenced with the generation of an active catalyst Cp*Rh(OAc)$_2$ **14**, which cleaves the C−H bond of *N*-alkoxycarbamoyl indoles **110** at the C2 position to generate five-membered rhodium species **114**. The metal carbene species **115** was then produced by coordinating iodonium ylide **111** to the metal center in **114**. The intermediate **116** was produced by following the migratory insertion and was protonated to produce intermediate **117** and restore active catalyst species **14**. Intermediate **117** adopted various annulation routes. The [4 + 2] annulation product **113** was produced by dehydration when the amide NH group nucleophilically attacked the carbonyl via **118** and **119**. In contrast, path b favored the synthesis of [3 + 3] annulation product **112** by removing NH$_2$OR by activating the amide group toward nucleophilic attack by the enol oxygen via **120** (Scheme 28). The synthetic protocol's usefulness was increased to include a wide range of chemical alterations and was easily scaled to a large level. Exclusively halogen-substituted indoles also experienced [3 + 3] cyclization to produce the necessary products, among the diversity of substrates for substituted indole H, Me, OMe, and OBn, offering outstanding yields for cyclized products. Notably, the indole's π-electron-withdrawing groups produced sluggish reactivity, leading to relatively reduced yields.

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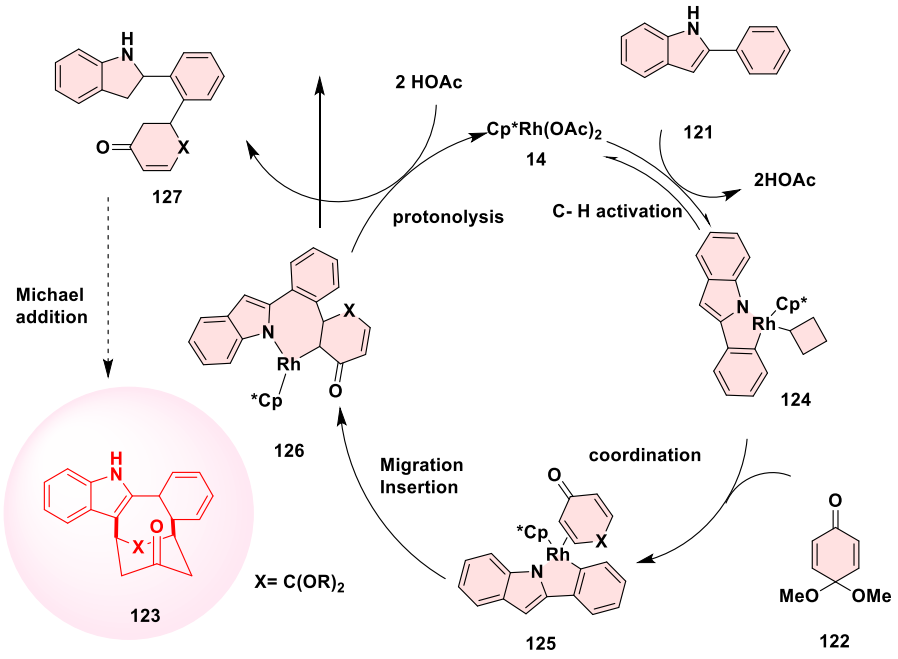
Scheme 30. Mechanistic Approach for C−H Activation of 2-Arylindole Quinone Monoacetals



The protocol provides novel tri- and tetracyclic scaffolds with a wide range of functional group tolerance and moderate to excellent yields, including 3,4-dihydroindolo[1,2-*c*]quinazoline-1,6(2*H*,5*H*)-dione and 1*H*-[1,3]oxazino[3,4-*a*]indol-1-one derivatives.

Gratifyingly, Zheng et al. described the easy synthesis of [4,3,1]-bridged carbocycles **123** with sole C(3) selectivity by the Rh(III)-catalyzed annulation of N-unprotected 2-arylindoles **121** with quinone monoacetals **122** (Scheme 29).[138] According to the mechanistic investigations, the developed coupling was most likely carried out via 2-fold C−H activation with 2-fold migratory insertion into the enone moieties and proved by deuterium-labeling experiments. To synthesize fused eight- and four-membered carbocycles, the same group described the Mn(I)-catalyzed coupling of 3-alkenyl/allyl indoles with propargylic carbonates, and the process took place in conjunction with pericyclic reactions and C−H allenylation.[139] Contrarily, the Reddy group created cyclohexenone-catalyzed bicyclization of 2-arylimidazo[1,2-*a*]pyridine with Rh(III) for the synthesis of [4,3,1]-bridged imidazopyridines.[140] Despite these advancements, there was still a high demand for simple and atom-efficient medium-sized carbocycles made from widely accessible building blocks. Thus, Zheng et al. further explored 2-phenylindole and quinone monoacetal to get the desired product, where the reaction commenced with the generation of 5-membered rhodacycle **124** by cyclorhodation of 2-phenylindole **121** from an active [Cp*Rh(OAc)$_2$] **14** species produced by anion exchange. Quinone monoacetal **122** was then coordinated to produce Rh(III) olefin complex **125**. A seven-membered rhodacycle **126** was produced by the migratory insertion of the RhC(aryl) bond into the olefin unit, and it was anticipated that this rhodacycle would undergo protonolysis to produce an alkylated intermediate and regenerate the Rh(III) catalyst. Finally, intermediate **127** underwent a Michael addition process to afford **123** as the desired product (Scheme 30). Alkyl, alkoxy, CF_3, NO_2, and halogens were all tolerated when added to the 5- and 6-positions of the indole ring, but no reactivity was seen with the 7-methy-2-phenylindole, probably because of steric hindrance surrounding the NH directing group. Under redox-neutral conditions, this coupling provided direct access to [4,3,1]-bridged carbocycles with excellent C(3) selectivity. Mechanistic research, in particular H/D exchange trials, points to a dual C−H activation/migratory insertion pathway as the most plausible pathway by which C(3) annulation occurs.

3. CONCLUSION

To conclude, this review reports substantial advances and promising selective functionalization of indoles with descriptive compilations powered by the Rh(III) catalysis [(RhCp*Cl$_2$)$_2$] pathway. The fascinating methods for modifying the essential components of the indole skeleton are discussed, paying particular attention to the fabrication of new catalysts based on Rh, the advancement of new site-specific C−H functionalization techniques, and the benefits of using catalytic manifolds to gain access to vital bioactive scaffolds. Since the development of new, extremely effective procedures, transition-metal-free aided protocols have made direct indole functionalizations that were previously thought to be impractical. Modern, sophisticated synthetic methods for functionalizing indoles and pertinent cores are frequently based on the use of less complex and inexpensive precursors. Implementing new procedures in the complete synthesis of natural products, along with better selective functionalization of indole-based scaffolds, will significantly impact the synthetic community. With the stated objective, we examined the fascinating recent indole functionalization discoveries that allow access to indole-based polycyclic scaffolds via the Rh(III) catalysis system. This review focuses mostly on introducing a significant catalyst to produce promising skeletons by functionalizing indole moieties at specific positions to provide 1-, 2-, 3-, and 4-indole-fused polycycles. With this review, we anticipate rapid and beneficial progress in the functionalization of indoles and their potential implementations for synthesizing complex frameworks.

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