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Review

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Mini-review on the progress in the synthesis of carbolines: classical and metal - catalyzed synthetic approaches (2020-2026)

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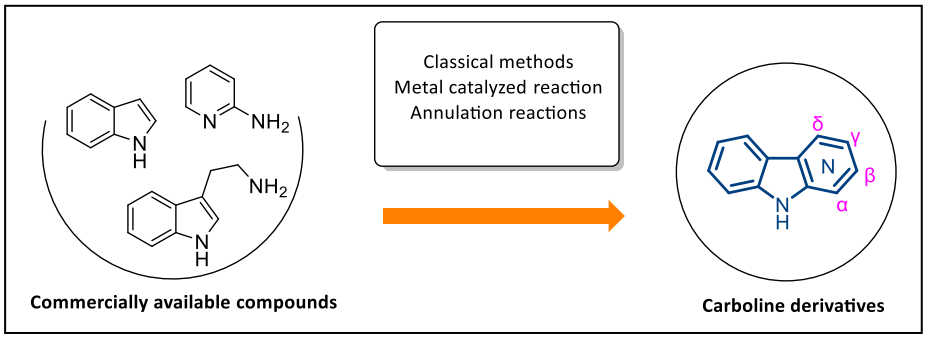
Abstract

Carbolines represent a versatile class of N-heterocyclic compounds with significant biological and synthetic interest. This review provides a focused overview of recent advances in the synthesis of carboline scaffolds via transition metal-catalyzed methodologies reported between 2020 and 2026. For contextual purposes, selected classical and non-catalyzed synthetic approaches are briefly introduced to highlight the evolution of carboline synthesis. The main discussion emphasizes modern annulation strategies and C–H functionalization methods that enable the regioselective construction of α-, β-, γ-, and δ-carboline frameworks. These approaches feature economical protocols, the use of readily available starting materials, and operational simplicity, facilitating access to structurally diverse and potentially bioactive carboline derivatives. Collectively, the methodologies discussed provide practical and versatile tools for the preparation of biologically relevant heterocycles, supporting further exploration of their medical and pharmacological potential.



Keywords: Carbolines, C–H functionalization, metal-catalyzed reactions, cyclization.

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1. Introduction

Among the N-heterocycles, carbolines represent a significant class of alkaloids belonging to the family of natural heterocyclic compounds. Structurally, they consist of a tricyclic fused system comprising an indole moiety condensed with a pyridine ring, being classified according to the position of the nitrogen atom in this last – *α-, β-, γ-,* or *δ-* isomers.[1] Carbolines are found in a wide variety of natural sources, possessing an unique heterocyclic core that endows them with a broad spectrum of biological activities, such as, antitumor activity, treatment of anxiety disorders, antipsychotic agent and antiviral. Thus, carbolines are extremely relevant in both natural product and medical chemistry (Figure 1).[1–4]

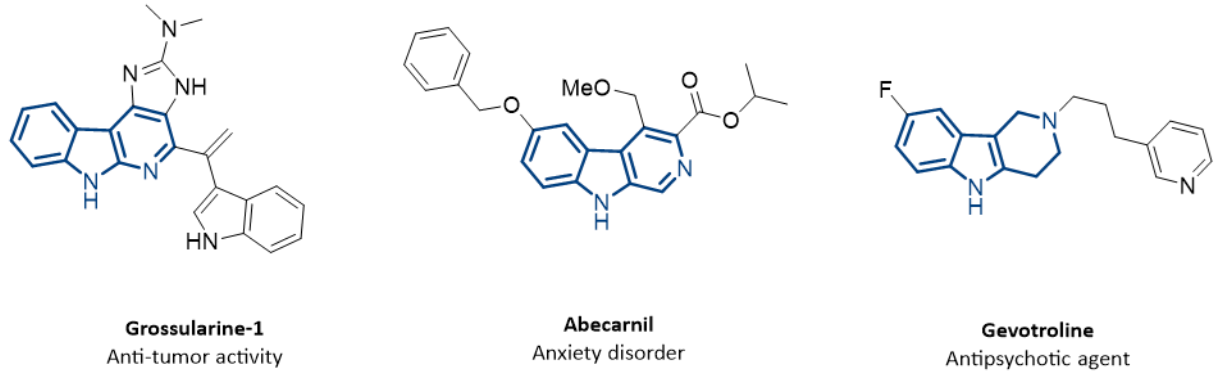

Figure 1. Representative examples of carbolines derivatives exhibiting biological activity.

Grossularine-1 is a naturally occurring α-carboline alkaloid and was among the first compounds isolated from *Dendrodoa grossularia* by Pattey and Guyot, in 1989. It was shown to exhibit cytotoxic activity against human tumor cells. Since then, numerous synthetic methodologies have been developed to access Grossularine-1 and other biologically active carbolines, underscoring their importance. Their relevance spans from medicinal chemistry to organic synthesis, due to their interesting biological activity, novel synthetic strategies have been developed.[5]

Recently, β-carboline based scaffolds have been identified as promising antidiabetic agents.[6] β-carboline hybrids have been shown to effectively inhibit α-amylase and α-glucosidase, key enzymes in carbohydrate digestion and post-meal glucose control. Their inhibitory activity is greatly influenced by the functional groups on aromatic rings and hydrazone moiety, halogens (bromo, chloro) and methoxy groups

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enhance binding through hydrophobic contacts, hydrogen bonding, and π-π stacking. Docking studies highlight how these substituents optimize binding by interacting with specific amino acids, underscoring the potential of β-carboline scaffolds for designing effective antidiabetic drugs.

In addition to their established importance in medicinal chemistry, carboline frameworks have attracted increasing interest in materials science due to their distinctive electronic, photophysical, and charge-transfer properties. The extended π-conjugated structure of carbolines enables tunable optical responses, including fluorescence and photoinduced electron-transfer behavior, making them valuable scaffolds for the development of functional materials and sensing platforms. Consequently, carboline-based derivatives have been investigated as molecular probes and sensing motifs for applications ranging from biological imaging to the detection of environmentally relevant analytes. Recent studies have highlighted their potential in the construction of fluorescent sensors and analytical systems, further expanding the significance of carboline chemistry beyond pharmaceutical applications.[7–9]

Carboline synthesis has been extensively explored over the past decades, as reflected by numerous comprehensive reviews covering classical approaches, total syntheses, and diverse functionalization strategies.[4,10–17] These studies highlight the richness and continued evolution of methodologies for assembling carboline frameworks.

This mini-review surveys the classical synthetic methodologies that have historically underpinned the construction of carboline *N*-heterocycles. Established approaches, including Pictet–Spengler cyclization, Fischer indole synthesis, and other condensation reactions, that have enabled the synthesis of a wide range of carbolines. In contrast, recent developments have emphasized transition-metal (TM)-catalyzed strategies, such as cross-coupling, C–H functionalization, and cyclization reactions, which offer enhanced selectivity, allow for greater structural complexity and functional-group tolerance. By examining both classical and contemporary synthetic routes, this mini-review aims to provide a comprehensive perspective on carboline synthesis, essentially the TM-catalyzed methodologies between 2020 and 2026 with significance for both medicinal chemistry and synthetic methodology development.

2. Classical Approaches to Carboline Synthesis

The growing interest in the carboline scaffold, largely driven by its diverse biological activities, has stimulated the development of numerous synthetic methodologies. A wide array of strategies has been reported for the preparation of different carboline isomers, frequently employing pyridine and aniline derivatives as key starting materials. Broadly, these approaches can be classified into two main categories: TM-catalyzed methodologies and classical, non-catalytic strategies, including reactions such as modified Graebe–Ullmann protocols and Diels–Alder cycloaddition reactions (Scheme 2).

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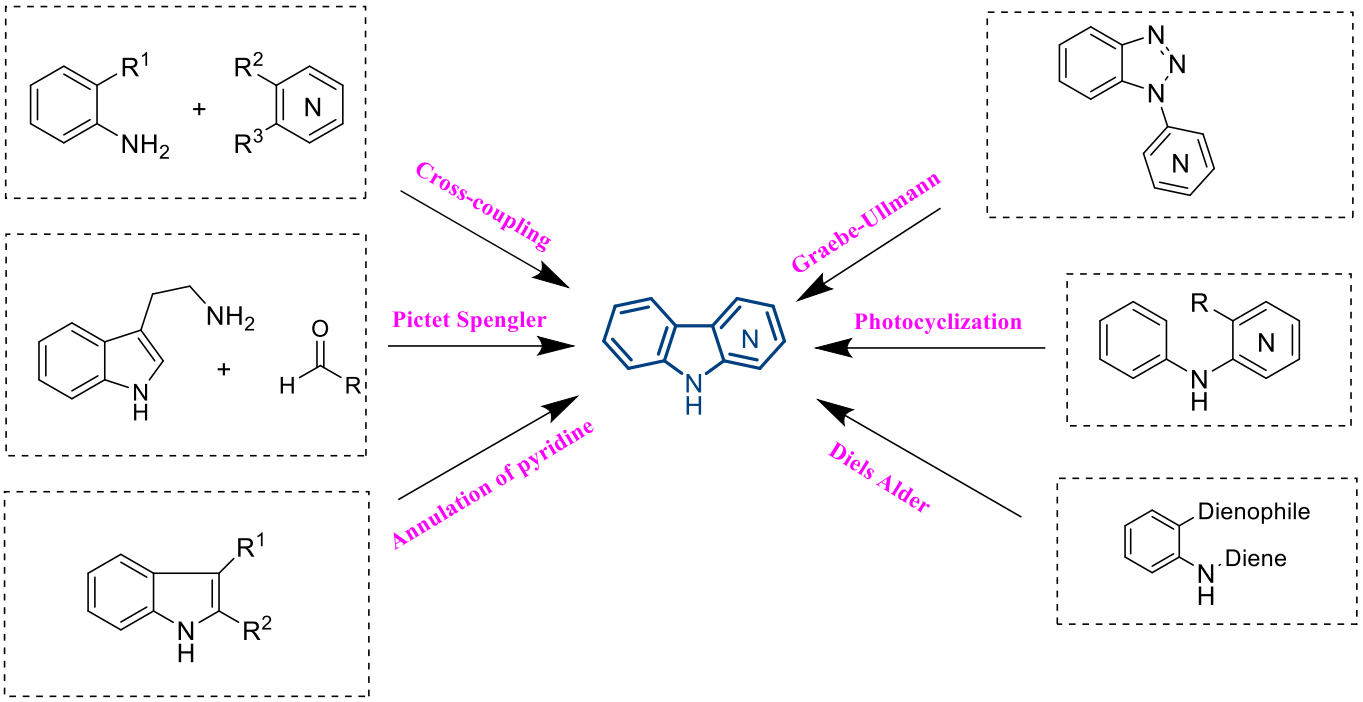
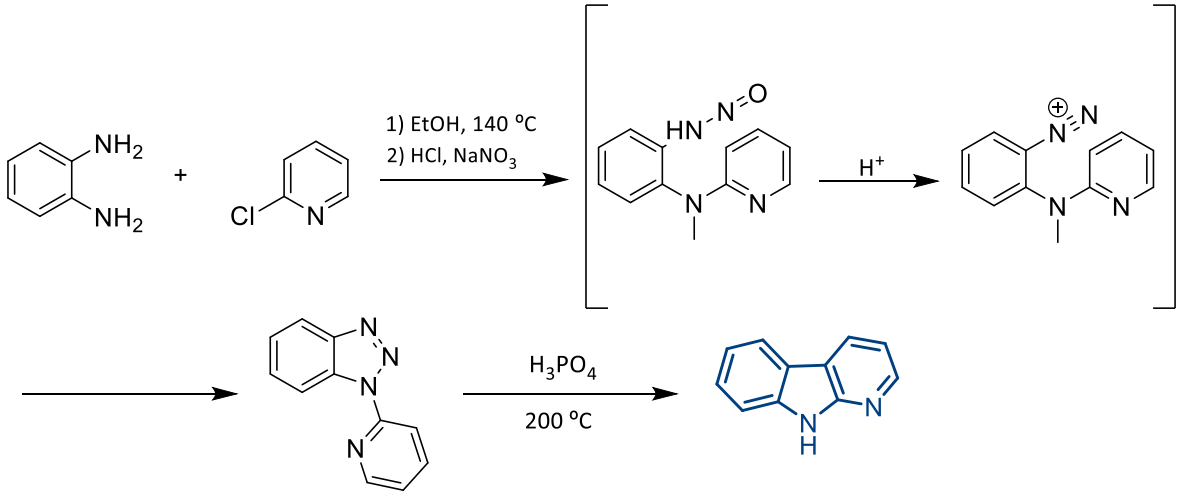


Scheme 2. Classical synthetic methods for carbolines.

The Graebe–Ullmann reaction, first reported in 1889 for the synthesis of carbazole, later emerged as a foundational strategy for the preparation of carboline derivatives—particularly α- and γ-carbolines—through the so-called modified Graebe–Ullmann protocol.[8] In this approach, *o*-phenylenediamine reacts with 2-chloropyridine to form an intermediate that, upon diazotization with nitrous acid, generates a diazonium species and subsequently an N-pyridyl triazole. Acid-induced cyclization, typically promoted by phosphoric acid, ultimately furnishes the carboline core (Scheme 3).[18,19]



Scheme 3. Modified Graebe-Ullmann reaction described by Robinson et al.[19]

Another well-established method for the synthesis of carbolines, particularly β-carbolines, is the Pictet-Spengler reaction. Typically, this transformation involves the condensation of tryptamine or a related derivative with an aldehyde or ketone to generate an iminium ion intermediate. Nucleophilic attack of the indole ring at the

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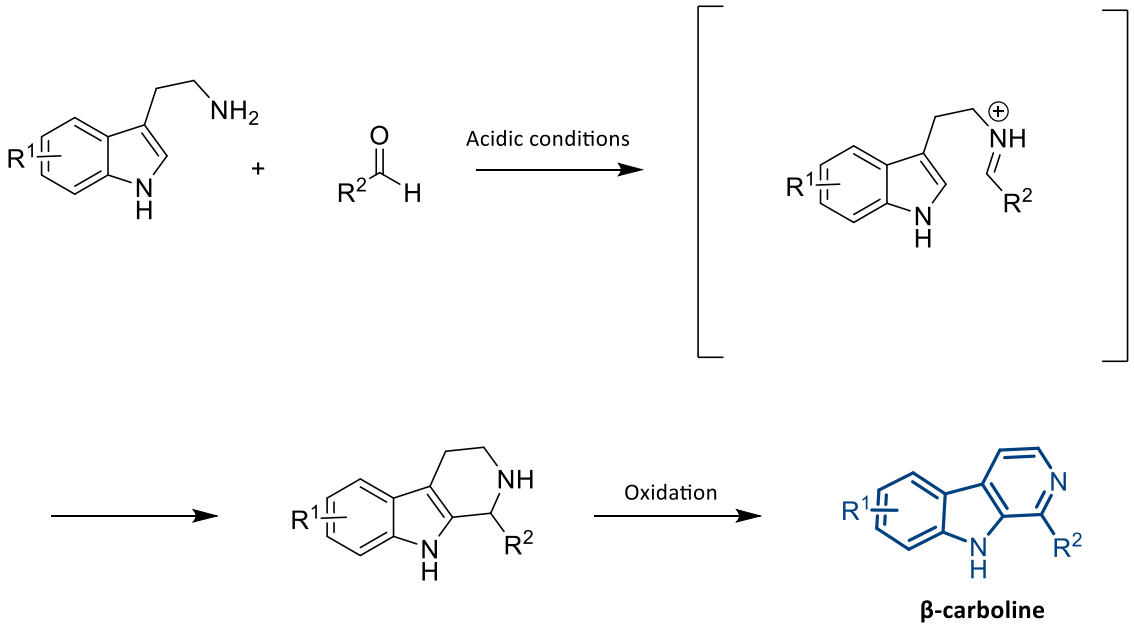
iminium carbon forms a new C–N bond, leading to cyclization and construction of the carboline framework. Aromatization of the resulting β-carboline skeleton is then achieved through a subsequent oxidation step (Scheme 4).[12,20,21]



Scheme 4. General scheme of the Pictet-Spengler reaction towards *β*-carboline.[12,20]

Although classical methodologies have provided reliable access to carboline core structure, these approaches often present challenges, such as restricted substrate scope, functional group tolerance, harsh reaction conditions and low overall efficiency. These drawbacks have motivated the development of (TM)-catalyzed transformations, which offer more versatile and selective routes to carboline frameworks.

3. Transition-Metal (TM)-catalyzed approaches to carboline synthesis (2020-2026)

In the context of carboline synthesis, TM catalysis has emerged as a particularly powerful strategy, enabling the formation of C–C and C–N bonds with enhanced selectivity and broad functional-group tolerance. These TM-catalyzed processes often proceed under milder conditions and allow access to highly substituted and structurally diverse carboline derivatives. A variety of transition metals, including ruthenium, rhodium, iridium, copper, have been employed in the synthesis of this important class of N-heterocycles.[22–25]

3.1. Rhodium catalyzed approaches

Rhodium catalysts are among the most powerful TM-catalysts in modern organic synthesis, valued for their exceptional reactivity, selectivity, and broad applicability. Although rhodium is less abundant and more expensive than many other transition metals, its remarkable catalytic efficiency and ability to operate under mild conditions often justify its use in both academic research and industrial processes. Rhodium complexes are particularly renowned for their high chemo-, regio-, and enantioselectivity, making them indispensable in the synthesis of structurally complex molecules.[25]

Among the many studies employing rhodium catalysis, Yang and co-workers reported in 2020 an efficient

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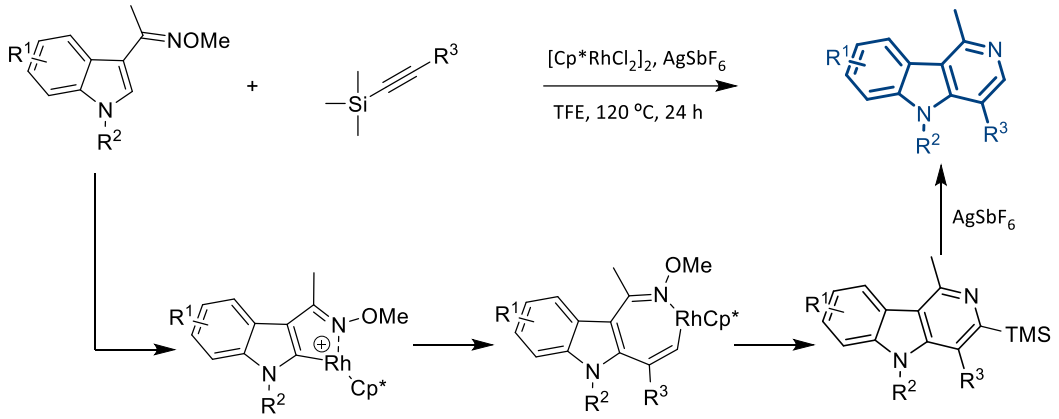
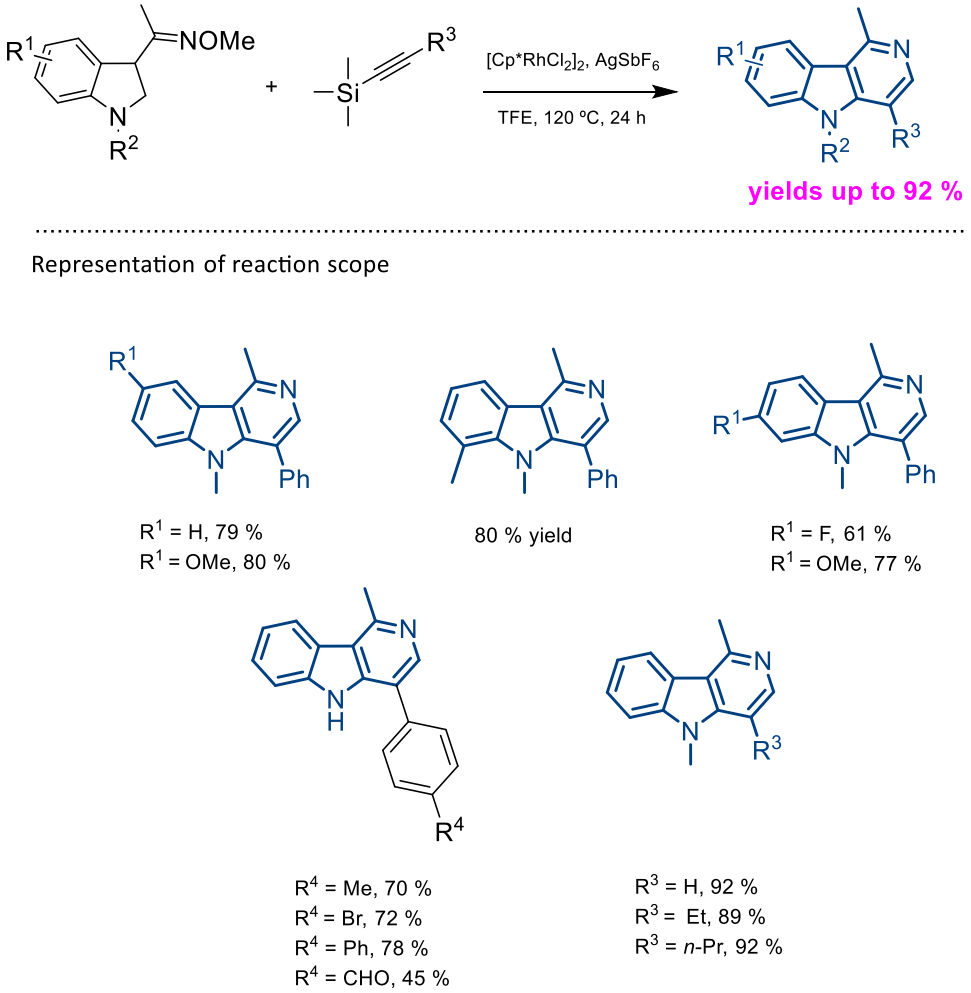
strategy for the synthesis of γ-carboline derivatives (Scheme 5 and 6).[26] In this transformation, an N-protected indole *O*-methyloxime reacts with alkynyl silanes in the presence of a rhodium catalyst, affording the desired carboline frameworks in high yield.



Scheme 5. Synthesis of y- carbolines via rhodium (III) catalysed from N-protected indole-*O*-methyloxime.[26]



Scheme 6. Representation of reaction scope of y- carbolines via rhodium (III) catalyzed from N-protected indole-*O*-methyloxime.[26]

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This rhodium-catalyzed C–H annulation strategy provides an efficient route to γ-carbolines under redox-neutral and relatively mild reaction conditions. Employing a catalytic system based on $[Cp^*RhCl_2]_2$ and $AgSbF_6$, the methodology exhibits a broad and versatile substrate scope, tolerating a wide range of functional groups, including halogens, esters, nitriles, aldehydes, alkyl, phenyl, bromo, and heteroaryl substituents such as thienyl and naphthyl derivatives. One of the most notable features of this protocol is its excellent regioselectivity, displaying an unusual reverse regioselectivity while maintaining high reaction efficiency across diverse substrates. These characteristics, together with the mild reaction conditions and redox-neutral nature of the transformation, make this approach an attractive strategy for the synthesis of structurally diverse γ-carbolines.

However, the methodology is not without limitations, as it relies on bulky alkynyl silanes to achieve the desired selectivity and exhibits poor reactivity with conventional terminal alkynes, which restricts its general applicability. Consequently, although this rhodium-catalyzed annulation represents a significant advance in γ-carboline synthesis, the development of catalytic systems capable of accommodating more readily available alkynes while preserving the excellent regioselectivity would further enhance its synthetic utility.

In addition, a variety of rhodium-catalyzed strategies have been developed for the construction of carboline frameworks. These include C–H activation/annulation processes involving indole derivatives and alkynes, oxidative coupling reactions, and intramolecular cyclization approaches, which enable the efficient synthesis of α-, β-, and γ-carbolines with high regioselectivity. These contributions collectively highlight the central role of rhodium catalysis in advancing modern methodologies for carboline synthesis.[27–29]

3.2. Copper catalyzed approaches

Copper catalysts are among the most widely used TM- catalysts in organic synthesis, due to their low cost, ready availability, low toxicity, and tolerance of a wide range of functional groups. These properties make copper particularly attractive for both academic research and large-scale industrial applications. Beyond these practical advantages, copper catalysis is highly versatile, enabling a variety of reactions including C–C, C–N, and C–O bond formation, as well as cyclization and annulation processes.[30]

In 2020, Zhao and his co-workers reported an atom economical synthesis of α- carbolines scaffolds with substitutions at C-2 and C-4 positions, by a domino reaction between o-alkenyl aryl isocyanides and vinyl azides using a dual catalyst of rhodium and cooper under oxygen atmosphere (Scheme 7 and 8).[31] This methodology generated diverse α-carbolines structures in good yields, with a key advantage of this protocol be the one-pot construction of two C–C bonds and one C–N bond, accompanied by the formation of two aromatic rings, under low catalyst loading.

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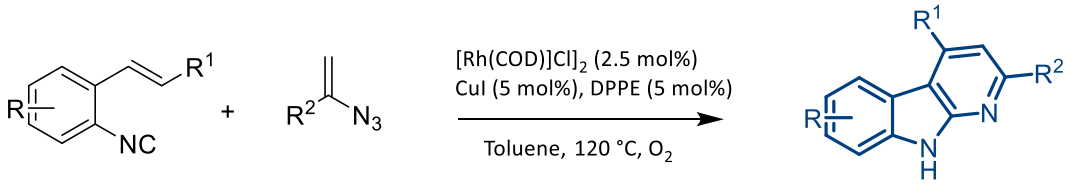
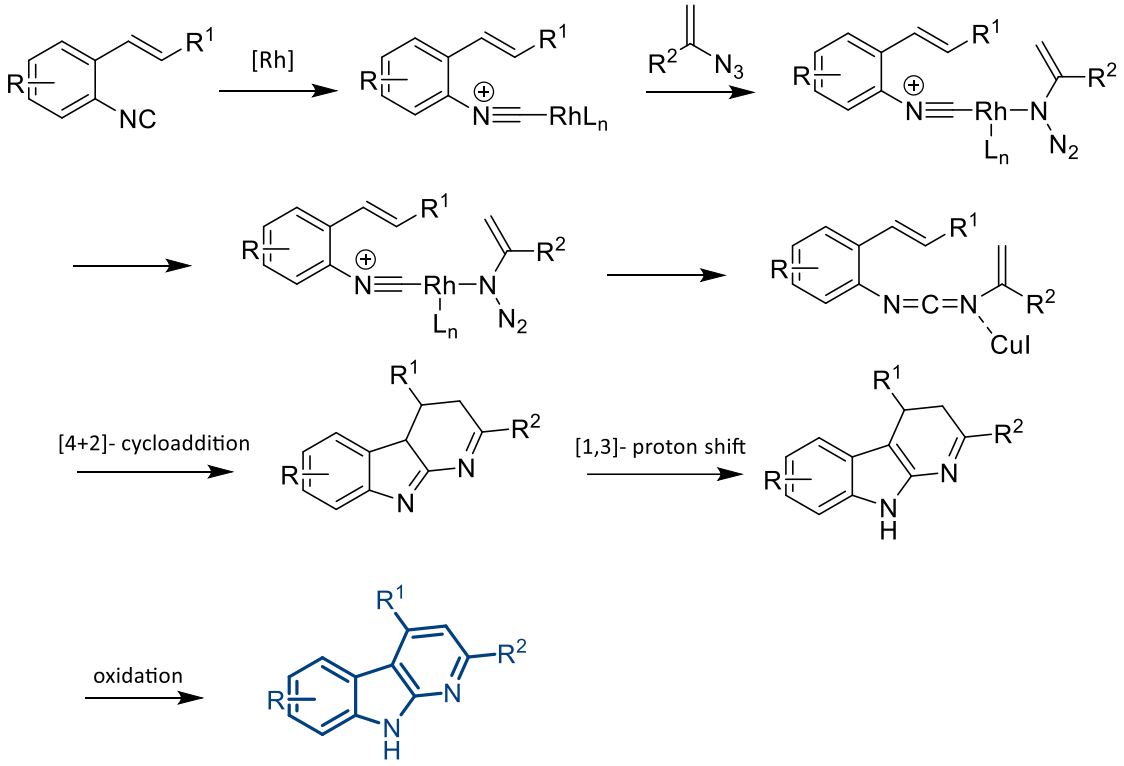


Proposed Mechanism



Scheme 7. Synthesis of α-carbolines using a rhodium/copper dual catalyst from o-alkenyl aryl isocyanides.[31]

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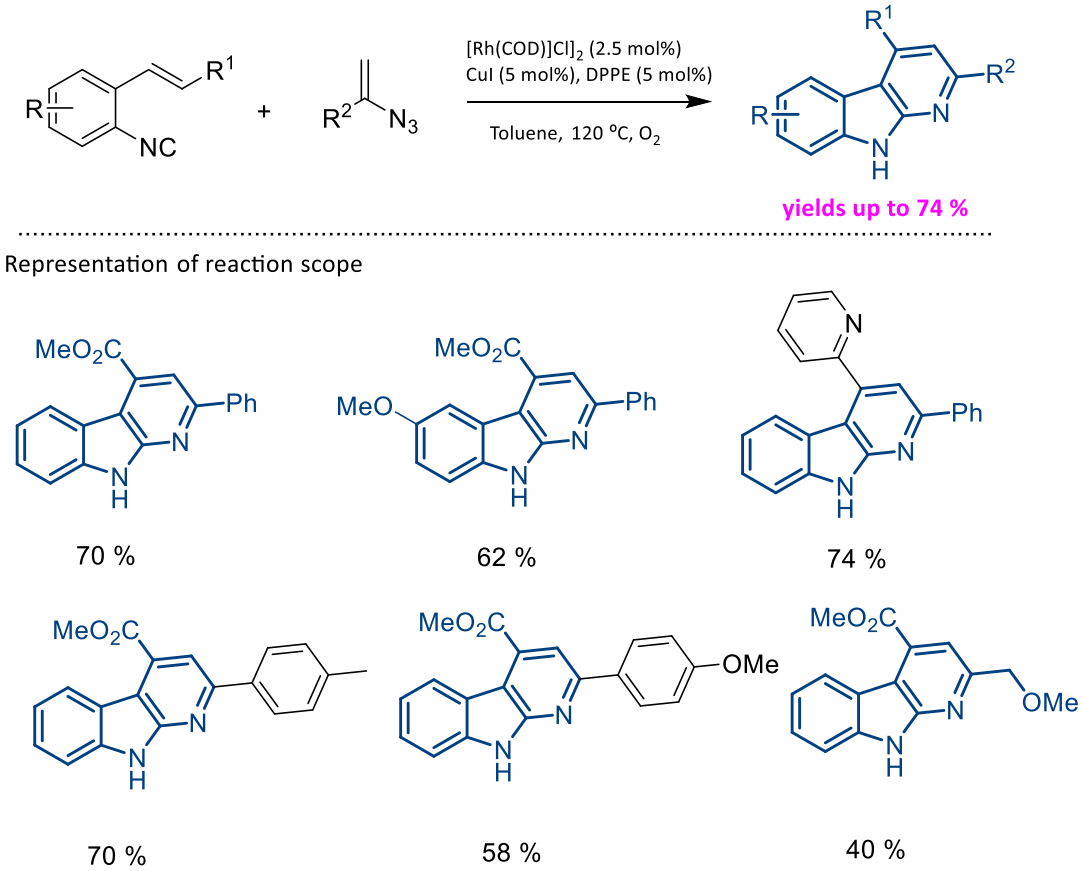

Scheme 8. Representation of scope for α-carbolines using a rhodium/copper dual catalyst from o-alkenyl aryl isocyanides.[31]

This Rh/Cu cocatalyzed methodology provides an efficient one-pot approach to α-carbolines with moderate to broad substrate scope and good functional-group tolerance toward both electron-donating and electron-withdrawing substituents. A key advantage is its excellent regioselectivity, enabling the rapid construction of structurally complex α-carbolines in a single operation. However, the protocol relies on a dual catalytic system containing expensive rhodium and affords only moderate yields for some substrates. Although the one-pot cascade improves step economy by avoiding the isolation of intermediates, the use of precious-metal catalysis limits the overall sustainability of the methodology.

In contrast to cooperative Rh/Cu system, Langer and co-workers reported a purely copper-catalyzed approach for the synthesis of carboline derivatives via one-pot synthesis of β and δ-carbolines through N-arylation of primary amines with 3,4-dibromopyridine or similar dihalo-biaryl compounds (Scheme 9).[32] This approach afforded diverse carboline structures with good yields and high functional group tolerance providing a sustainable route for these potential bioactive compounds.

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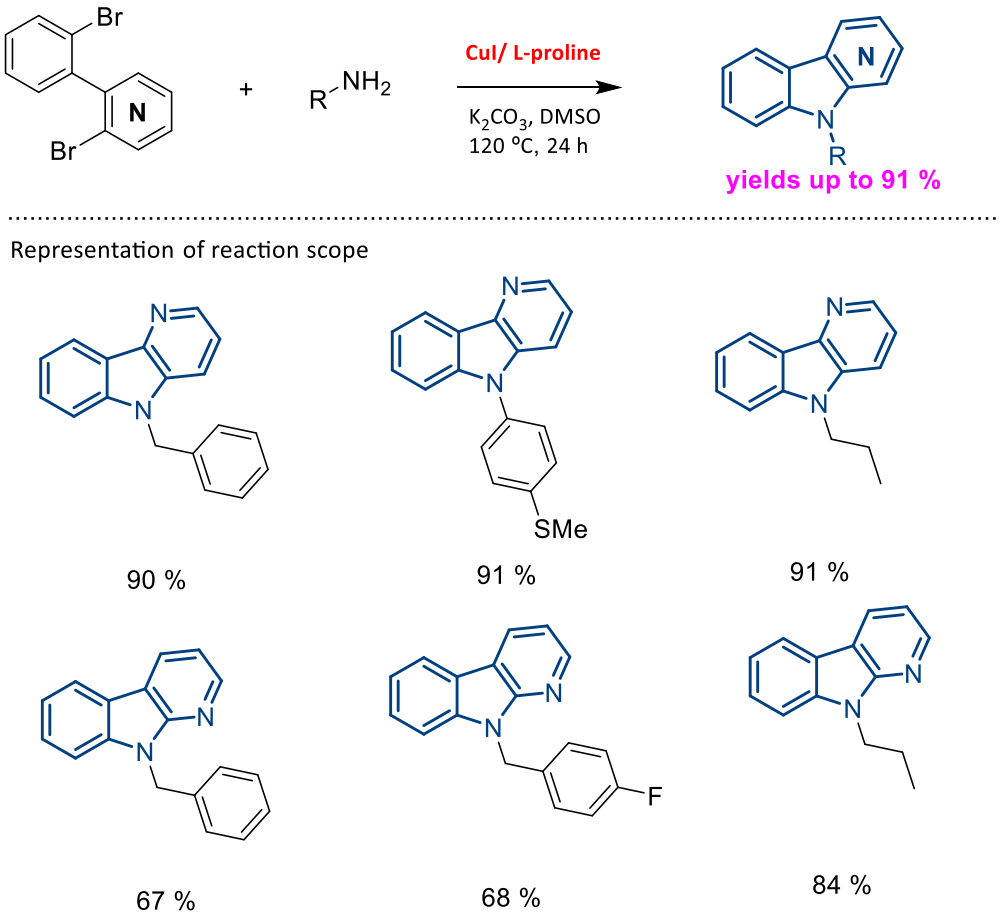

Scheme 9. Site selective copper catalyzed preparation of β- and δ-carbolines from 3,4-dibromopyridine.[32]

The copper-catalyzed double N-arylation strategy provides an efficient route to β- and δ-carbolines using an inexpensive CuI catalytic system. The methodology exhibits a moderate substrate scope and good functional-group tolerance toward both electron-donating and electron-withdrawing substituents, affording the desired products with excellent regioselectivity and generally moderate to high yields. Although the reaction requires relatively high temperatures and prefunctionalized dihalogenated substrates, it offers a straightforward one-pot cyclization process and represents a cost-effective alternative to precious-metal-catalyzed methodologies. From a sustainability perspective, the use of an earth-abundant copper catalyst is a notable advantage; however, the elevated reaction temperatures and the need for prefunctionalized substrates somewhat reduce its overall green chemistry profile.

Beyond these examples, copper-catalyzed approaches to carboline synthesis have been extensively developed, encompassing Ullmann-type C–N coupling reactions, oxidative C–H activation processes, and a range of intramolecular annulation strategies. These studies highlight the adaptability of copper catalysis in enabling efficient and economically viable access to structurally complex and functionally diverse carboline derivatives, reinforcing its central role in modern heterocyclic synthesis.[33–36]

3.3. Palladium catalyzed approaches

Although copper-based catalysts have proven effective in various transformations, palladium remains the most widely used transition metal-catalyst in synthetic organic chemistry, particularly for the formation of C–C and C–N bonds across a broad range of substrates. Consequently, palladium-catalyzed reactions have become

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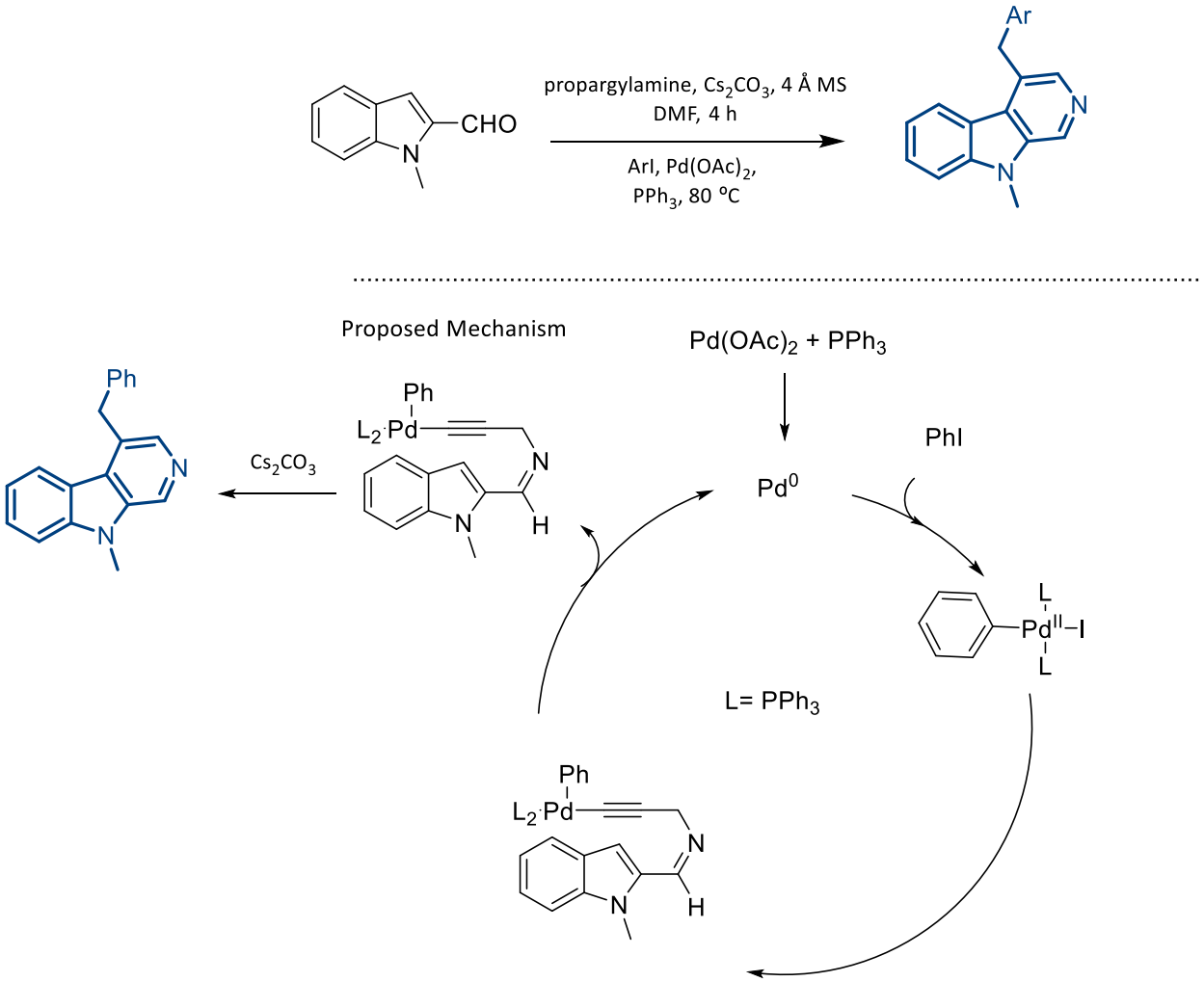
central to the construction of carbolines in recent years, enabling the efficient synthesis of these complex heterocyclic structures with high selectivity and yields. Among these palladium-catalyzed methods, the Suzuki–Miyaura cross-coupling reaction has been extensively employed for assembling carboline frameworks.

Uredi, Burra, and Watkins reported in 2021 a copper-free, palladium-catalyzed one-pot, three-component domino Sonogashira cross-coupling/6π-aza cyclization sequence that enables rapid access to 3-substituted pyridines and β-carbolines from readily available aromatic aldehydes, propargylamine, and aryl iodides (Scheme 10 and 11).[37] This methodology efficiently forms C–C bonds via palladium-catalyzed arylation of *in situ* formed imines, followed by base-promoted cyclization to yield fused heterocycles in good to excellent yields (67–92%) with complete selectivity. A key advantage of this protocol lies in its copper-free conditions, avoidance of preformed propargylamines, broad substrate scope including electron-rich and electron-deficient aryl iodides, and mild reaction conditions that facilitate rapid synthesis of diverse, functionalized pyridine and carboline scaffolds in a single operational step.



Scheme 10. Preparation of 3-substituted pyridines and carbolines via copper-free, palladium-catalyzed Sonogashira cross-coupling with aryl iodides.[37]

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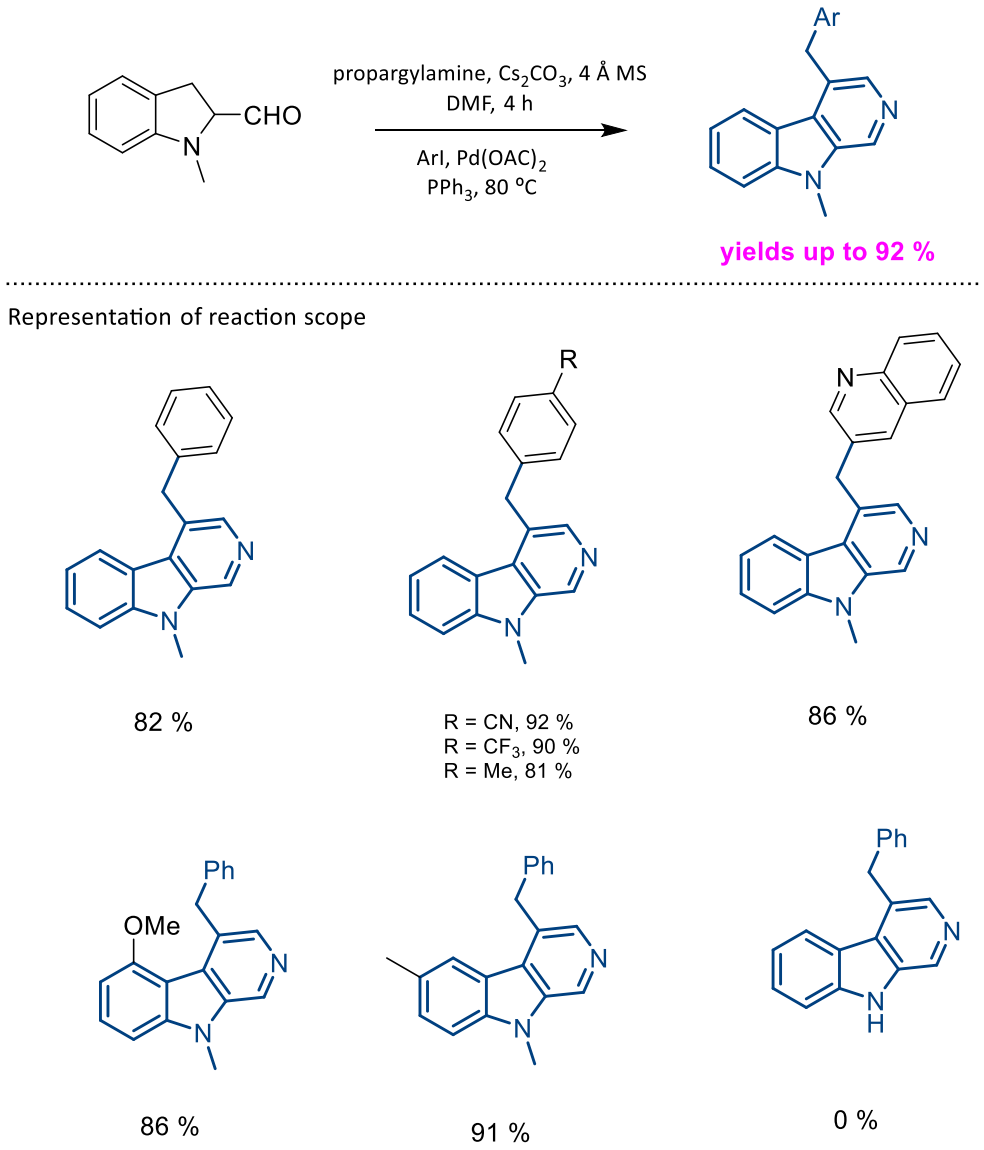

Scheme 11. Representation of scope for 3-substituted pyridines and carbolines via copper-free, palladium-catalyzed Sonogashira cross-coupling with aryl iodides.[37]

Chowdhury and his colleagues recently reported a regioselective methodology for the preparation of 2- and 4-sybstituited α-carbolines, from readily available tosyliminoindolines (using indole as precursor) and unsaturated aldehydes (Scheme 12 and 13).[38] The reaction was carried out at 80 °C with the use of $Pd(bpy)Cl_2$ and NaOAc with the particularity of the existence of two paths – Path A use of DMF as solvent to obtain 4-substituted carbolines frameworks – and Path B use of N-methylamine (NMA) for 2-substituted α-carbolines. This chemodivergent synthesis enabled the generation of several carbolines in very good or excellent yields.

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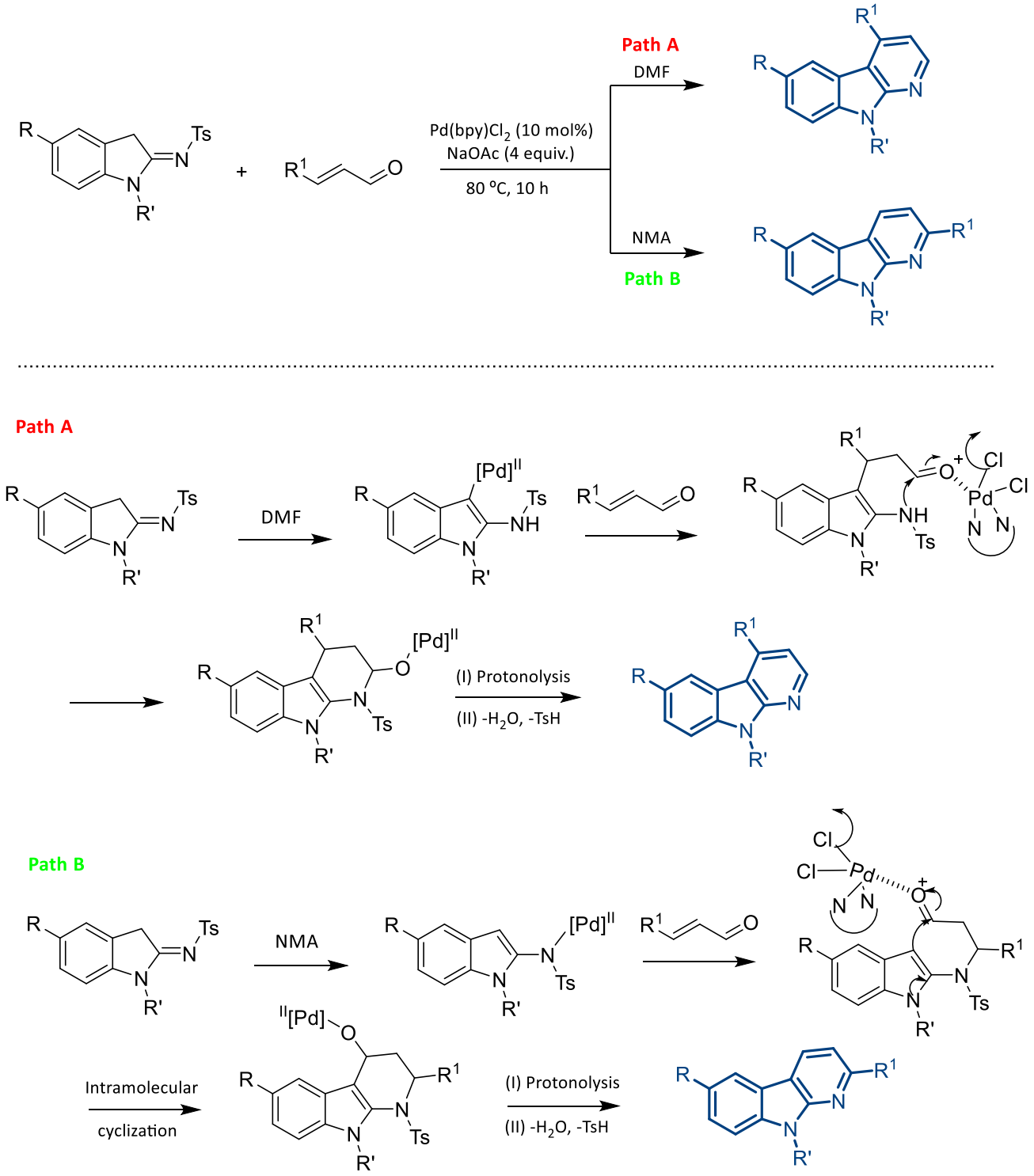

Scheme 12. Regioselective synthesis of α-carbolines under palladium catalysis.[38]

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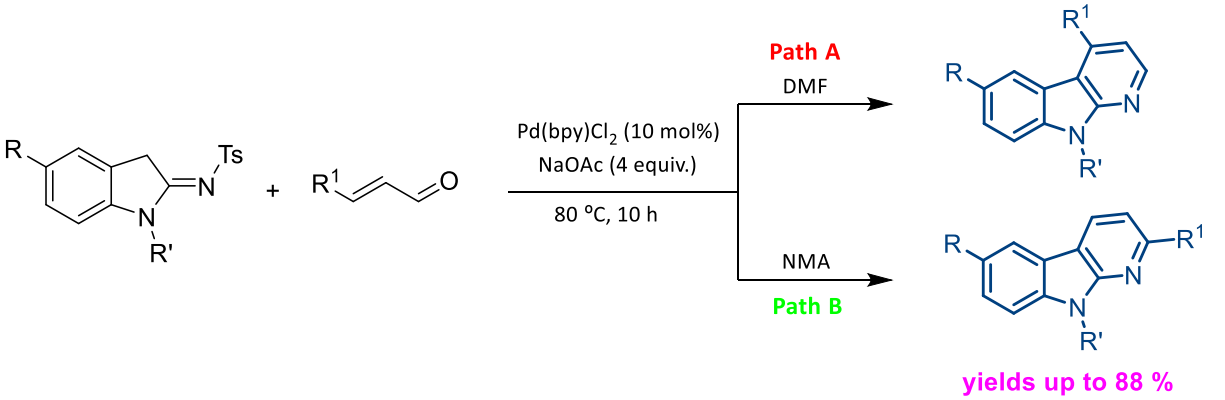
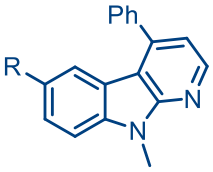
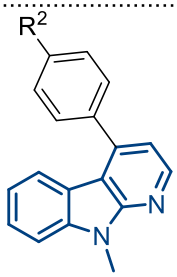


Representation of reaction scope

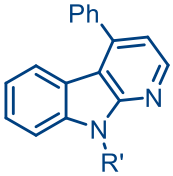
R´ = Me, 74 %
R' = Bn, 71 %
R' = H, 0 %



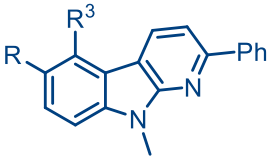
R = Me, 81 %
R = OMe, 84 %



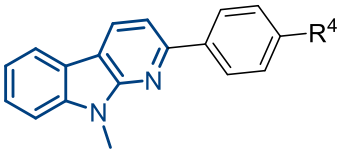
R^2 = Me, 70 %
R^2 = OMe, 67 %
R^2 = Br, 70 %



R´ = Me, 76 %
R' = Bn, 78 %
R' = H, 0 %



R = H, R^3 = Me, 76 %
R = H, R^3 = Cl, 64 %



R^4 = Me, 73 %
R^4 = NMe_2, 68 %
R^4 = OMe, 72 %

Scheme 13. Representation of reaction scope for the synthesis of α-carbolines under palladium catalysis.[38]

Mechanistically, the reaction proceeds via initial palladation of 2-aminotosylindole at the C3 position to form a palladium intermediate. In DMF, this species undergoes a Heck-type (Michael) addition to the alkene, whereas in NMA, an amino-palladated intermediate promotes an aza-Michael-type insertion. In both cases, the resulting intermediates undergo intramolecular cyclization facilitated by the palladium (II) catalyst to generate a cyclic species. Subsequent protonolysis, followed by dehydration and base-induced elimination (loss of TsH), furnishes the corresponding α-carboline products, with the solvent influencing the reaction pathway but not the overall transformation.

This palladium-catalyzed methodology provides an efficient and versatile approach for the synthesis of 2- and 4-substituted α-carbolines through solvent-controlled regioselective cyclization. The protocol exhibits a broad substrate scope, accommodating both electron-rich and electron-deficient substrates, and demonstrates good functional-group tolerance toward substituents such as halogens, alkyl, alkoxy, trifluoromethyl, cyano, and ester groups. A key advantage of this methodology is its excellent regioselectivity, as the desired regioisomer can be selectively obtained by simply modifying the reaction solvent without altering the substrate or catalyst

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system. Furthermore, the reaction generally proceeds in moderate to high yields under relatively straightforward palladium-catalyzed conditions, making it an attractive strategy for the preparation of structurally diverse α-carbolines. Nevertheless, the methodology relies on prefunctionalized substrates and a precious-metal catalyst, which increases both the synthetic cost and the environmental impact. Although the solvent-controlled approach improves step economy by avoiding additional directing groups or synthetic manipulations, the use of palladium and organic solvents limits the overall sustainability of the process. Consequently, future developments employing earth-abundant catalysts and greener reaction media could further enhance the applicability of this synthetic strategy.

Beyond these examples, palladium-catalyzed approaches to carboline synthesis have been extensively developed, encompassing cross-coupling reactions, C–H activation processes, and a range of intramolecular annulation strategies.[39–43] These studies highlight the versatility of palladium catalysis in enabling efficient and selective access to structurally complex and functionally diverse carboline derivatives, reinforcing its central role in modern heterocyclic synthesis.

3.4. Other metal catalyzed approaches

While palladium-, rhodium-, and copper-catalyzed methodologies dominate the field of carboline synthesis, a number of alternative transition metals have also been investigated, offering complementary reactivity profiles and expanding the diversity of accessible scaffolds. Although comparatively less explored, these systems have demonstrated promising potential in enabling novel bond-forming strategies, often under mild conditions and with distinct selectivity patterns. Metals such as gold, silver, and nickel have been employed in various annulation and cyclization processes, contributing to the development of efficient routes toward structurally complex carboline derivatives.[44–48]

Chatterjee et al. reported in 2025 a gold(I)-catalyzed tandem cyclization of indole- and benzofuran-based N-propargylsulphonamide acetylenic substrates that enables efficient and mild access to δ-carbolines and benzofuro[3,2-b]pyridines (Scheme 14 and 15).[49] The protocol employs $Au(PPh_3)Cl$ and $AgNTf_2$ in dichloromethane at room temperature to activate the alkyne moiety, triggering intramolecular cyclization to form dihydro intermediates. Subsequent treatment with the organic base DBU at 50 °C induces 1,2-elimination of the tosyl group, yielding the fused heterocycles in good to excellent yields (62–97%). Alternatively, an iodocyclization method using iodonium monochloride (ICl) and K_2CO_3 in refluxing dichloromethane furnishes 3-iodo-substituted δ-carbolines and benzofuro[3,2-b]pyridines within 2 hours, with yields ranging from 44 to 86%. This approach offers a mild, one-pot sequence with broad substrate scope, including various N-protecting groups and aryl substitutions, facilitating rapid construction of complex fused nitrogen- and oxygen-containing heterocycles of medicinal and materials interest.

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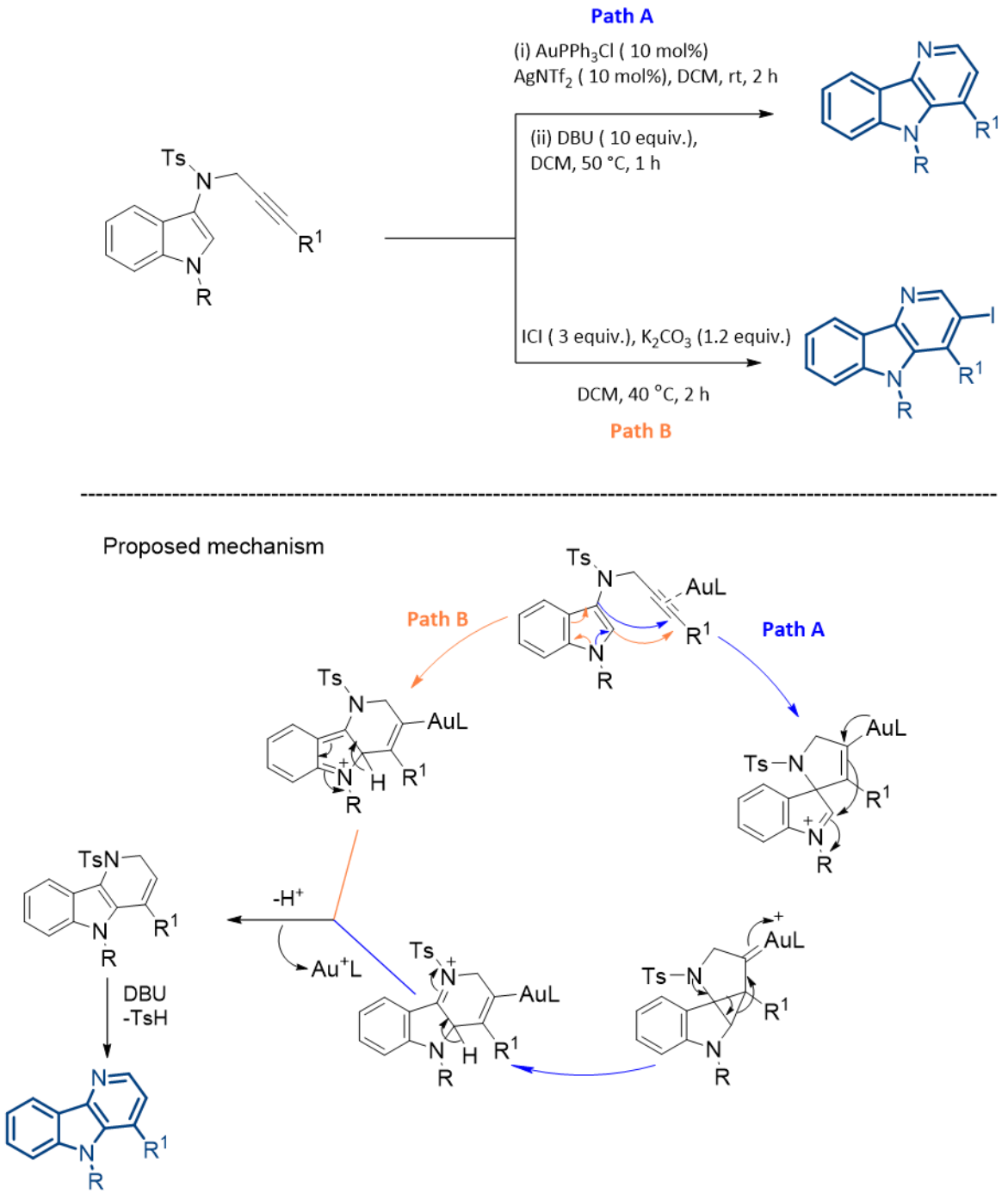

Scheme 14. Synthesis of δ-carbolines using a gold(I) catalyst.[49]

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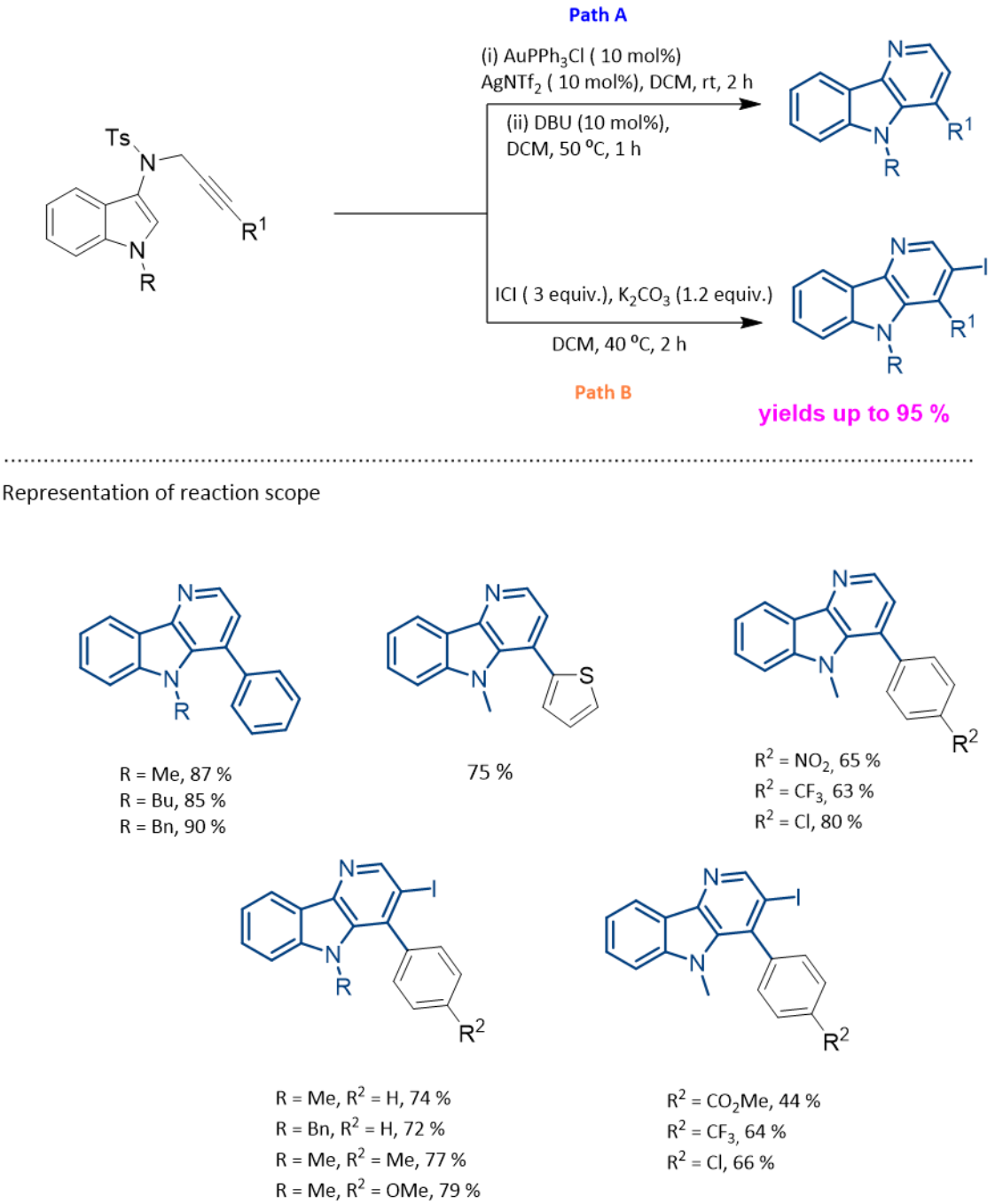

Scheme 15. Representation of reaction scope for the synthesis of δ-carbolines using a gold(I) catalyst.[49]

The gold(I)-catalyzed carbo-annulation provides an efficient one-pot approach to δ-carbolines under relatively mild reaction conditions. The methodology exhibits a moderate to broad substrate scope with good functional-group tolerance, accommodating alkyl, aryl, benzyl, allyl, methoxy, nitro, fluoro, chloro, bromo, trifluoromethyl, and heteroaryl substituents while affording the desired products in moderate to excellent yields (62–95%). A notable advantage of this protocol is its excellent regioselectivity together with the efficient construction of the fused δ-carboline framework in a single operation. However, the methodology requires prefunctionalized acetylenic substrates and relies on a gold catalyst and silver activator, increasing both the cost

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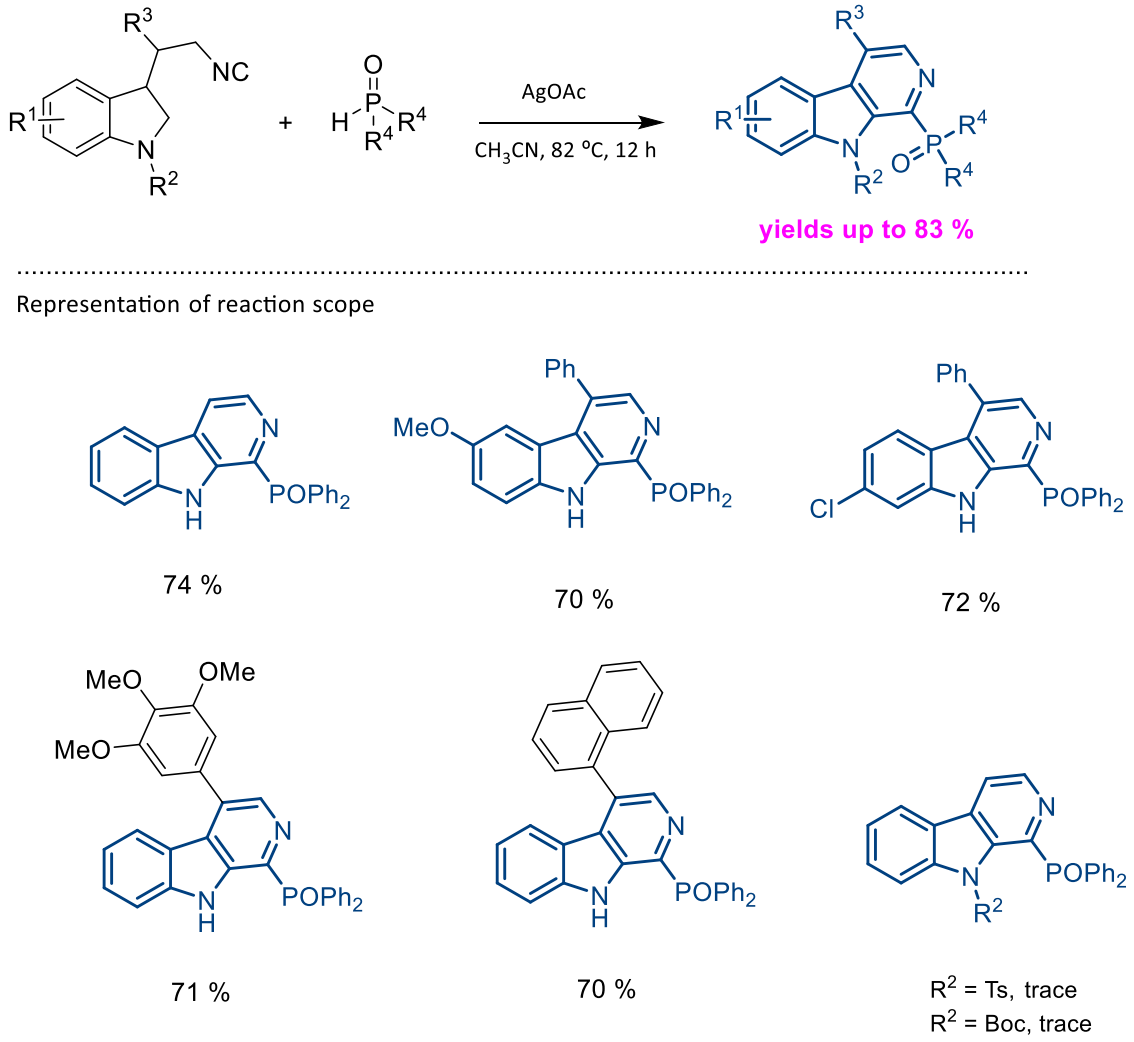
and the environmental impact of the process. Although the one-pot strategy enhances step economy, the dependence on precious-metal catalysis limits its overall sustainability.

In 2025, Das *et al.* reported an AgOAc-mediated radical insertion strategy for the synthesis of 1-phosphino β-carbolines from tryptamine-derived indole isocyanides (Scheme 16)[50]. In this one-pot cascade, AgOAc promotes the generation of phosphorus-centered radicals from phosphine oxides, which undergo radical addition and intramolecular cyclization to afford the corresponding β-carbolines under mild reaction conditions. The methodology provides an efficient and straightforward approach to phosphorus-containing β-carbolines, featuring broad functional-group tolerance and good synthetic versatility.



Scheme 16. Radical synthesis of 1-phosphino β-carbolines via silver-catalyzed isocyanide insertion.[50]

The AgOAc-mediated radical insertion methodology represents an efficient approach to the synthesis of 1-phosphino β-carbolines, displaying a broad substrate scope and good functional-group tolerance toward both electron-donating and electron-withdrawing substituents. The reaction proceeds with excellent regioselectivity under mild conditions, providing moderate to high yields through a straightforward one-pot cascade process. A major advantage of this protocol is the direct incorporation of phosphorus functionality into the β-carboline scaffold without the need for expensive transition-metal catalysts or prefunctionalized substrates. However, the

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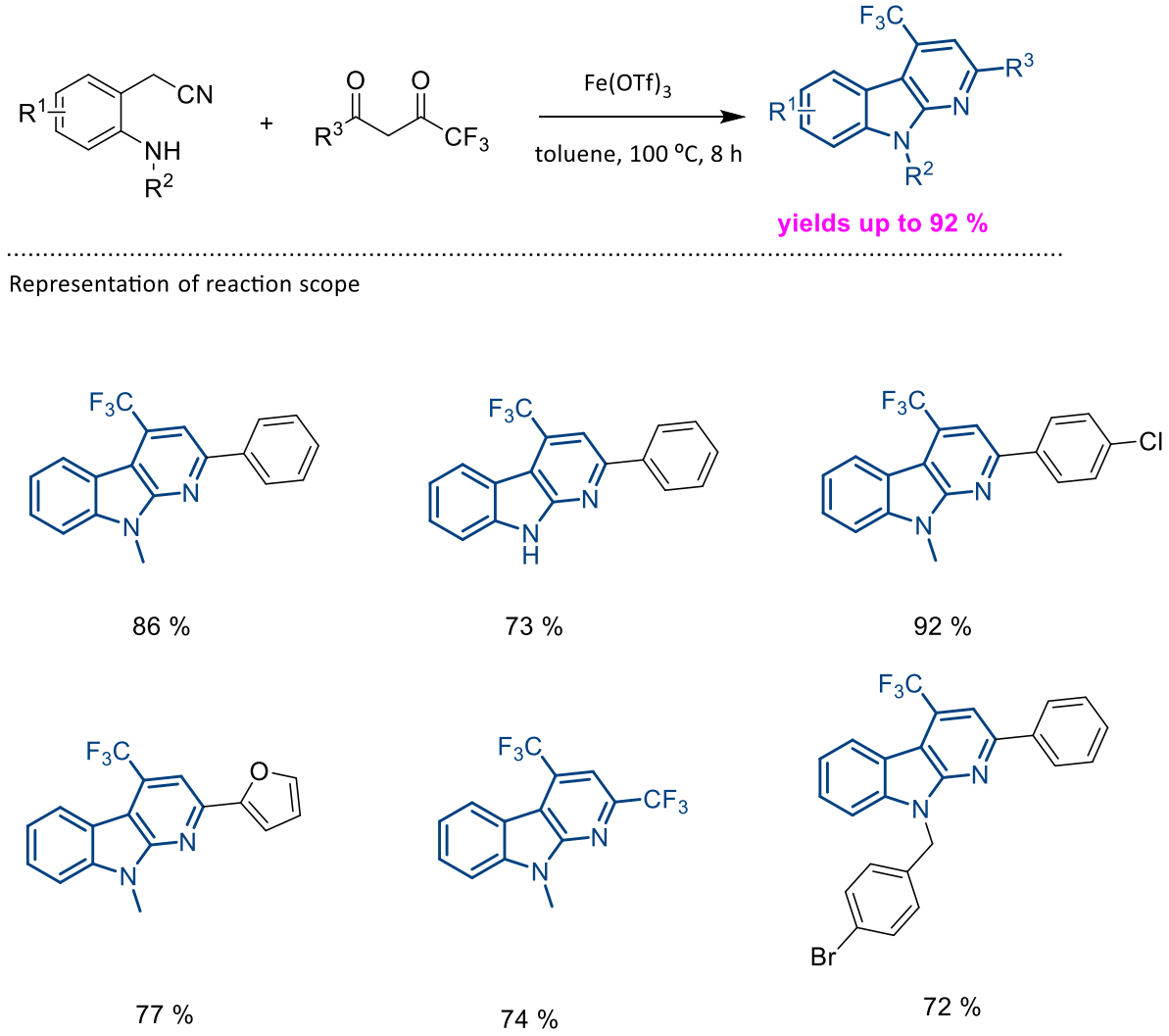
methodology relies on stoichiometric AgOAc for radical generation, which reduces its atom economy and overall sustainability despite its operational simplicity.

In 2020, Xu et al. reported an iron-catalyzed tandem cyclization strategy for the synthesis of trifluoromethyl- and ester-substituted α-carbolines (Scheme 17).[51] Using environmentally benign iron salts, the tandem cyclization of 2-(2-aminophenyl) acetonitriles with trifluoromethyl 1,3-diones or β,γ-unsaturated α-ketoesters afforded the corresponding α-carbolines in moderate to excellent yields. This methodology provides an efficient and practical approach to functionalized α-carbolines under relatively mild reaction conditions.



Scheme 17. Iron-Catalyzed Synthesis of Trifluoromethyl-Substituted α-Carbolines.[51]

This iron-catalyzed tandem cyclization provides an efficient and sustainable approach to trifluoromethyl-substituted α-carbolines. The methodology exhibits a moderate to broad substrate scope with good functional-group tolerance, accommodating electron-donating and electron-withdrawing substituents, including methyl, fluoro, chloro, bromo, trifluoromethyl, and heteroaryl groups, while affording the desired products in good to excellent yields (71–92%). A major advantage of this protocol is the use of an inexpensive and earth-abundant iron catalyst, together with excellent regioselectivity and a straightforward tandem cyclization process. However, the reaction requires relatively high temperatures (100 °C) and is primarily limited to trifluoromethyl-

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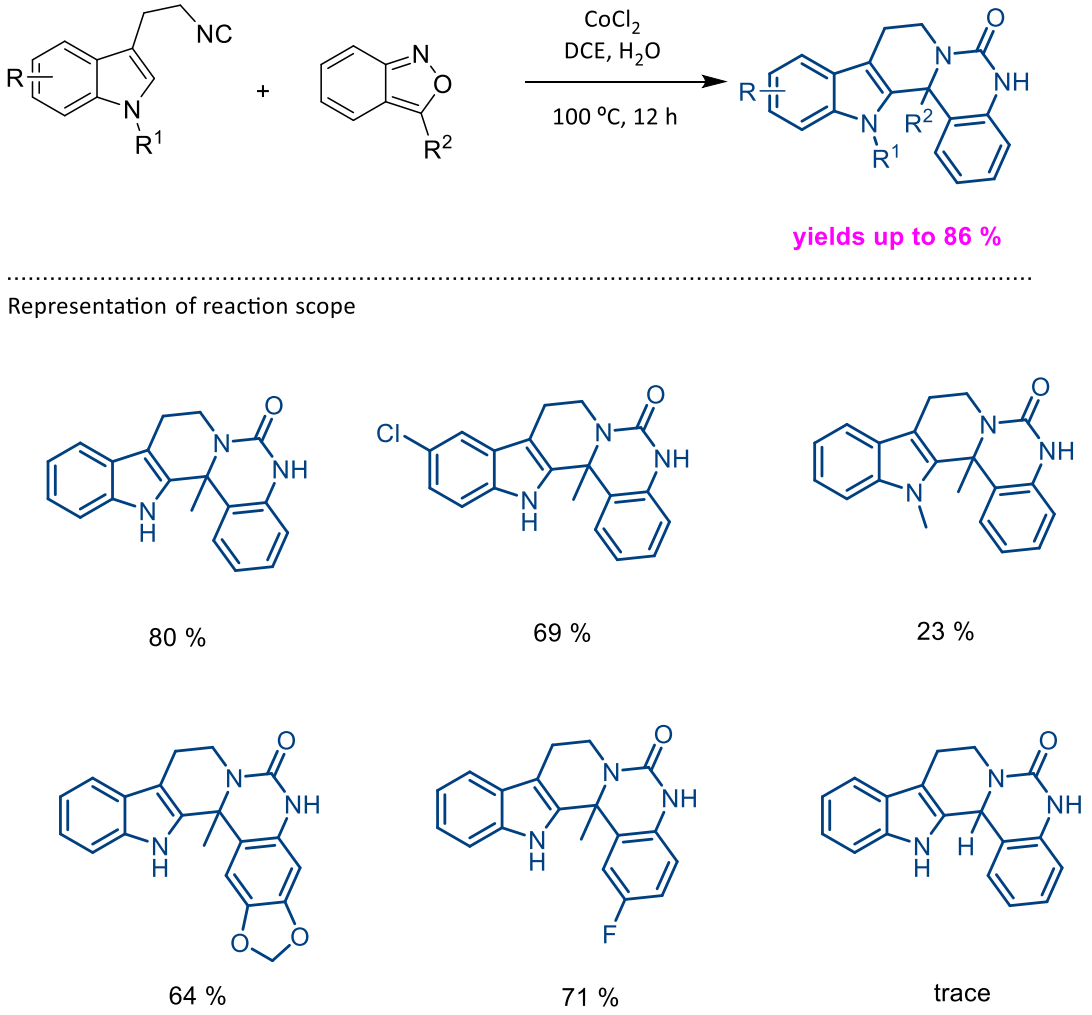
substituted α-carbolines, restricting the structural diversity of the products. Overall, the use of iron significantly improves the sustainability of the methodology compared with noble-metal-catalyzed approaches.

In 2026, Zhou et al. reported a cobalt-catalyzed hydrogen-bond-promoted tandem cyclization and oxygen migration strategy for the synthesis of sterically congested fused tetrahydro-carbolines (Scheme 18).[52] The one-pot protocol employs $CoCl_2$ to promote the tandem cyclization of tryptamine-derived isocyanides with 2-(1H-benzo[d]isoxazol-3-yl) anilines, affording the corresponding fused tetrahydro-β-carbolines in moderate to good yields. This methodology provides an efficient route to densely functionalized tetrahydro-carboline scaffolds through a tandem cyclization process.



Scheme 18. Cobalt-catalyzed synthesis of fused tetrahydro-β-carbolines.[52]

This cobalt-catalyzed tandem cyclization represents an efficient strategy for the synthesis of sterically congested fused tetrahydro-carbolines. The methodology displays a broad substrate scope and good functional group tolerance toward both electron-donating and electron-withdrawing substituents, affording the desired products in moderate to good yields with excellent regioselectivity. Compared with noble-metal-catalyzed protocols, the use of an earth-abundant cobalt catalyst together with a tandem oxygen migration/cyclization sequence provides a more sustainable and step-economical approach for the rapid construction of complex fused frameworks. Furthermore, the hydrogen-bond-promoted mechanism, in which water acts as both a hydrogen-bond donor and proton shuttle, represents an innovative feature that enhances reaction efficiency.

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Nevertheless, the requirement for elevated temperatures and the reduced efficiency observed for certain substrates indicate that further expansion of the substrate scope and optimization of the reaction conditions are still needed.

4. Conclusions

Over the past decade, the synthesis of carbolines has evolved considerably from traditional multistep approaches toward more efficient catalytic methodologies. While classical reactions remain valuable for accessing specific carboline frameworks, recent advances in transition-metal catalysis have significantly expanded the synthetic toolbox, enabling the rapid and regioselective construction of α-, β-, γ-, and δ-carbolines and saturated carbolines. In particular, the emergence of tandem and cascade reactions, C–H activation, and one-pot strategies has improved step economy and facilitated the preparation of increasingly complex and highly functionalized carboline derivatives.

Despite these significant advances, several challenges remain. Many methodologies still rely on precious-metal catalysts such as palladium, rhodium, and gold, which increases both the economic cost and environmental impact of the processes. In addition, numerous protocols require prefunctionalized substrates, elevated reaction temperatures, or stoichiometric oxidants, limiting atom economy and overall sustainability. Although many catalytic systems exhibit excellent regioselectivity, substrate scope is often restricted to specific substitution patterns, and the development of broadly applicable methodologies capable of accommodating structurally diverse substrates remains an important objective.

Future research should focus on the development of more sustainable catalytic systems based on earth-abundant metals, as well as metal-free alternatives that reduce both cost and environmental impact. The integration of photocatalysis, electrocatalysis, and direct C–H functionalization is expected to further simplify synthetic routes while improving atom and step economy. Furthermore, the development of asymmetric methodologies for the synthesis of enantioenriched carbolines remains comparatively underexplored despite the biological importance of chiral carboline derivatives.

Beyond methodological developments, opportunities also exist for applying these synthetic strategies to the late-stage functionalization of biologically active molecules, natural product synthesis, and the discovery of new pharmaceuticals. The combination of efficient synthetic methodologies with computational catalyst design and high-throughput experimentation may further accelerate the development of structurally diverse carboline libraries with improved biological and physicochemical properties.

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Leonardo Pirvu obtained his Bachelor's degree in Biochemistry from Universidade Lusófona de Humanidades e Tecnologias in 2022, and completed his Master's degree in Bioorganic Chemistry at the Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa (NOVA FCT), in 2024. His Master's research, supervised by Maria Manuel Marques, focused on the synthesis of pharmaceutically relevant N-heterocycles via metal-catalysed reactions, involving transition metal catalysis and organometallic chemistry. In January 2026, he joined the research project "Hi2E-Synth" focusing on hypervalent iodine chemistry for modern organic synthesis. His research interests include medicinal chemistry, synthetic organic chemistry, metal catalysis, natural product chemistry, and biochemistry.

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