RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 30231

Received 11th July 2025
Accepted 13th August 2025

DOI: 10.1039/d5ra04962h

rsc.li/rsc-advances

Greener alternatives for synthesis of isoquinoline and its derivatives: a comparative review of eco-compatible synthetic routes

Shivani Kirad,[a] P. R. Deepa [b] and Murugesan Sankaranarayanan *[a]

Isoquinoline derivatives, a prominent class of nitrogen-containing heterocycles, serve a pivotal role in medicinal chemistry due to their broad spectrum of bioactivities. While traditional synthetic routes for these scaffolds are well-established, conventional methods often rely on transition-metal catalysts, harsh conditions, expensive reagents, and toxic solvents, raising environmental and economic concerns. In response to the pressing demand for sustainable practices, this review underscores the integration of green chemistry principles into modern synthetic design, offering environmentally acceptable methods for accessing isoquinoline frameworks. Despite extensive research on isoquinoline synthesis and its therapeutic relevance, a dedicated analysis of sustainable methodologies remains absent. This work bridges that gap by critically evaluating recent innovations in green synthesis, including the use of benign solvents, recyclable catalytic systems, atom-economical reactions, and energy-efficient processes.

1 Introduction

Isoquinoline is a privileged nitrogen-containing heterocyclic scaffold with broad relevance in natural and synthetic chemistry.[1,2] Found extensively in bioactive alkaloids and therapeutic agents, isoquinoline derivatives have been documented to exhibit a wide range of pharmacological activities, including anticancer, antiviral, antitubercular, antifungal, antimalarial, and neuroprotective properties.[3–8] Moreover, their utility extends beyond pharmaceuticals into agrochemicals, dyes, and materials science, further underscoring their synthetic and industrial significance.[9,10]

The isoquinoline scaffold plays a pivotal role in diverse scientific fields due to its structural versatility and biological relevance. In medicinal chemistry, isoquinoline derivatives serve as key pharmacophores in several clinically approved drugs (Fig. 1), such as papaverine (a vasodilator),[11,12] emetine (an anti-amoebic agent),[13] palonosetron (used to treat chemotherapy-induced nausea),[14] gliquidone (anti-diabetic),[15] tetrabenazine (vesicular monoamine transporter type 2 inhibitor)[16] and revaprazan (treatment of peptic ulcer).[17]

Synthetic analogues have shown promising activity against cancer, malaria, tuberculosis, and neurodegenerative diseases, reflecting the scaffold's broad therapeutic potential. In natural product chemistry, isoquinoline alkaloids such as berberine, sanguinarine, and noscapine, which typically belong to Berberidaceae, Papaveraceae, and Ranunculaceae families, exhibit diverse pharmacological actions including antimicrobial, anticancer, and anti-inflammatory effects.[18] Isoquinoline and its structurally related heterocycles, including isoquinolinones, indolo-isoquinolines, and pyrido-isoquinolinones, represent a versatile family of nitrogen-containing frameworks with significant prominence in both natural products and synthetic chemistry. The structural diversity imparted by annulation (such as indole or pyridine fusion) and functionalization (such as oxidation to isoquinolinones) further enhances these heterocycles' utility across pharmaceuticals, agrochemicals, and materials science landscape.[19–21] Furthermore, in materials science, isoquinoline derivatives have been employed in the development of organic semiconductors, fluorescent dyes, and metal-chelating ligands due to their electronic and photophysical properties.[22–26] Fig. 2 highlights the application of the isoquinoline scaffold across various diverse fields.

Isoquinoline frameworks have traditionally been synthesized using various methods like the Bischler–Napieralski, Pomeranz–Fritsch, Pictet–Gams, and Pictet–Spengler reactions (Fig. 3). While commercially and pharmaceutically important and versatile, these methods pose challenges in modern green chemistry. These multistep protocols often employ harsh conditions, including strong acids (*e.g.*, $POCl_3$ or P_2O_5 in Bischler–Napieralski reaction),[27] toxic reagents, and hazardous solvents, while generating environmentally detrimental byproducts and exhibiting poor atom economy. The Pomeranz–Fritsch method[28–30] involves acid-catalyzed benzaldehyde-amine condensation, and the Pictet–Spengler reaction,[31] pivotal for tetrahydroisoquinoline alkaloid synthesis *via* β-arylethylamine-

---

[a] *Medicinal Chemistry Research Laboratory, Department of Pharmacy, Birla Institute of Technology and Science Pilani, Pilani Campus, Pilani-333031, Rajasthan, India. E-mail: murugesan@pilani.bits-pilani.ac.in*

[b] *Department of Biological Sciences, Birla Institute of Technology and Science Pilani, Pilani Campus, Pilani-333031, Rajasthan, India*

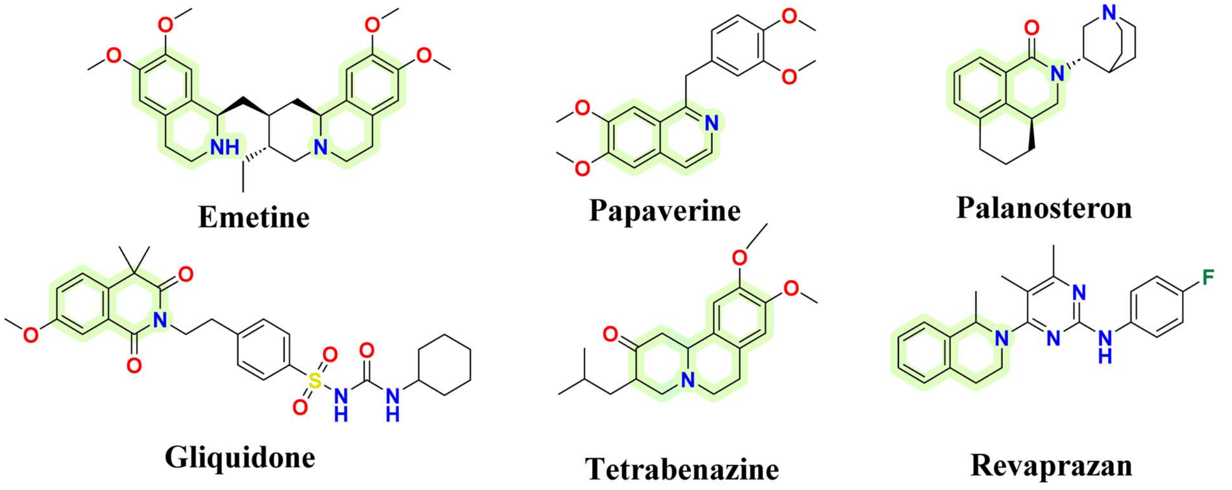


Fig. 1 Example of isoquinoline-based clinically approved drugs.

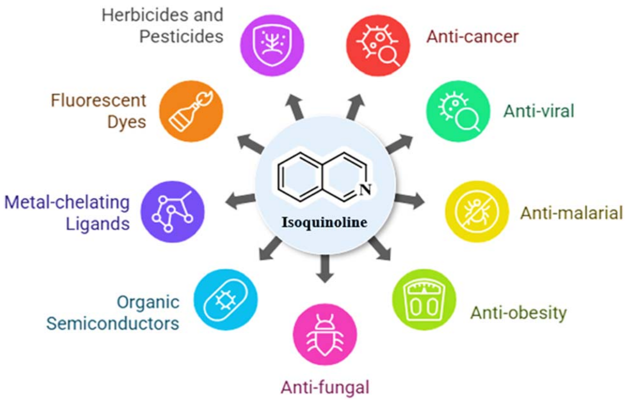


Fig. 2 Application of isoquinoline scaffold in various diverse fields.

aldehyde cyclization, further exemplifying these challenges through their narrow substrate scope, energy-intensive procedures, and reliance on precise parameter control. Over the years, the synthesis of isoquinoline derivatives has evolved considerably, expanding into a broad spectrum of modern methodologies. Many of these synthetic approaches involve transition metal catalysis playing key roles.[32–34] Nitrogen-containing substrates like benzylamines, arylnitriles, benzoic acid amides, imines, and oximes derived from aromatic aldehydes and ketones are frequently used in these transformations.[35,36]

Despite significant advancements, many existing methods suffer from drawbacks such as poor regioselectivity, generation of unwanted byproducts, and limited adherence to the principles of green chemistry. Since the late 1990s, rising environmental awareness has fuelled the growth of green chemistry, which advocates for the design of safer, cleaner chemical processes that reduce waste and rely on renewable feedstocks.[37,38] Green chemistry has emerged as a transformative paradigm in chemical synthesis, aiming to minimize the environmental footprint of chemical processes while maximizing efficiency and safety. The twelve principles of green chemistry, introduced by Anastas and Warner,[39] serve as the cornerstone for developing such environmentally responsible methodologies. The foundational principles of green chemistry-such as the use of renewable feedstocks, safer solvents, energy efficiency, catalysis, and waste prevention offer a roadmap for redesigning traditional synthetic pathways. Within the realm of isoquinoline chemistry, researchers have increasingly adopted these principles to develop greener methodologies that reduce reliance on toxic reagents, minimize energy input, and improve overall. Non-metal catalyzed or organocatalytic methods utilize small organic molecules as catalysts, offering environmentally friendly and operationally simple alternatives. Ultrasound-assisted catalysis leverages sound waves to enhance reaction rates and yields through improved mixing and energy transfer, supporting greener processes. Visible light and photoredox catalysis harness light energy to activate catalysts, enabling redox reactions under mild conditions and facilitating the construction of intricate molecular architectures. Nanocatalysts, with their high surface area-to-volume ratio, play a crucial role by increasing the interaction between reactant molecules, which leads to higher yields, shorter reaction times, and improved efficiency; they are often reusable, environmentally benign, and can be magnetically separated for easy recovery, making them highly attractive for sustainable synthesis. Electrochemical catalysis uses electrical energy to drive chemical reactions, offering precise control over redox processes and reducing reliance on hazardous reagents. Metal-free or non-metal catalyzed syntheses advance green chemistry by eliminating metals altogether, employing organic molecules or ionic liquids to achieve high efficiency and selectivity while minimizing environmental impact. Fig. 4 highlights the advantages of the green methods over the classical methods of synthesis. Several reviews have been published highlighting the pharmacological importance of isoquinoline derivatives[40,41] and their synthetic strategies.[42,43] However, to the best of our knowledge, there is no comprehensive review focused specifically on the green and sustainable synthesis of isoquinoline

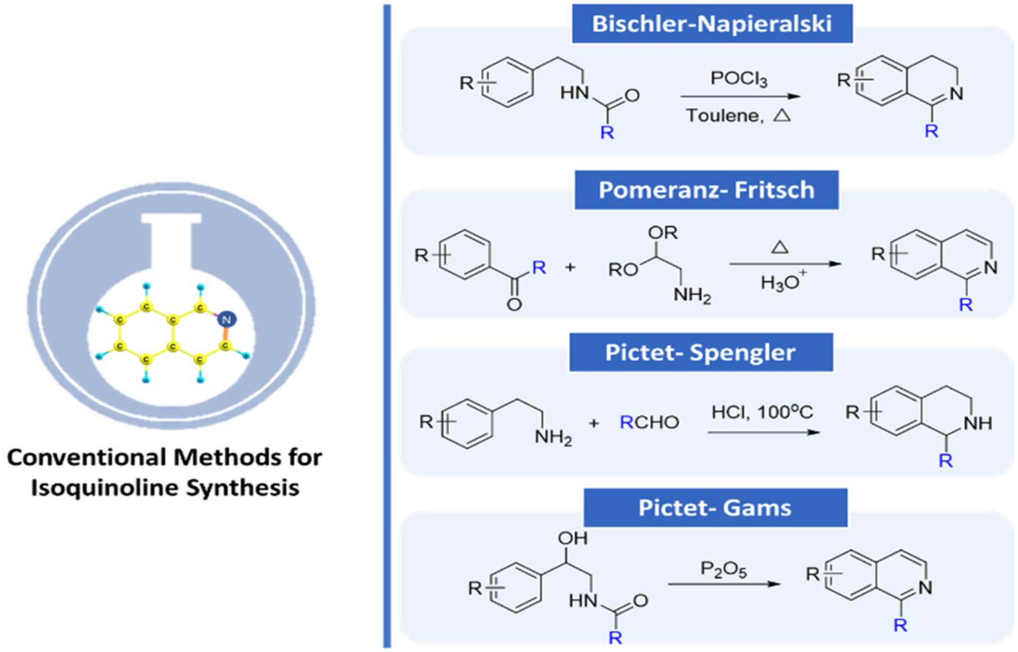


Fig. 3 Representative schemes for the conventional isoquinoline synthesis.

based scaffolds. Therefore, this review aims to highlight and consolidate the eco-friendly methods currently used for the synthesis of isoquinoline and its' derivative compounds. This review aims to bridge this gap by providing an in-depth analysis of the methodological innovations in the green synthesis of isoquinoline and isoquinoline-based scaffolds. Examples of various isoquinoline-based heterocycles—including isoquinolines, isoquinolinones, indolo-isoquinolines, pyrido-isoquinolinones, and their derivatives—are comprehensively included in the current review. The study is structured to

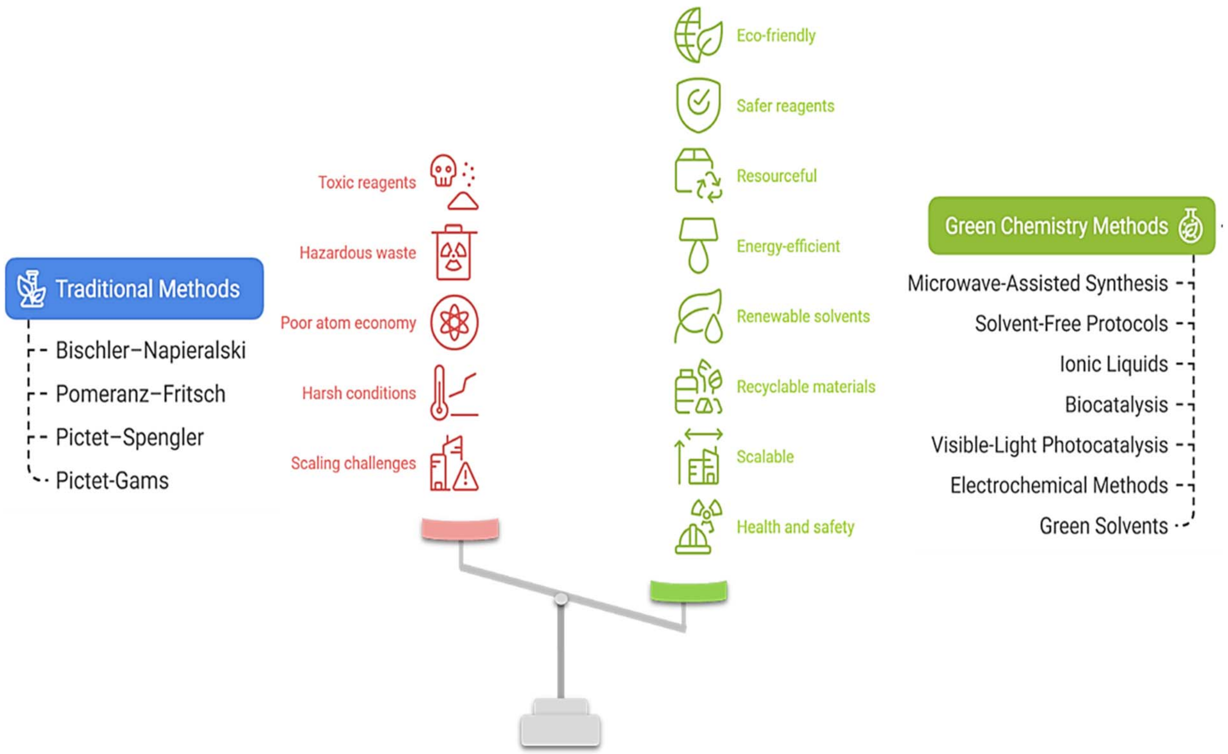
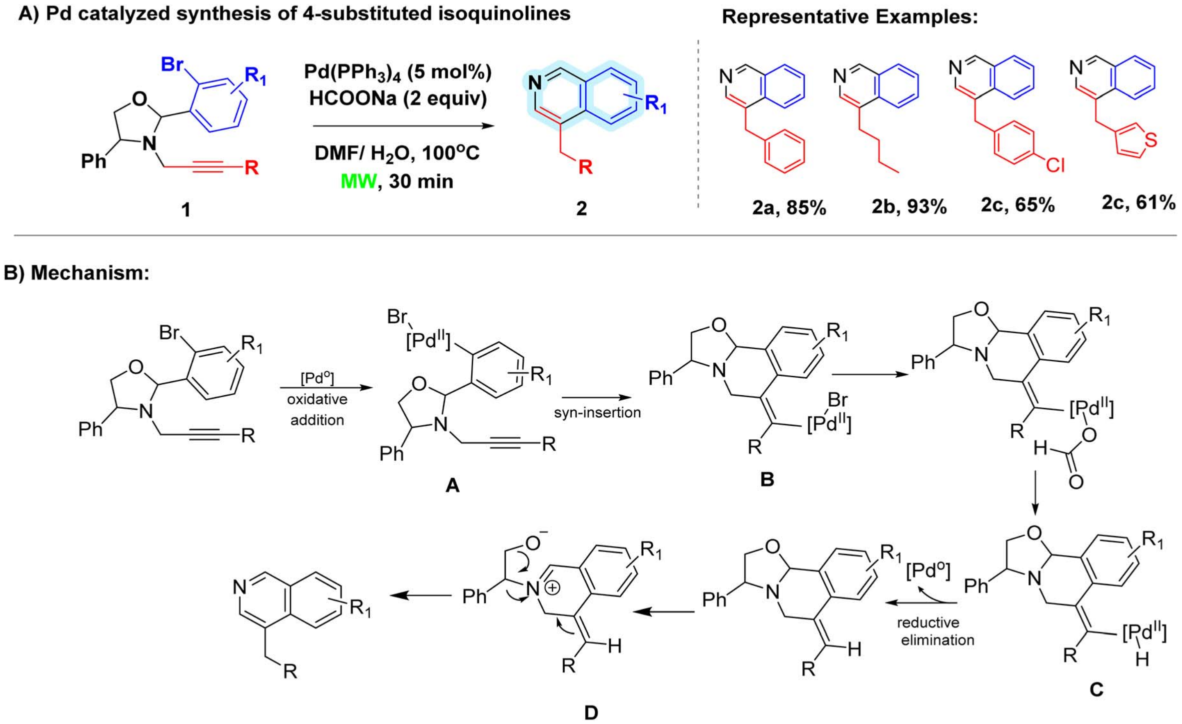


Fig. 4 Overview of classical *vs.* green isoquinoline synthesis methods.



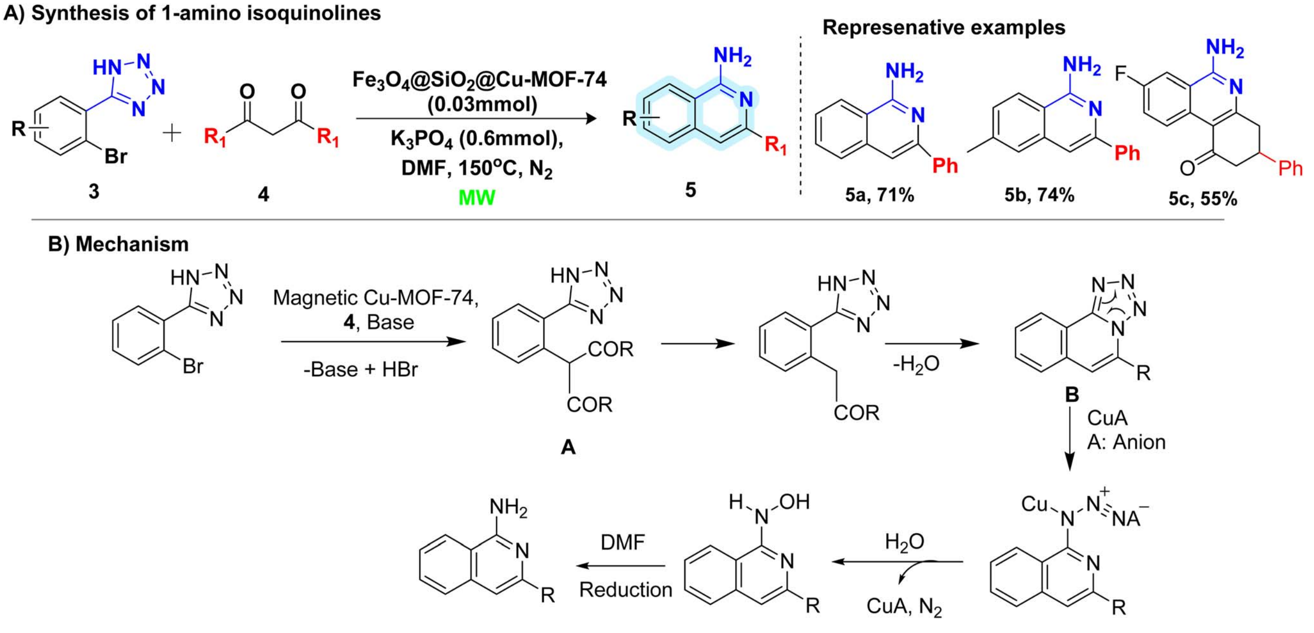
Scheme 1 Pd catalyzed domino reaction for the synthesis of 4-substituted isoquinolines by Xu *et al.*[46]

highlight recent developments categorized by the green technique used. The advantages, limitations, and environmental metrics of these approaches are highlighted compared to classical synthesis. We hope that this critical assessment will help to map the current landscape of sustainable synthesis of isoquinoline and its' derivatives, as well as highlight research gaps and future initiatives in this quickly growing subject.

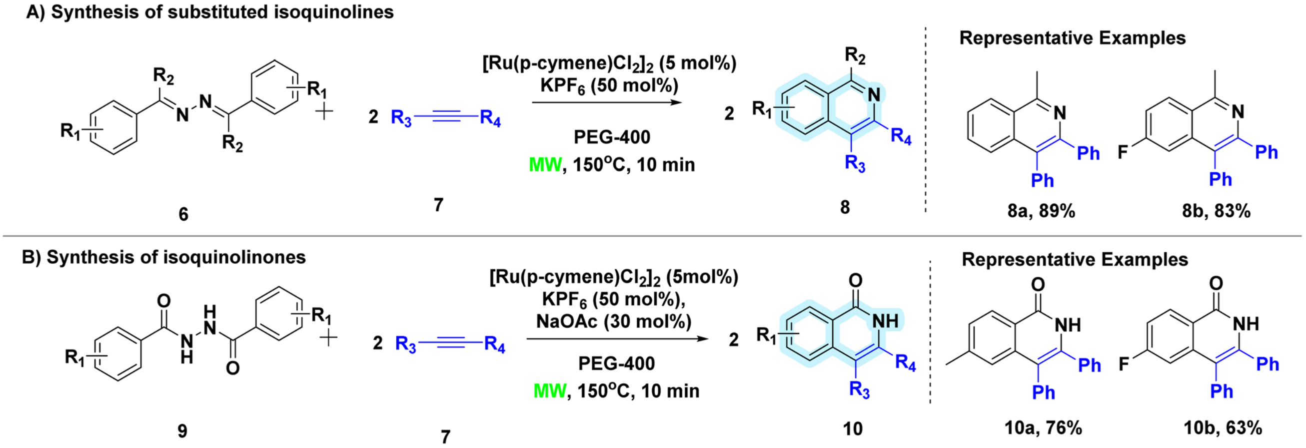
2 Green synthesis of isoquinoline and isoquinoline derivatives

2.1 Microwave assisted synthesis

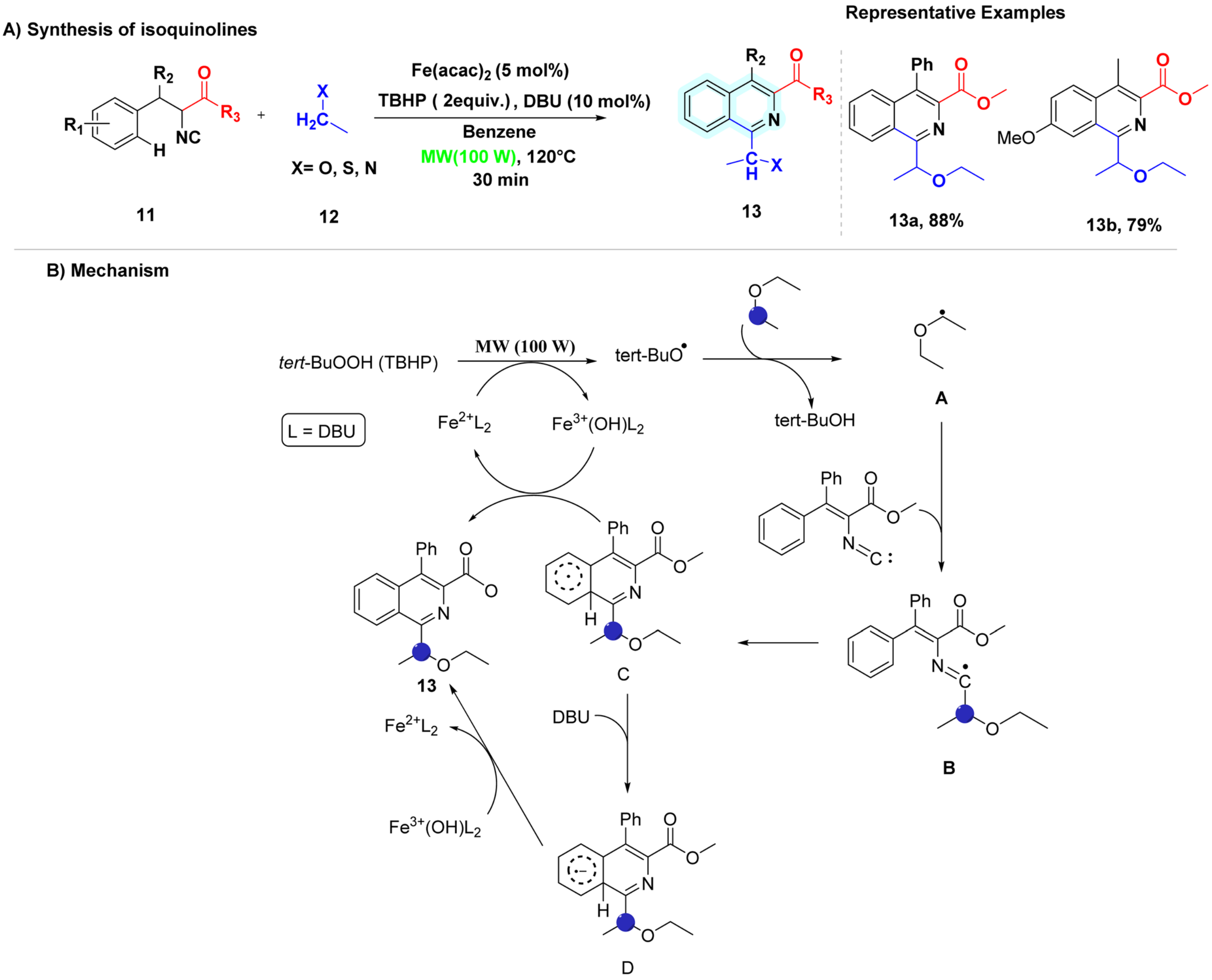
Microwave (MW) irradiation is widely used in chemistry due to its ability to rapidly and uniformly heat substances, leading to faster reaction rates, higher yields, fewer side products, and



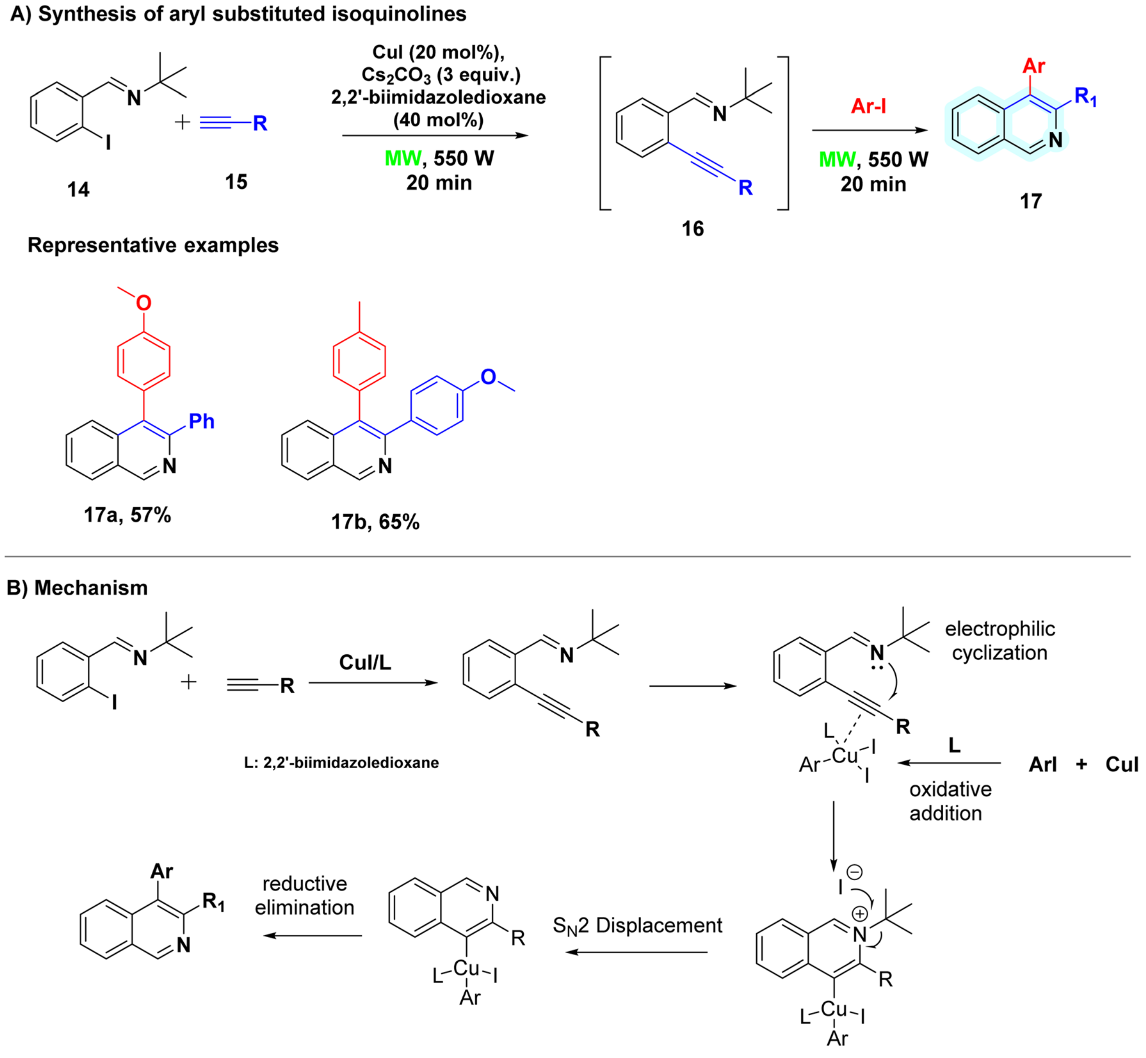
Scheme 2 Synthesis of 1-aminoisoquinolines by Dao *et al.*[50]



Scheme 3 Microwave assisted synthesis of isoquinolines and isoquinolinones by Deshmukh *et al.*[52]



Scheme 4 Microwave irradiated isoquinoline synthesis by Xu *et al.*[53]

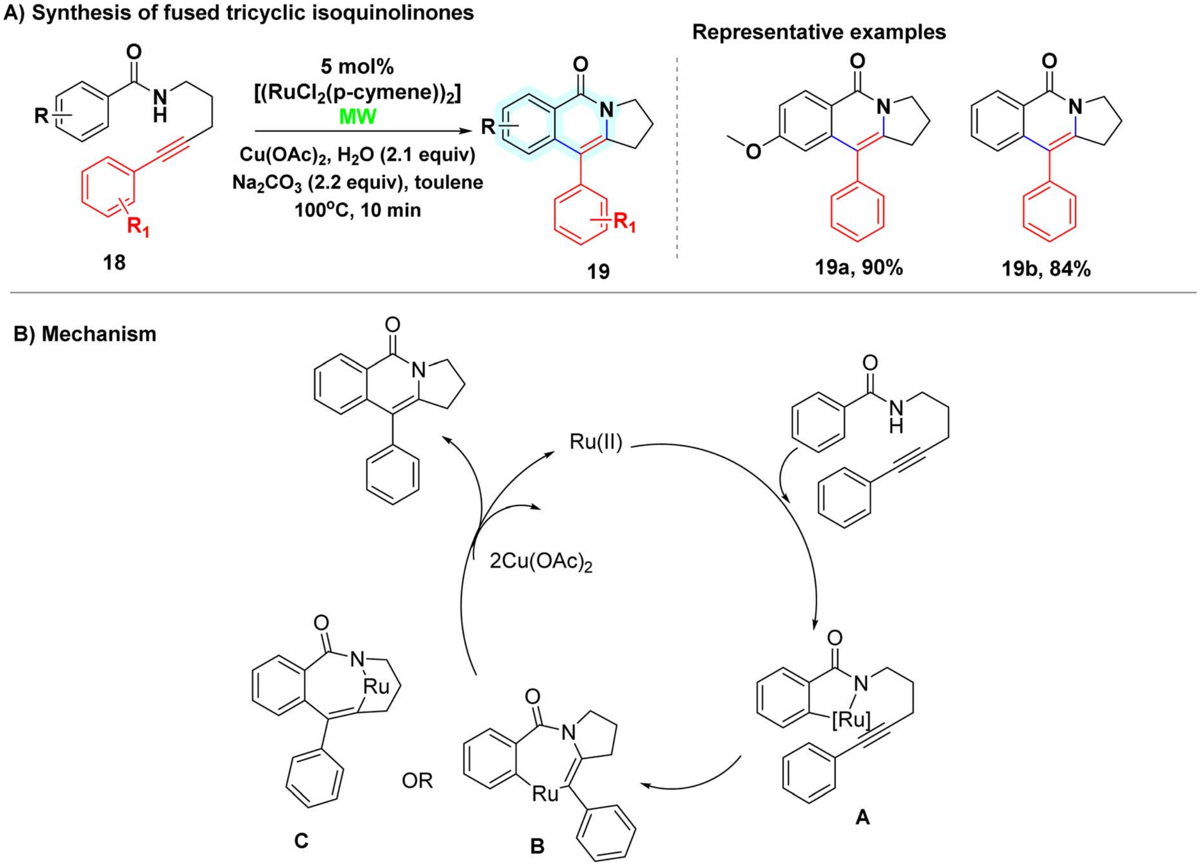


Scheme 5 Synthesis of aryl-substituted isoquinoline by Hu *et al.*[55]

easier purification compared to conventional heating. It also enables unique reactions and selectivities not achievable by traditional methods.[44,45]

2.1.1 Metal catalyzed-microwave assisted methods. In 2021, Xu *et al.*[46] and the group developed an efficient palladium-catalyzed reaction of *N*-propargyl oxazolidines (**1**) for the construction of 4-substituted isoquinolines (**2**) under microwave irradiation (Scheme 1). The protocol is flexible with a larger substrate scope than that of other 4-substituted isoquinoline synthesized by the cross-coupling of 4-bromoisoquinolines with organometallic reagents or dehydrogenation of *N*-heterocycles.[47–49] The optimal conditions were obtained using Pd(PPh$_3$)$_4$, HCOONa, and a DMF/H$_2$O (3 : 1) system at 100 °C for 30 min. Electron-donating aryl (**2a**) and alkyl groups (**2b**) gave higher yields than electron-withdrawing ones (**2c–d**). Water was key for proton transfer, as confirmed by deuterium labelling. The reaction follows a cascade mechanism starting with Pd(0) catalyzed oxidative addition to the aryl bromide (**A**), followed by syn-insertion into a triple bond to form a cyclized intermediate (**B**). Ligand exchange with sodium formate and decarboxylation generate a Pd–H species, which undergoes reductive elimination to yield a new intermediate (**C**) while regenerating Pd(0). Subsequent C–O and C–N bond cleavages in the oxazole ring produce a rearranged intermediate (**D**) and an epoxide by product. Final aromatization delivers the target molecule. Overall, this efficient, oxidant free process allows rapid and scalable synthesis.

Quang Dao *et al.*[50] reported a microwave-assisted synthesis of 1-aminoisoquinolines (**5**) from 5-(2-bromoaryl)-tetrazoles (**3**) and 1,3-diketones (**4**) using a recyclable magnetic Cu-MOF-74 (Fe$_3$O$_4$@SiO$_2$@Cu-MOF-74) catalyst they previously synthesized in DMF.[51] The reaction proceeds *via* copper-catalyzed C–C coupling, *retro*-Claisen or direct cyclo-condensation, and denitrogenation. The proposed mechanism, supported by control experiments and prior literature, begins with a Cu-MOF-catalyzed C(sp^2)–C(sp^3) coupling between substrates (**3**) and (**4**), forming intermediate (**A**). This intermediate undergoes either *retro*-Claisen deacylative cyclocondensation (for acyclic diketones) or direct cyclocondensation (for cyclic diketones), leading to the formation of tetrazole-fused isoquinolines (**B**).

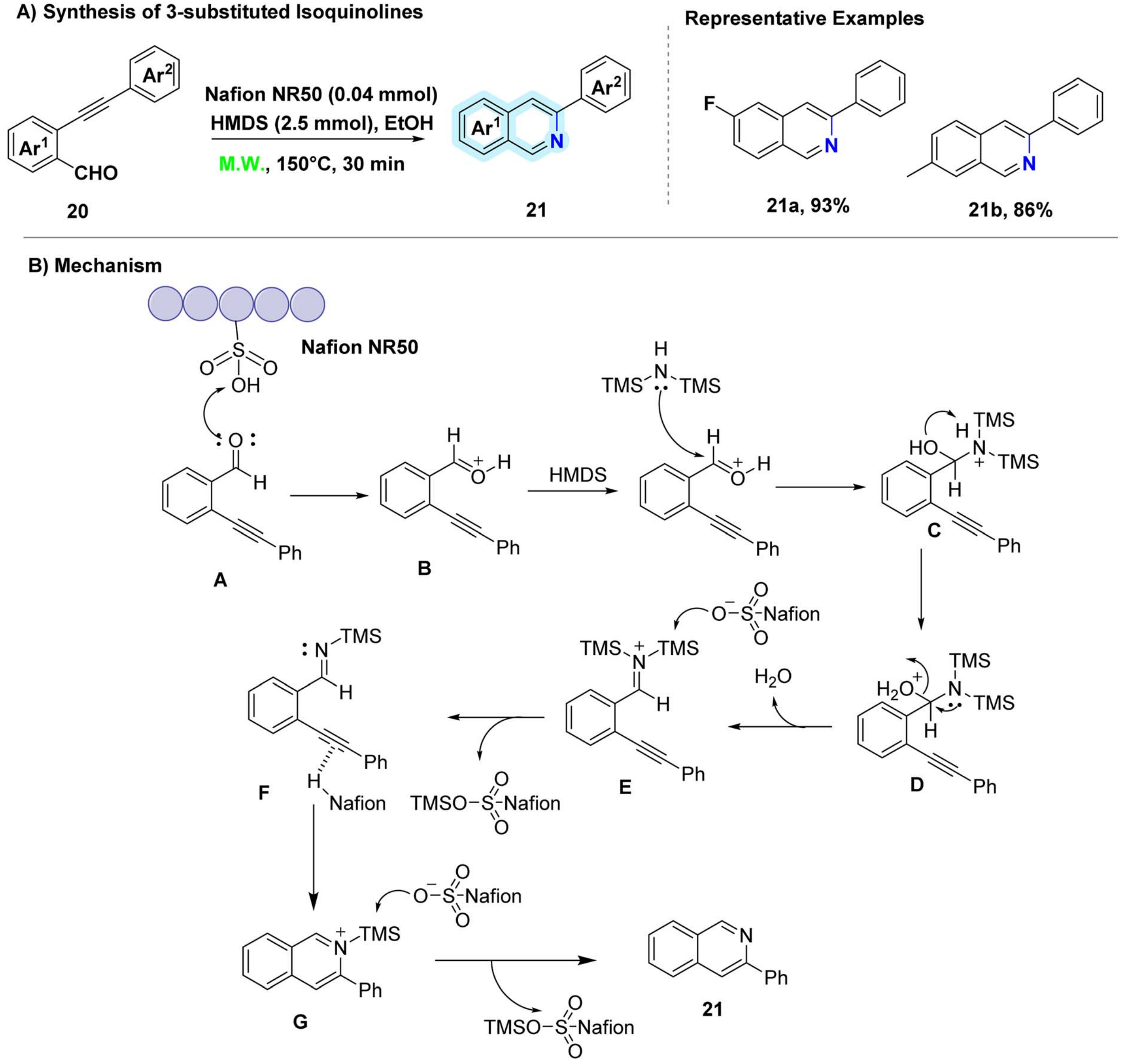


Scheme 6 Synthesis of tricyclic isoquinolinones by Swamy *et al.*[56]

These intermediates are subsequently transformed into 1-aminoisoquinolines *via* a copper-catalyzed denitrogenation involving N–N bond cleavage, formation of a copper–azide complex, hydrolysis, and DMF-assisted reduction. Optimal conditions involved excess diketone, Cs_2CO_3 or K_3PO_4 base, and 150 °C heating. Electron-donating diketones gave higher yields, and L-proline enhanced outcomes with electron-withdrawing or cyclic substrates. The catalyst was reusable for four cycles with minimal activity loss, and intermediate studies confirmed the proposed mechanism (Scheme 2).

Deshmukh *et al.*[52] reported a green, efficient method for synthesizing isoquinolines (**8**) and isoquinolinones (**10**) using a recyclable homogeneous ruthenium catalyst in PEG-400 under microwave irradiation (Scheme 3). The protocol employs dibenzoyl hydrazine (**6**) and ketazine (**9**) for C–H/N–N activation and annulation with internal alkynes (**7**), avoiding external oxidants, silver, or antimony salts. Optimized conditions (Ru catalyst, KPF_6, 150–160 °C, 10–15 min) gave high yields (62–92%) across a broad substrate scope, including heterocyclic and aliphatic alkynes. The Ru/PEG system is recyclable up to five times with minimal loss in activity and scalable to gram level synthesis, offering an eco-friendly, rapid, and atom efficient alternative. A similar Co-based annulation which uses conventional heating reported by the researchers has been included in Scheme 40.

Xu *et al.*[53] developed a microwave-assisted method for multi-substituted isoquinolines (**13**), which proceeded *via* SEAr (Electrophilic Aromatic substitution) radical insertion/cyclization of vinyl isocyanides (**11**) having a C(sp3)-H bond adjacent to a heteroatom (Scheme 4). The method comprises an oxidative cascade reaction, consisting of environmentally benign iron, tertiary-butyl hydrogenperoxide (TBHP) as oxidant, and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) as ligand. The proposed mechanism begins with the generation of a tertiary-butoxy radical and Fe^{3+} (OH) from Fe^{2+} under microwave-assisted conditions. The tertiary-butoxy radical then abstracts a hydrogen from the substrate (**12**), forming a radical intermediate (**A**). This radical adds to methyl 2-isocyano-3,3-diphenylacrylate, yielding the imidoyl radical intermediate (**B**), which undergoes intramolecular hydrogen atom shift (HAS) to form the cyclized radical intermediate (**C**). From here, two possible pathways may lead to the final product: either intermediate (**C**) loses a hydrogen atom (abstracted by Fe^{3+} (OH)) to form isoquinoline (**13**), or it undergoes deprotonation in the presence of DBU to form a radical anion (**D**), which is then oxidized by Fe^{3+} (OH) to produce the same isoquinoline product. The developed method showed broad substrate scope, environmentally benign iron catalysis, shorter reaction time, and gram-scale scalability compared to conventional methods that employ Friedel–Crafts-type acylation with drawbacks such

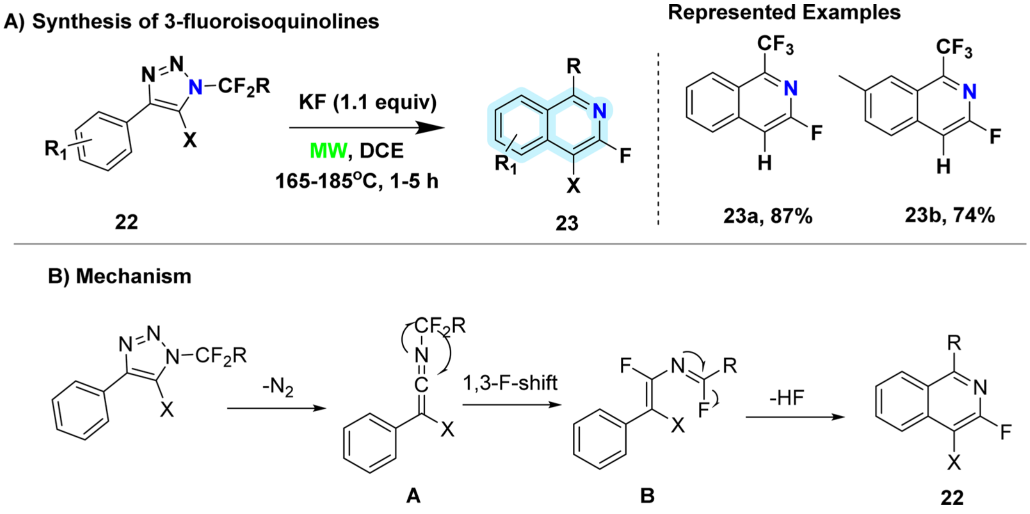


Scheme 7 Synthesis of 3-aryl substituted isoquinolines by Lin *et al.*[60]

as harsh reaction conditions, strong acidic groups, and low functional group tolerance.[54]

Hu *et al.*[55] reported a simple Cu-catalyzed, one -pot, microwave assisted method for the synthesis of 3,4-diaryl isoquinolines (**17**) (Scheme 5). The reaction proceeded *via* CuI/2,2′-biimidazole-catalyzed tandem process from *N-tert*-butyl-*o*-iodobenzaldimine (**14**). The mechanism involves two main steps. First, CuI/2,2′-biimidazole catalyzes the coupling of *N*-tertiary-butyl-*o*-iodobenzaldimine (**14**) with an aryl alkyne (**15**) to form compound (**16**). Then, oxidative addition of an aryl iodide to CuI forms an electrophilic copper species that coordinates with the alkyne to activate it, forming a π-complex. This undergoes electrophilic cyclization, followed by S_N2 displacement of the tertiary-butyl group to form. Finally, reductive elimination yields the 3,4-diaryl isoquinoline product (**17**). The reaction showed poor yields in the case of an electron-withdrawing aryl acetylene.

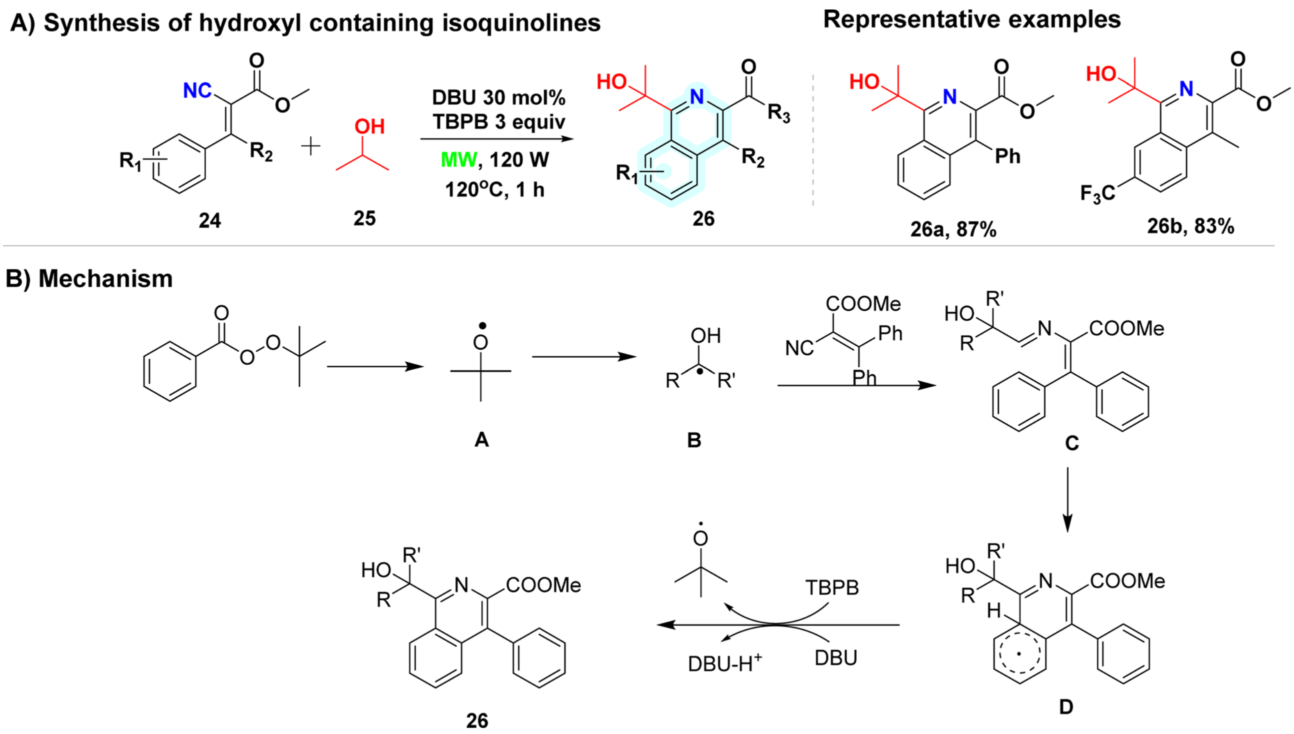
Swamy *et al.*[56] replaced a costly rhodium catalyst with a low-cost alternative, Ruthenium catalyst to develop intermolecular alkyne-amide (**18**) annulation under microwave irradiation to give fused tricyclic isoquinolinones (**19**) (Scheme 6). The reaction was highly efficient using Ru(II) as a catalyst and $Cu(OAc)_2 \cdot H_2O$ as a co-oxidant and toluene as a solvent. The one-pot strategy proceeds *via* domino C–C and C–N bond formation, with advantages of improved yields and milder and better reaction rates over the conventional C–H activation methods.[57–59] The proposed mechanism involves initial formation of a five-membered ruthenacycle (**A**) *via* oxidative insertion of Ru(II) into the *ortho* C–H bond of the benzamide. This metallacycle then reacts with a tethered alkyne, leading to either C–N bond formation (**B**) or *ortho*-functionalization (**C**). Reductive elimination from the Ru(0) intermediate yields the final product, and Ru(0) is reoxidized to Ru(II) by $Cu(OAc)_2$, completing the catalytic cycle.



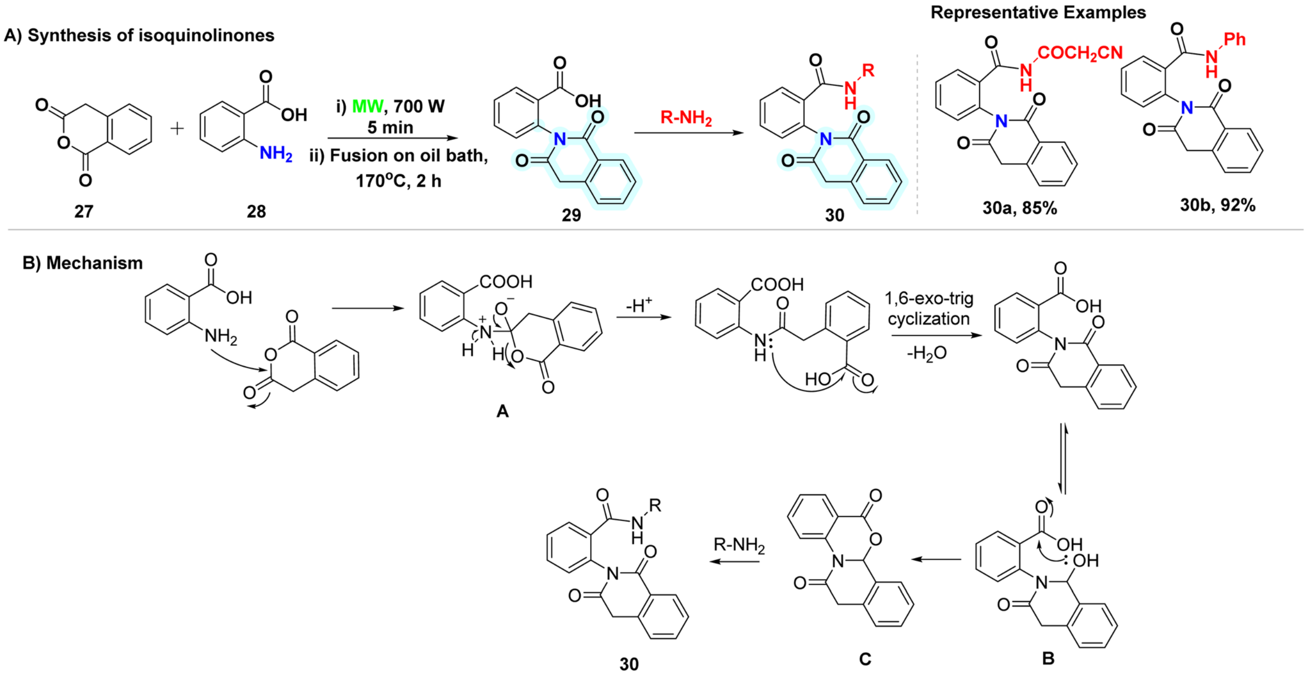
Scheme 8 Synthesis of fluoro isoquinolines by Kubickova *et al.*[61]

2.1.2 Non-metal catalysed-microwave assisted methods. In 2023, *et al.*[60] developed an eco-friendly method to synthesize 3-arylisoquinoline (**21**) from 2-alkynylbenzaldehydes (**20**) using Nafion® NR50 as an acidic catalyst and hexamethyldisilazane (HMDS) as a nitrogen source (Scheme 7). The reaction proceeded *via* a 6-*exo-dig* cyclization under microwave irradiation, giving the corresponding isoquinolines in excellent yields. The proposed mechanism begins with protonation of substrate (**A**) by Nafion® NR50, forming intermediate (**B**). Upon addition of HMDS, a nucleophilic addition occurs, yielding intermediate (**C**), which undergoes proton transfer to form (**D**), followed by dehydration to give (**E**). The Nafion® NR50 anion then activates the TMS group in intermediate (**F**). Coordination of the alkynyl group with the Nafion–H complex facilitates cyclization *via* the nitrogen atom, forming TMS-isoquinoline (**G**). Finally, activation by the Nafion anion leads to the formation of the desired isoquinoline product (**21**). The advantages of this protocol over the conventional methods that use toxic chemicals and require high temperatures include the use of recyclable acid catalysts, transition metal free catalysis, and better yields.

Kubickova *et al.*[61] reported a one-pot, microwave-assisted method for synthesizing 1-fluoroalkyl-3-fluoroisoquinolines

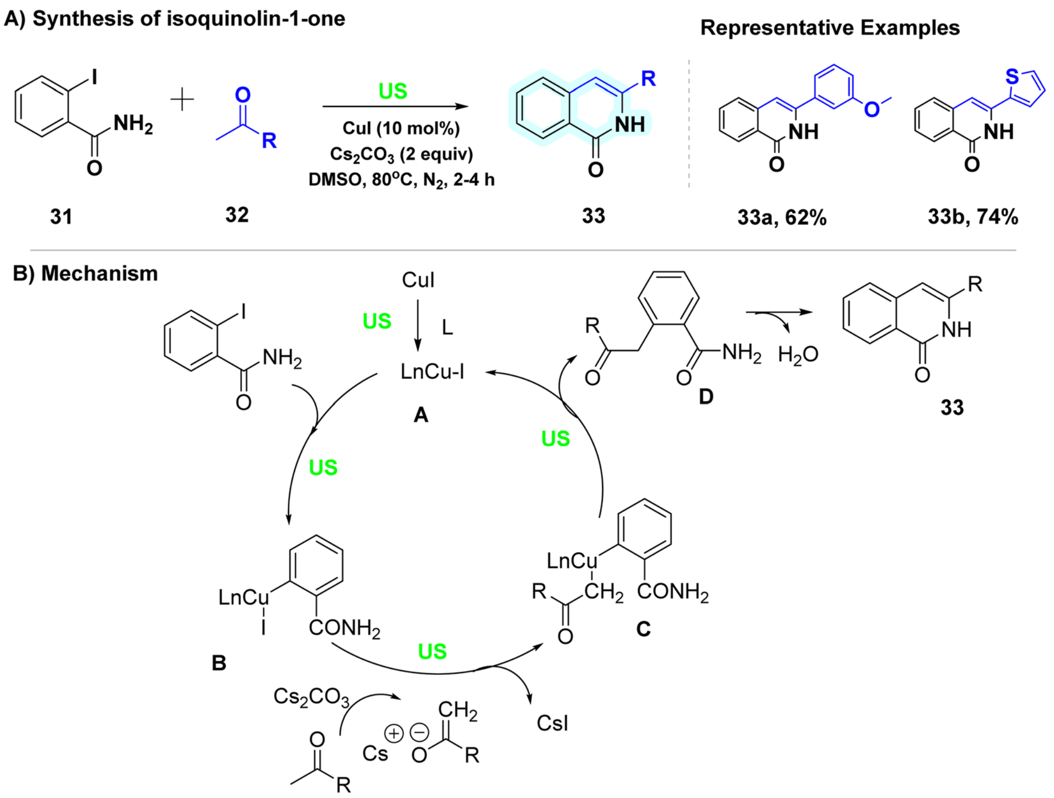


Scheme 9 Synthesis of hydroxyl-containing isoquinolines by Xue *et al.*[62]

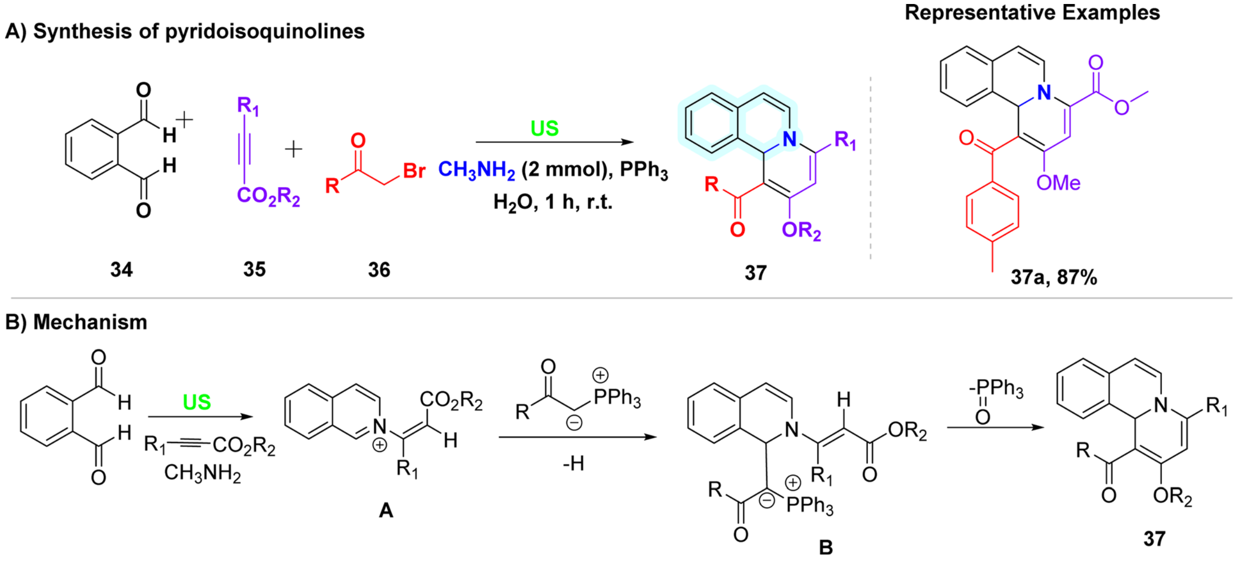


Scheme 10 Synthesis of isoquinolinones by Hekal *et al.*[63]

(**23**) from *N*-fluoroalkylated 1,2,3-triazoles (**22**) using potassium fluoride (Scheme 8). The reaction features broad substrate scope and proceeds *via N*-fluoroalkylated ketenimines (**A**), and difluoroazadiene (**B**) intermediates. The mechanism involves triazole ring opening, $-N_2$ elimination, 1,3-F-shift, and cyclization. The resulting isoquinolines, bearing fluorine at position 3



Scheme 11 Synthesis of 3-substituted isoquinolinone by Sangepu *et al.*[66]

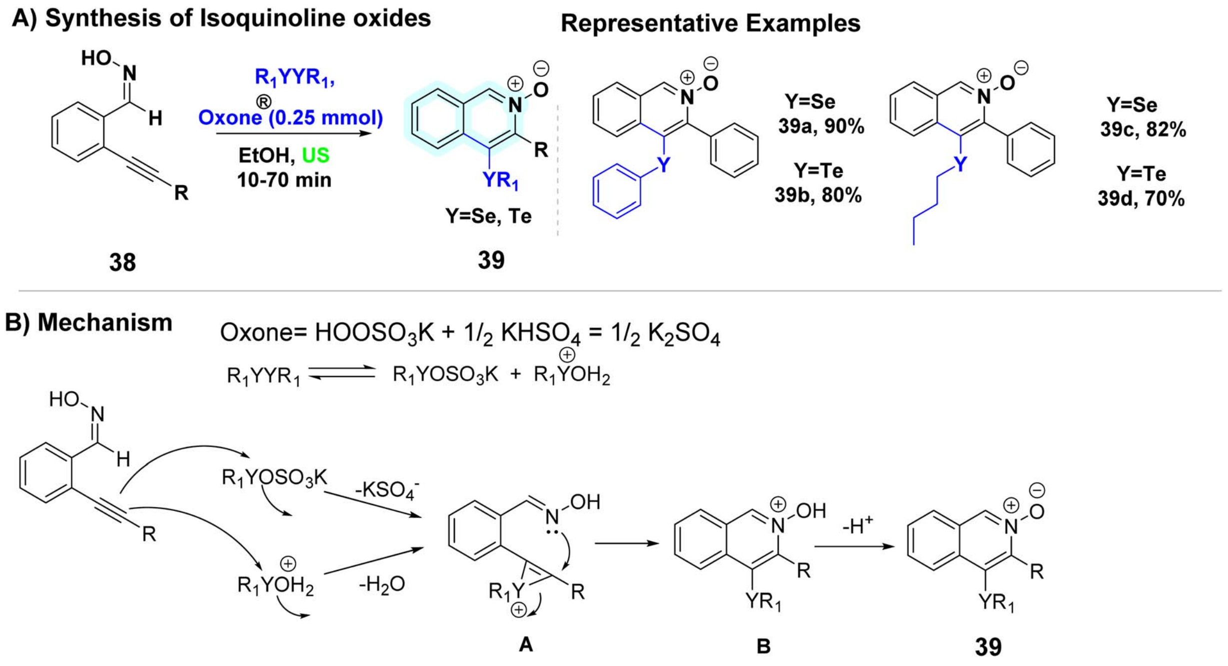


Scheme 12 Synthesis of fused pyrido isoquinoline scaffold by Sharafian *et al.*[67]

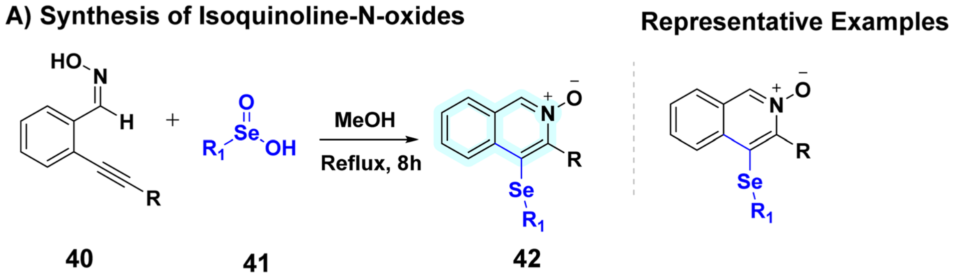
and halogens at position 4, enable further functionalization *via* substitution and cross-coupling. The method was applied to synthesize several derivatives of drug candidates.

Xue *et al.*[62] reported a metal-free, microwave-assisted radical cyclization of vinyl isonitriles (**24**) with alcohols (**25**) to give hydroxyl-containing isoquinolines (**26**) (Scheme 9). Vinyl isonitriles undergo coupling with alkyl radicals *via* direct catalytic activation of the α-sp^3 C–H bond in alcohols. This approach features a wide substrate range, excellent compatibility with various functional groups, and offers high atom economy and efficiency. Mechanistic studies, including KIE experiments, revealed that C–H bond cleavage in alcohols is the rate-determining step, as shown by a significant KIE ($k_H/k_D = 6.7$) with methanol/[D4]-methanol. The reaction was strongly inhibited by TEMPO, and a radical adduct was detected, confirming a radical pathway. The mechanism involves tertiary-butoxy radical generation from TBPB (**A**), which abstracts an α-hydrogen from alcohol to form a hydroxyalkyl radical (**B**). This undergoes radical addition (**C**) and cyclization (**D**), followed by hydrogen abstraction or oxidation to give the final product (**26**).

In 2017, Hekal *et al.*[63] gave an efficient method for the synthesis of isoquinolinone (**29**) using homophthalic anhydride



Scheme 13 Synthesis of isoquinoline-N-oxide by Araujo *et al.*[68]



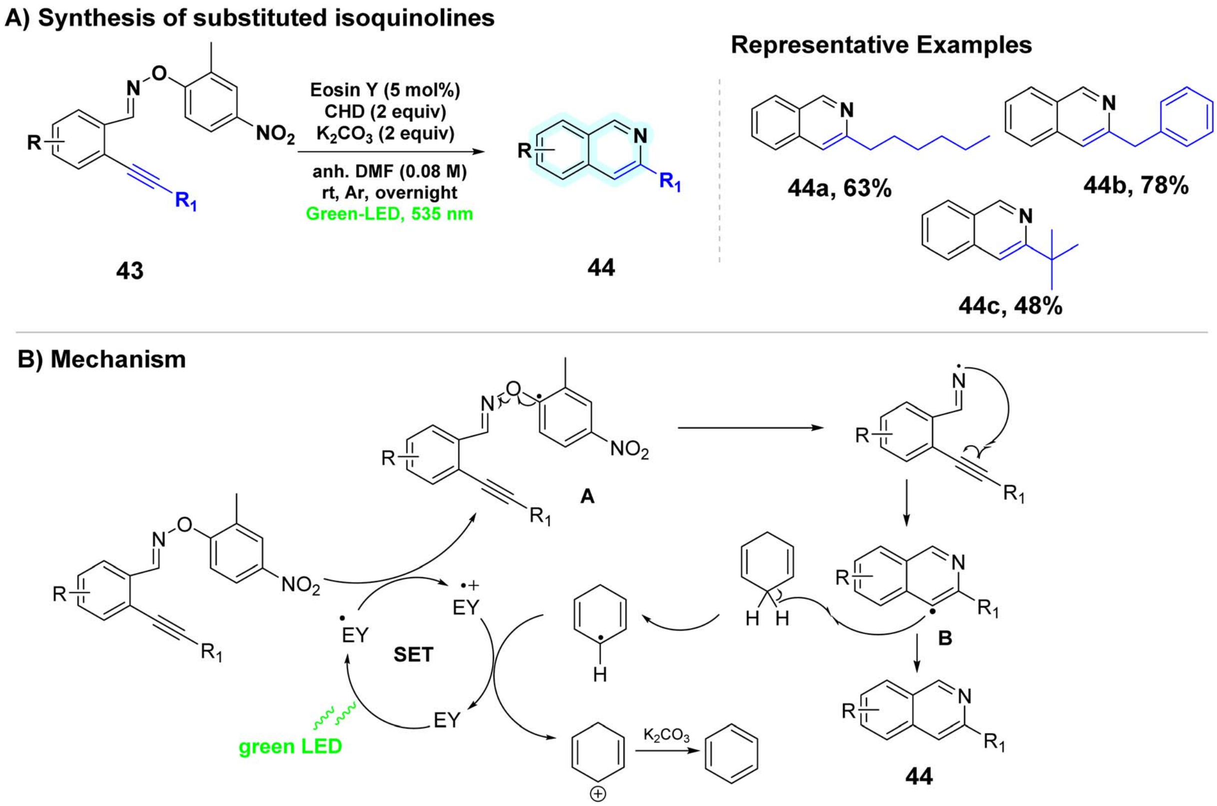
Scheme 14 Greener modification to isoquinoline-N-oxide synthesis by Anghinoni et al.[71]

(**27**) and anthranilic acid (**28**) under microwave irradiation (Scheme 10). The reaction proceeded *via* a tetrahedral mechanism-nucleophile attack of the amino group of anthranilic acid at the carbonyl of homopthalic anhydride to give (**A**), followed by removal of proton and 1,6-*exo*-trig cyclization with water elimination to give isoquinolone (**B**), which undergoes cyclization to give (**C**). Further, amine was added to get the final product (**30**). The method provided improved yields and shortened reaction time.

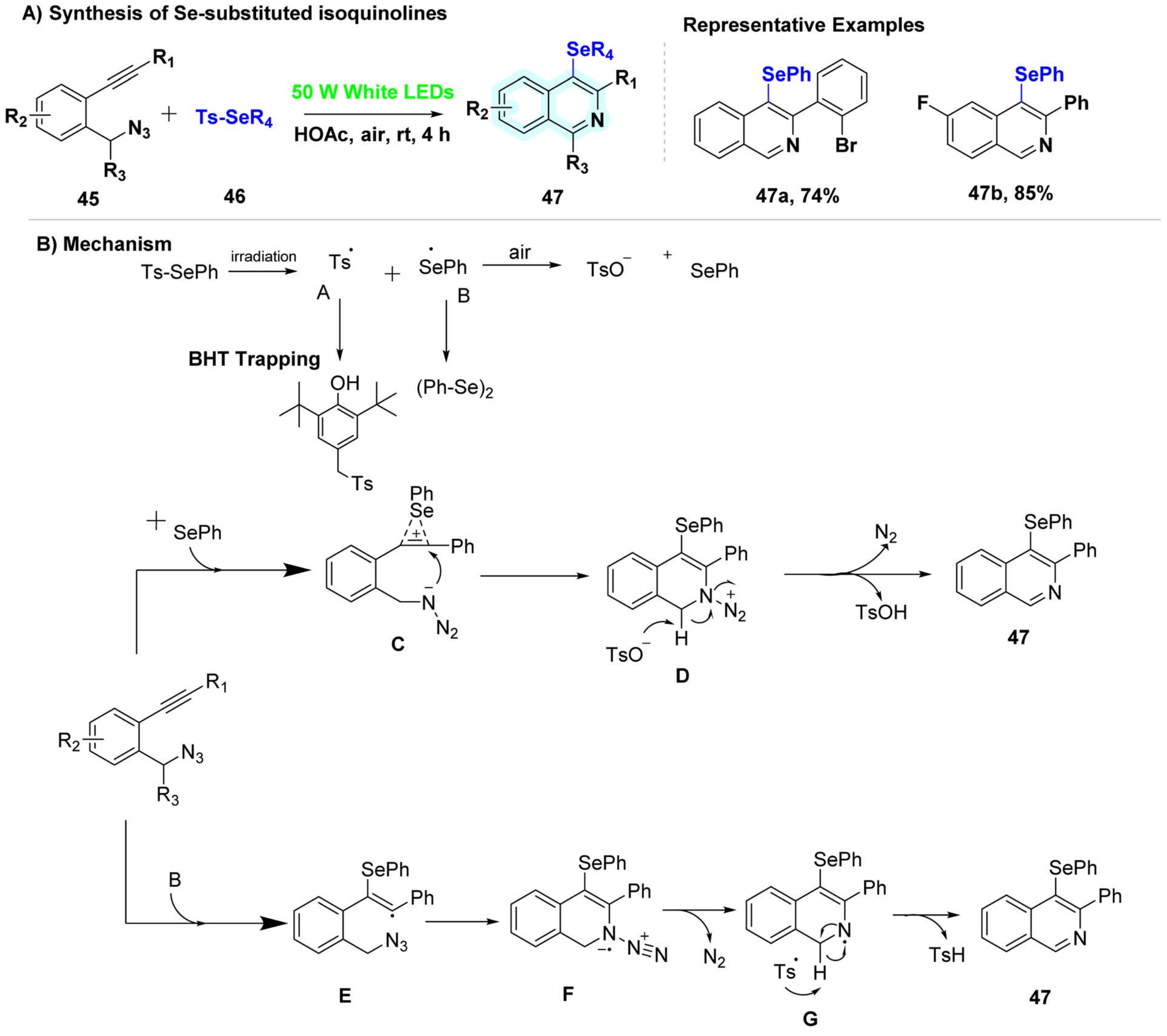
2.2 Ultrasound-assisted synthesis

In recent years, ultrasound (US) irradiation has emerged as a powerful technique in modern science, particularly within medicinal and organic chemistry.[44] Compared to conventional methods, the use of ultrasound energy in chemical reactions offers several notable advantages, such as higher yields, improved product purity, shorter reaction times, and the ability to achieve selectivity and reactivity. Furthermore, ultrasound-assisted reactions often operate under milder conditions, require less energy, minimize or eliminate side reactions, and can be performed with little or no solvent, making these processes more environmentally friendly.[64,65]

Sangepu *et al.*[66] demonstrated a green and efficient ultrasound-assisted one-pot synthesis of isoquinolin-1(2*H*)-one derivatives (**33**) (Scheme 11). The methodology involves a sequential two-step transformation: a copper-catalyzed α-arylation of ketones (**32**) with 2-iodobenzamide (**31**) *via* C–C bond formation, followed by intramolecular C–N bond cyclization—both steps occurring in the same reaction pot under ultrasound irradiation. The mechanism starts with ultrasound-assisted



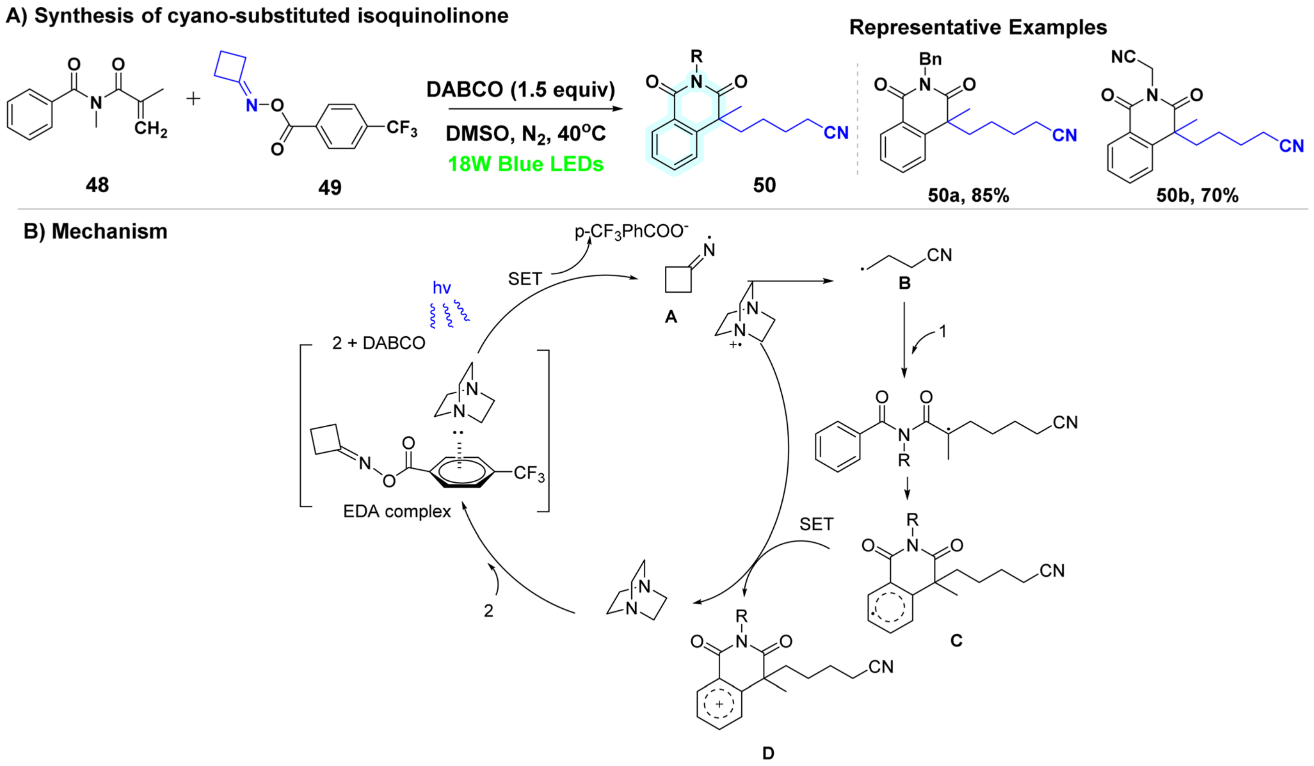
Scheme 15 Synthesis of alkyl/aryl substituted isoquinolines by Yuan *et al.*[75]



Scheme 16 Synthesis of Se-substituted isoquinolines by Gong *et al.*[76]

formation of a Cu(I)–DMSO complex (**A**), which undergoes oxidative addition with an aryl iodide to form a Cu(III) intermediate (**B**). This reacts with a ketone-derived enolate to give a Cu(III)-alkyl species (**C**), which undergoes reductive elimination to form intermediate (**D**) and regenerate the catalyst. Intermediate (**D**) quickly cyclizes to form isoquinolinone (**33**). The synergy between ultrasound and catalysis, likely through cavitation induced catalyst activation, significantly enhances reaction efficiency. The process does not require additional ligands or additives, making it environmentally benign. The scope of the method was explored using a wide range of substrates, affording moderate to excellent yields (49–93%). However, the reaction failed when a nitro-substituted 2-iodobenzamide was used, indicating some limitations in functional group tolerance.

An efficient and environmentally friendly multi-component synthetic protocol for pyrido-[2,1-*a*]-isoquinoline derivatives (**37**) was developed by Sharafian *et al.*[67] utilizing ultrasonic irradiation to drive the reaction in water at room temperature (Scheme 12). This method involves the combination of phthalaldehyde (**34**), methylamine, α-halo substituted carbonyl compounds (**36**), activated acetylenes (**35**), and triphenylphosphine (PPh_3), affording the target compounds in excellent yields within short reaction times. The ultrasonic conditions significantly accelerate the transformation, providing clean reaction profiles and simplifying product isolation. Under ultrasonic irradiation in water at room temperature, phthalaldehyde reacts with methylamine to form an iminium intermediate (**A**), while triphenylphosphine (PPh_3) and an α-halo carbonyl compound generate a phosphorus ylide. The activated acetylene undergoes Michael addition with the iminium ion, followed by a Wittig-type olefination with the ylide to give (**B**). This sequence leads to intramolecular cyclization, forming pyrido-[2,1-*a*]-isoquinoline derivatives (**37**) in excellent yields. Furthermore, additional Diels–Alder transformations of the resulting heterocycles under similar ultrasonic conditions were explored, expanding the scope of the methodology. The presence of the isoquinoline core also prompted an



Scheme 17 Synthesis of cyano-substituted isoquinolinones by Zhang *et al.*[77]

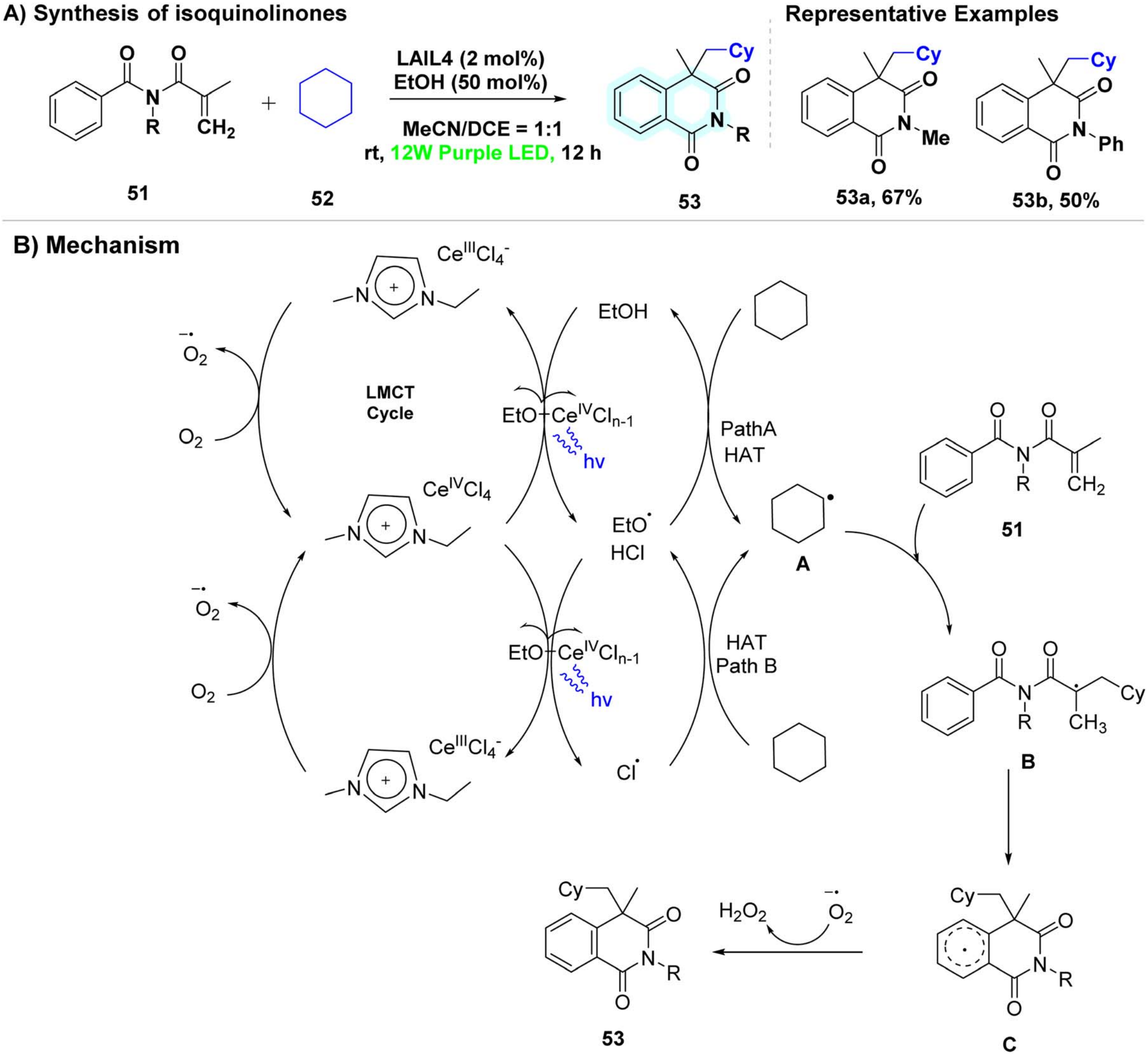
investigation into the antioxidant potential of selected products, confirming their relevance for medicinal chemistry applications. Additionally, a Diels–Alder reaction of the formed isoquinoline with activated acetylenes under ultrasound further expands the molecular framework. Ultrasonication enhances reaction rates, product purity, and supports green synthesis.

In 2020, Araujo *et al.*[68] reported a green and efficient ultrasound-assisted method for synthesizing 3-organyl-4-(organyl chalcogenyl)-isoquinoline-2-oxides (**39**) *via* Oxone-promoted electrophilic cyclization of 2-alkynylbenzaldoximes (**38**) with diorganyl dichalcogenides (Scheme 13). The reaction, driven by ultrasound irradiation as an alternative energy source, proceeds under mild conditions with short reaction times (10–70 min) and delivers high yields (up to 93%) across a broad substrate scope. This protocol extends the authors' previous work,[69,70] on oxone/dichalcogenide-mediated heterocycle synthesis and highlights the compatibility of ultrasound with green synthetic strategies. These results underscore the method's potential for generating novel organochalcogen–isoquinoline *N*-oxide hybrids with promising synthetic and pharmacological relevance. They also reported the synthesis of 4-(selanyl)-isoquinoline-*N*-oxides *via* ultrasound-assisted selenocyclization of *o*-alkynyl benzaldehyde oximes with diorganyl diselenides (**39a, c**) in the presence of Oxone. The proposed mechanism for the 6-*endo*-dig electrophilic cyclization begins with the activation of the dichalcogenide reagent by oxone, generating electrophilic chalcogenium species. These react with the oxime substrate to form a three-membered chalcogeniranium intermediate (**A**). Intramolecular nucleophilic attack by the oxime nitrogen then initiates ring closure, yielding an isoquinoline intermediate (**B**). Subsequent deprotonation of this intermediate furnishes the final isoquinoline product (**39**). This approach delivered excellent yields in short reaction times; however, it required a high loading of oxidants, resulting in increased waste generation and limiting its sustainability.

To overcome these drawbacks, a novel and greener protocol was developed by Anghinoni *et al.*[71] using benzeneseleninic acid (BSA) (**41**) derivatives as bench-stable, odorless, and easy to handle selenium sources (Scheme 14). This method involves the thermal selenocyclization of *o*-alkynyl benzaldehyde oximes (**40**) in refluxing methanol, enabling the *in situ* generation of electrophilic selenium species without the need for strong oxidants or additives. The process afforded up to 96% yields, displayed excellent substrate tolerance, and was successfully scaled up by 10-fold. Additionally, the only by product formed was water, making it a more sustainable and environmentally friendly alternative to previous methods.

2.3 Visible light and photo-redox-assisted synthesis

Visible light and photo-redox assisted synthesis has emerged as a transformative approach in organic chemistry, enabling the activation of molecules under mild, sustainable conditions. By harnessing visible light and suitable photocatalysts often transition metal complexes or organic dyes this method facilitates single-electron transfer and energy transfer processes, generating reactive intermediates such as radicals.[72] This allows chemists to perform highly selective and previously challenging transformations, including C–H functionalization, cross-

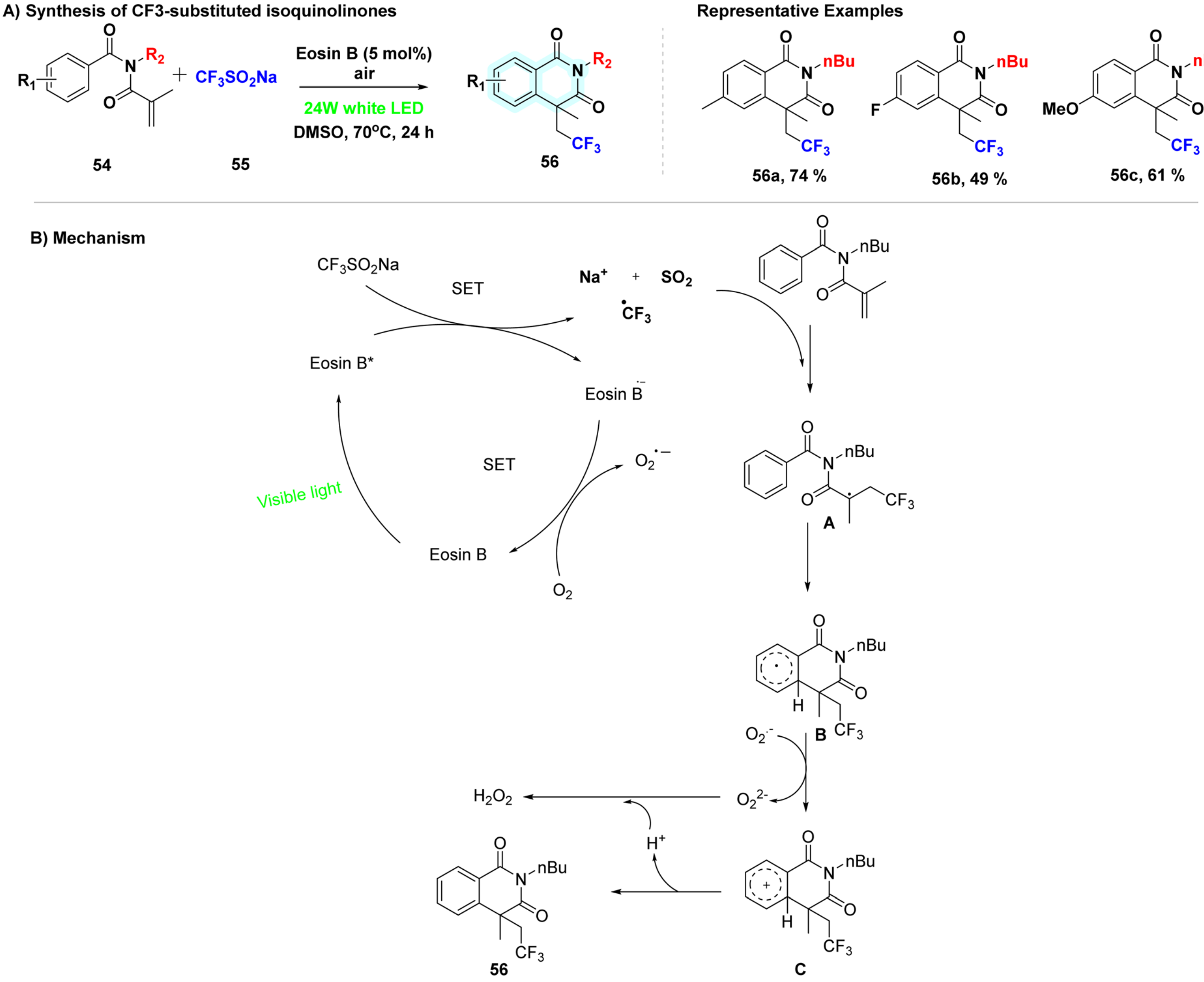


Scheme 18 Synthesis of isoquinolinone by T. Zhang *et al.*[78]

coupling, and late-stage modifications, with broad functional group tolerance and operational simplicity.[73] The mild reaction conditions, compatibility with aqueous environments, and avoidance of harsh reagents make visible light photo-redox catalysis especially attractive for pharmaceutical and natural product synthesis, driving innovation in both academic and industrial settings.[74]

Yuan *et al.*[75] introduced a sustainable and efficient method for synthesizing isoquinolines using inexpensive organic dyes as visible-light photoredox catalysts, with a focus on the underexplored nitrogen-centered radical (NCR) chemistry. The authors generate iminyl radicals from dinitroaryloxime derivatives (**43**), which undergo intramolecular 6-*endo*-dig cyclization on vicinal alkynes to form isoquinoline scaffolds (**44**) (Scheme 15). Addressing the scarcity of NCR-mediated cyclizations, especially on alkynes, they optimize reaction conditions using eosin Y (EY) as the photocatalyst under green LED irradiation, with 1,4 cyclohexadiene (CHD) as a hydrogen donor and K_2CO_3 in DMF as the base-solvent system conditions where conventional metal-based photocatalysts proved ineffective. The mechanism involves eosin Y-mediated single-electron transfer producing iminyl radicals (**A**) that attack nearby alkyne, triggering 6-*endo*-dig cyclization to form carbon-centered radicals (**B**), which upon hydrogen abstraction from CHD yield the final product (**44**), regenerating the catalyst and giving benzene as a by-product. Substrate scope reveals that electron-withdrawing groups on alkynes and aromatic rings enhance yields, while steric hindrance and electron-donating substituents lower efficiency. Overall, this work offers a novel, metal-free, and green approach to construct biologically important isoquinolines *via* visible-light induced NCR cyclization on alkynes, significantly advancing sustainable radical-based heterocycle synthesis.

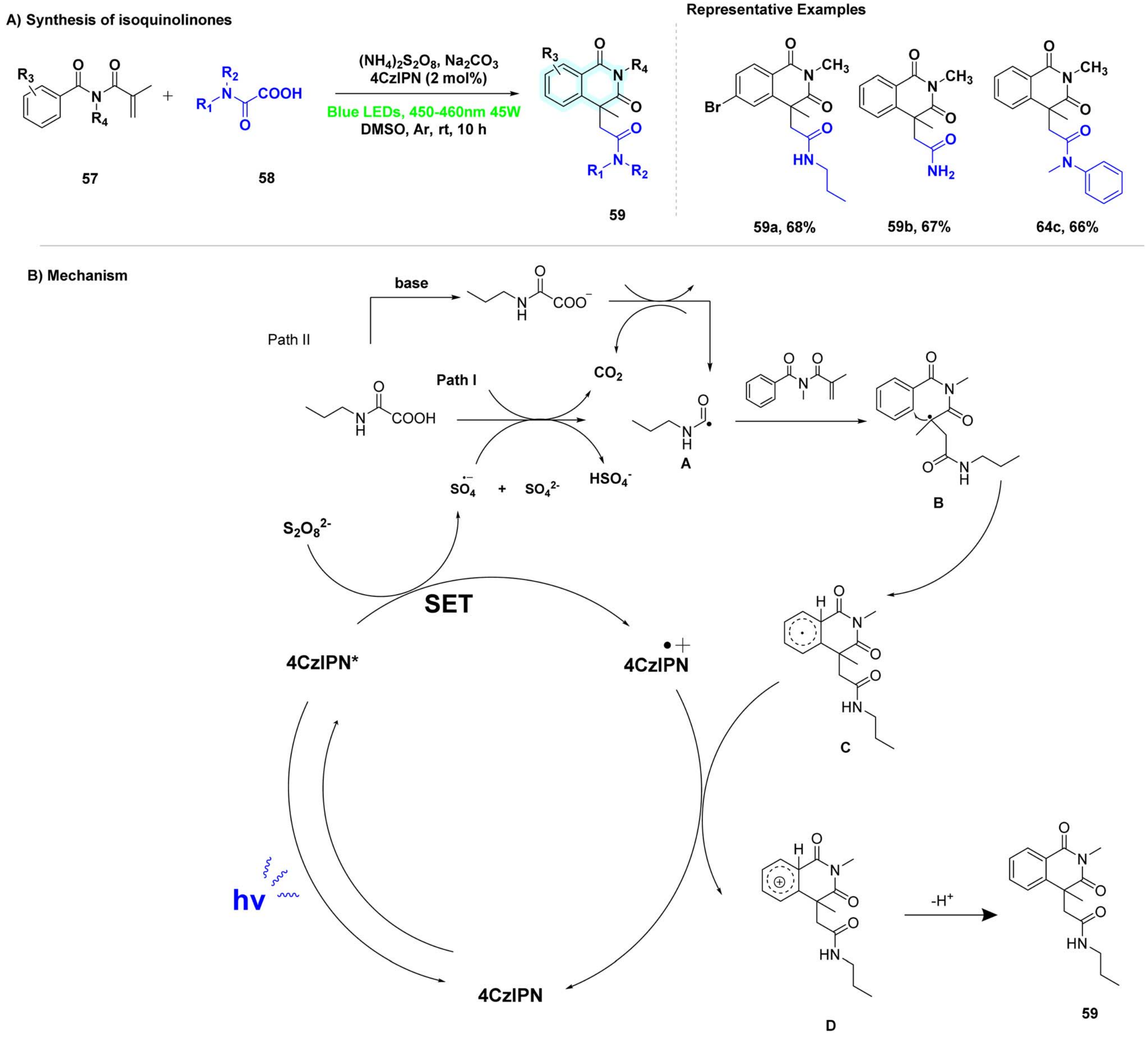
Gong *et al.*[76] developed a simple and efficient visible-light-promoted selenylation/cyclization method for the synthesis of seleno-substituted isoquinoline derivatives (**47**) from *o*-alkynyl benzylazides (**45**) and *o*-propargyl arylazides (Scheme 16). This strategy enables the construction of one C(sp^2)–Se bond and



Scheme 19 Synthesis of CF_3-substituted isoquinolinones by Wang *et al.*[79]

one C–N bond in a single step, providing access to valuable seleno-substituted heterocycles. Based on experimental results, two possible reaction pathways are proposed. Upon irradiation, Se-phenyl 4-methylbenzenesulfonoselenoate (**46**) generates $Ts^•$ (**A**) and $PhSe^•$ (**B**) radicals, which are oxidized under air to TsO^- and $PhSe^+$, respectively. In path (a), electrophilic addition of $PhSe^+$ to the alkyne forms a selenonium ion intermediate (**C**). Subsequent intramolecular nucleophilic cyclization by the azide group yields intermediate (**D**), which undergoes deprotonation by TsO^+ (with TsOH detected by LC-MS) and nitrogen extrusion to produce the final product (**47**). In path (b), the $PhSe^•$ radical adds to the alkyne to form intermediate (**E**), which undergoes a 6-*endo*-dig cyclization to give radical anion intermediate (**F**). Loss of nitrogen leads to nitrogen radical intermediate (**G**), which abstracts a hydrogen atom from $Ts^•$ (with TsH detected by LC-MS) to furnish product (**47**).

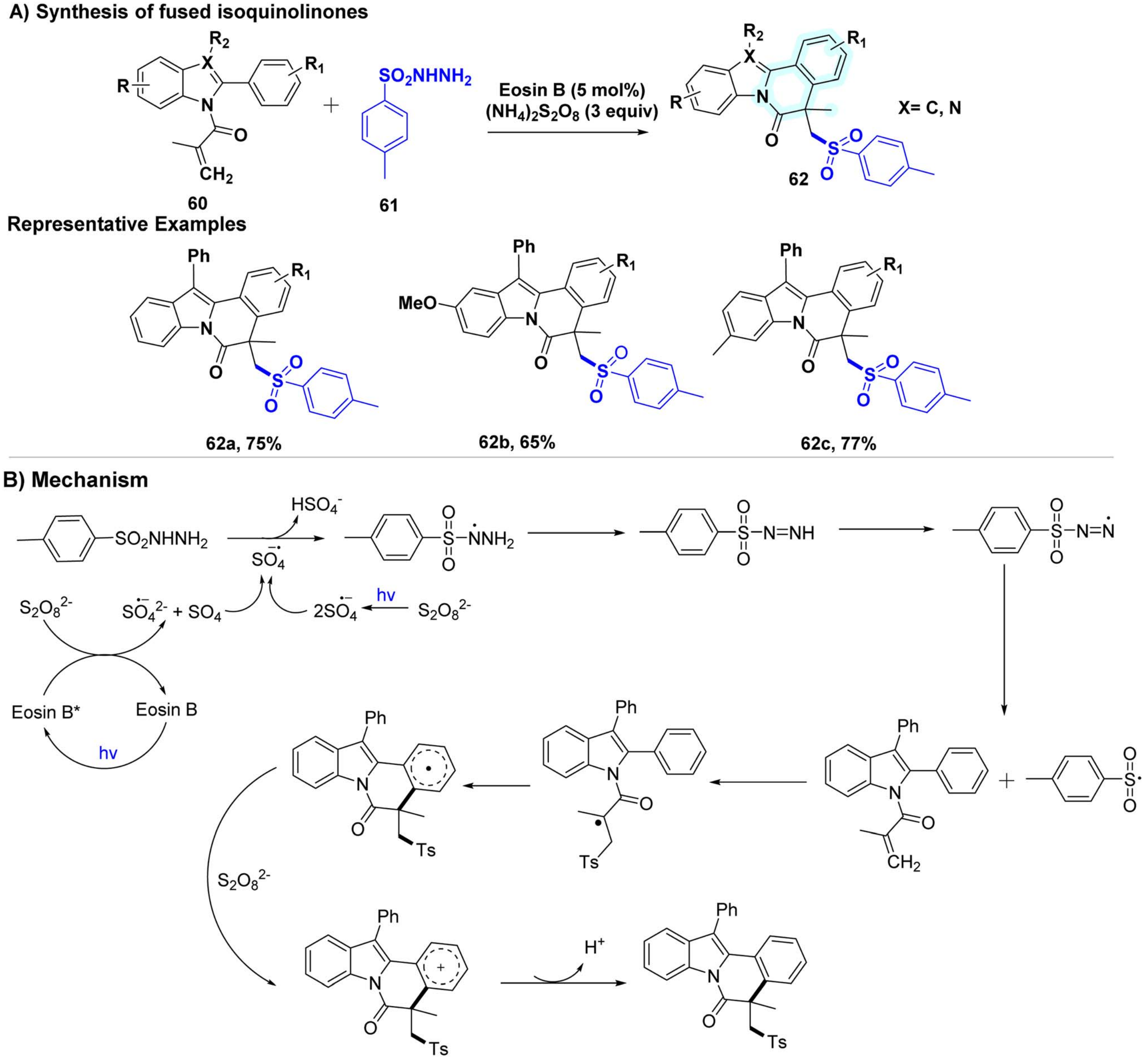
Zhang *et al.*[77] introduced a novel and sustainable cascade cyclization strategy that utilizes visible light and operates without metal catalysts for the synthesis of 4-cyanoalkyl isoquinoline-1,3-diones (**50**) (Scheme 17). The method employs an electron donor–acceptor (EDA) complex mechanism, beginning with the ring-opening of cycloketone oxime esters (**49**) and followed by coupling with *N*-methacryloyl benzamides (**48**). A small amount of 1,4-diazabicyclo-[2.2.2]-octane (DABCO) serves as the catalyst, and prolonged reaction times aid in completing the transformation. The procedure is straightforward, showcasing a wide functional group tolerance and broad substrate compatibility under mild, photocatalyst-free conditions. Various radical acceptors can be integrated into the reaction, enabling the construction of a diverse range of heterocycles. Mechanistic studies confirmed that the formation of EDA complexes between Lewis bases and cycloketone oxime esters through weak interactions is essential for reactivity. The reaction begins with the formation of an electron donor–acceptor (EDA) complex between cyclobutanone oxime ester and DABCO. Upon blue LED irradiation, the complex undergoes single-electron transfer (SET), generating a benzoate anion, an imine radical (**A**), and a DABCO radical cation. The imine radical undergoes C–C bond cleavage to form a cyanoalkyl radical (**B**), which adds to a radical acceptor *via* cyclization, yielding



Scheme 20 Synthesis of isoquinolinones by Niu *et al.*[80]

a radical intermediate (**C**). Another SET between (**C**) and DABCO$^+$ forms a cationic intermediate (**D**). Finally, deprotonation of (**D**) by DABCO or benzoate gives the final product. Impressively, high product yields were achieved even with only catalytic amounts of DABCO. This approach provides an efficient and environmentally friendly route to isoquinoline-1,3-dione derivatives.

T. Zhang *et al.*[78] reported a sustainable and metal-free method using reusable Lewis acidic ionic liquids (LAILs) as catalysts for the radical-cascade alkylation and cyclization of *N*-alkyl-*N*-methacryloyl benzamides (**51**) with unactivated alkanes (**52**) to synthesize alkylated isoquinoline-1,3-(2*H*,4*H*)-diketones (**53**) (Scheme 18). This reaction proceeds efficiently under mild conditions in a mixed MeCN/DCE solvent system with ethanol as a hydrogen transfer agent, without requiring stoichiometric oxidants or high temperatures. The LAILs function as recyclable light-mediated charge-transfer (LMCT) catalysts, supporting green chemistry principles. The proposed mechanism begins with the oxidation of Ce^{3+}-LAILs in air and ethanol, forming an EtO–Ce^{4+} complex and a superoxide radical ($O_2^{-\bullet}$). Upon light irradiation, ligand-to-metal charge transfer (LMCT) generates an ethoxy radical (EtO$^\bullet$), which abstracts a hydrogen atom from cyclohexaneto form a cyclohexyl radical. This radical undergoes addition and cyclization with compound (**51**) to yield intermediate (**C**). A final HAT from (**C**) to the superoxide radical forms the product (**53**) and hydrogen peroxide. Alternatively, a chloride radical could also initiate the HAT step, suggesting a possible parallel pathway. The protocol accommodates a broad range of electron-rich and electron-poor *N*-substituted benzamides, delivering the desired products in moderate to good yields. This approach offers excellent catalyst recyclability, scalability, and high atom economy, making it a promising

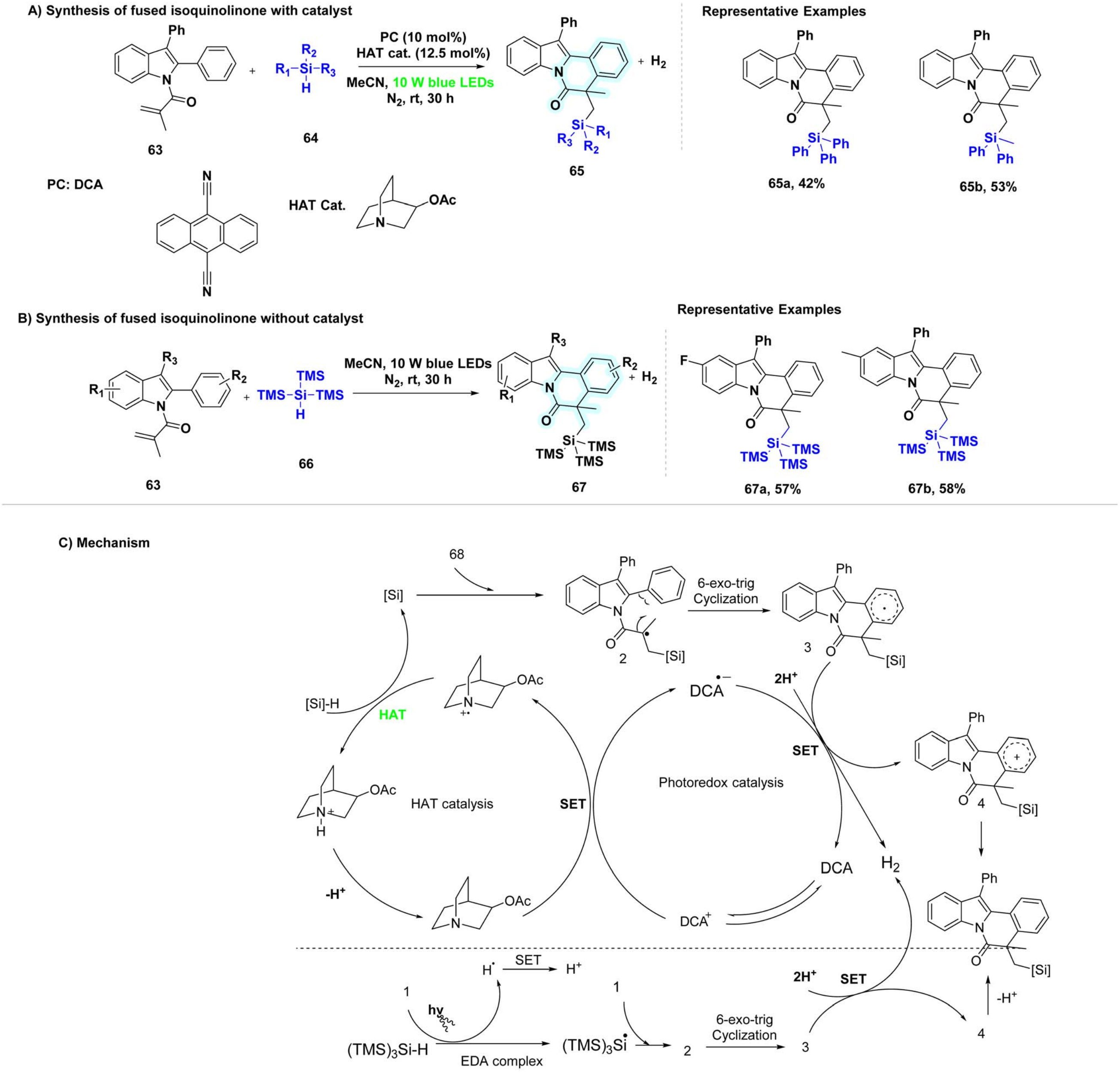


Scheme 21 Synthesis of fused isoquinolinones by Tang *et al.*[81]

alternative for the eco-friendly synthesis of functionalized isoquinoline derivatives.

Wang *et al.*[79] reported a novel, visible-light induced, radical cascade trifluoromethylation/cyclization of *N*-benzamides (**54**) using sodium trifluoromethanesulfinate (CF_3SO_2Na) (**55**) has been developed for the synthesis of CF_3-containing isoquinoline-1,3-diones (**56**) (Scheme 19). This metal-free protocol operates under air, without additives or expensive reagents, offering a practical and operationally simple method. The reaction utilizes CF_3SO_2Na as an inexpensive CF_3 source and proceeds *via* a radical pathway under visible light irradiation. Under visible-light irradiation, Eosin B is excited to its active form (Eosin B*), which accepts an electron from (**55**), generating a CF_3 radical and a radical anion of Eosin B. The CF_3 radical adds to the substrate, forming intermediate (**A**), which undergoes radical cyclization to give intermediate (**B**). Simultaneously, Eosin B* transfers an electron to O_2, producing superoxide ($O_2^{\bullet -}$) and regenerating Eosin B. The resulting intermediate (**C**) then undergoes deprotonation to yield the final product (**56**). Compared to previous methods requiring transition metals or additives, this approach stands out for its eco-friendliness and cost-effectiveness.

In 2025, Niu *et al.*[80] reported a novel, green, and efficient photocatalytic method for synthesizing amide-functionalized isoquinoline-1,3-diones *via* a cascade amidation/cyclization reaction (Scheme 20). The process utilizes readily available oxamic acids as amide donors and the organic photocatalyst 4CzIPN under mild, metal-free, and environmentally benign conditions. Upon irradiation with blue LED light, the organic photocatalyst 4CzIPN is excited to its singlet excited state

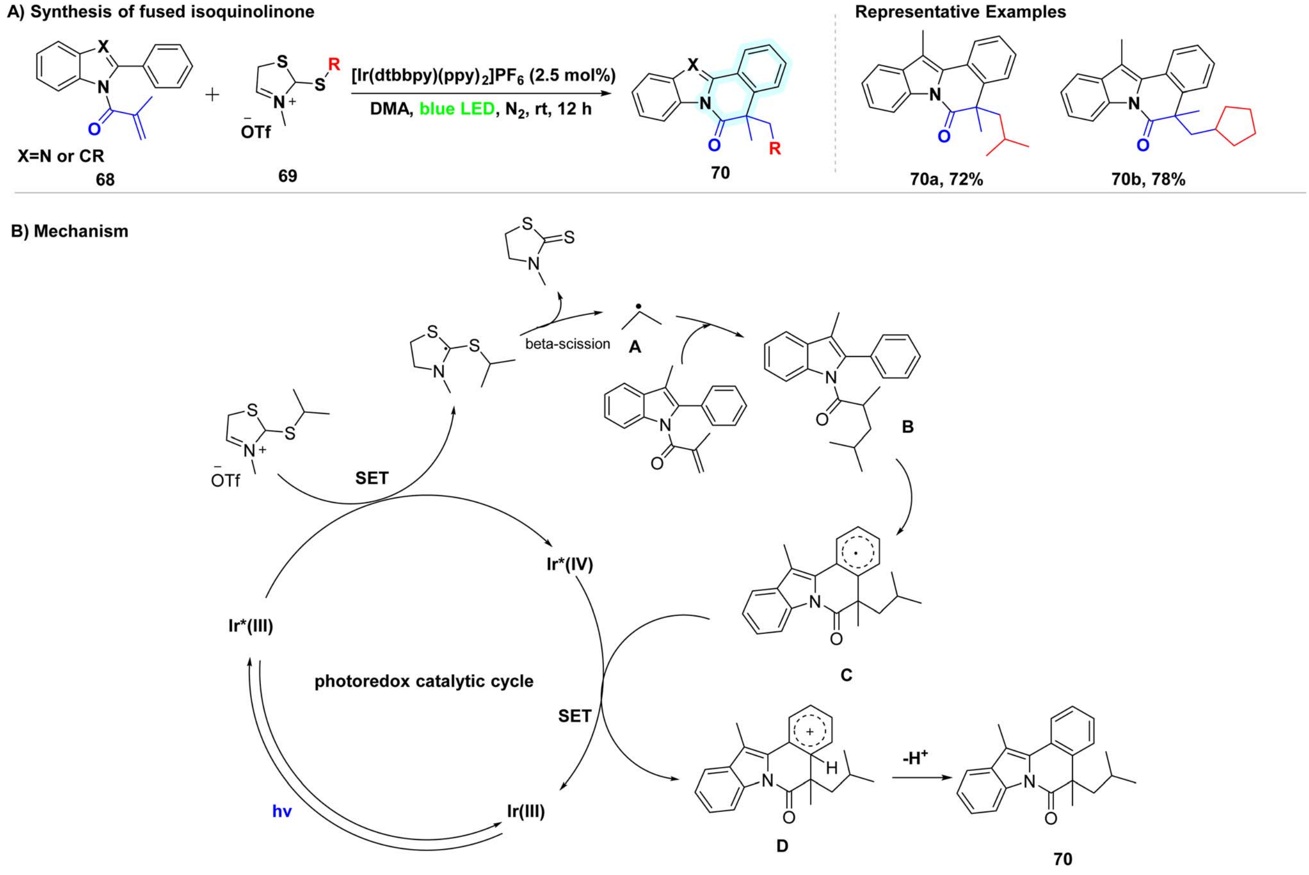


Scheme 22 Synthesis of indolo-isoquinolines by Lei *et al.*[84]

4CzIPN*. This excited species undergoes single-electron transfer (SET) with persulfate anion ($S_2O_8^{2-}$), resulting in the formation of the 4CzIPN radical cation ($4CzIPN^{\bullet+}$), sulfate radical anion ($SO_4^{\bullet-}$), and a sulfate dianion (SO_4^{2-}). The sulfate radical ($SO_4^{\bullet-}$) then interacts with oxamic acid, abstracting a hydrogen atom (*via* hydrogen atom transfer, HAT) and promoting decarboxylation, leading to the formation of a carbamoyl radical (**A**). This carbamoyl radical (**A**) then undergoes a radical addition to the alkene moiety of the substrate, generating a new carbon-centered radical intermediate (**B**). Following this, intermediate (**B**) undergoes an intramolecular cyclization, typically a 6-*endo*-trig or 5-*exo*-trig process, forming a cyclic radical intermediate (**C**). The radical (**C**) is then oxidized by the radical cation $4CzIPN^{\bullet+}$ (generated in the first SET), which regenerates the ground state 4CzIPN catalyst and forms a carbocation intermediate (**D**). Finally, this carbocation (**D**) undergoes deprotonation, restoring aromaticity and affording the final isoquinoline-1,3-dione product (**59**).

The protocol offers a broad substrate scope and excellent functional group tolerance. Moreover, its synthetic utility extends beyond isoquinoline diones to include the efficient preparation of amidated oxindoles and succinimides bearing α-quaternary carbon centers, highlighting the versatility and scalability of this approach.

Tang *et al.*[81] also developed an efficient visible-light-promoted, organic-dye-catalyzed radical cascade cyclization was developed for the rapid synthesis of sulfonyl-substituted indolo-[2,1-*a*]-isoquinolines and benzimidazo-[2,1-*a*]-

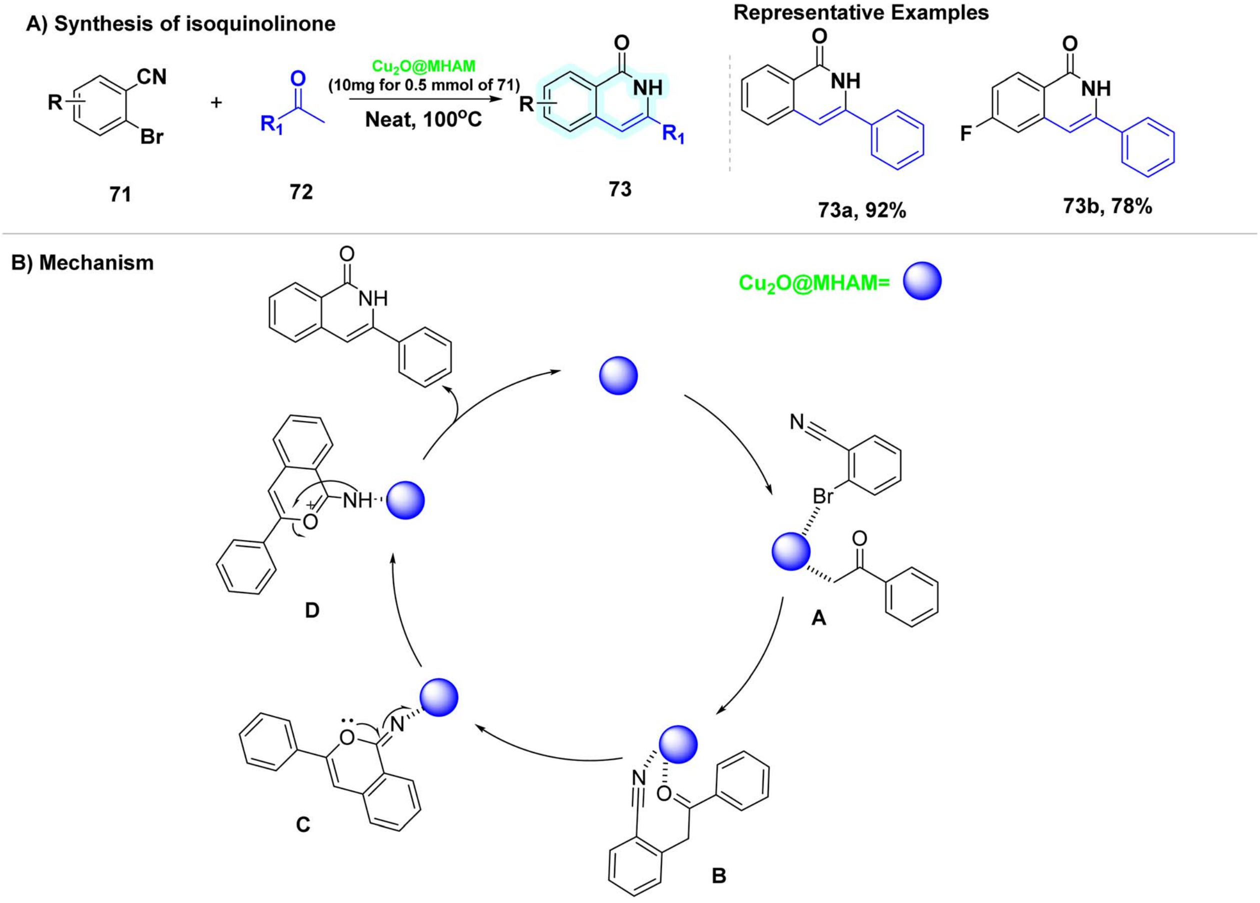


Scheme 23 Synthesis of fused isoquinolinones by Zhu *et al.*[85]

isoquinolin-6-(5*H*)-ones (**65**) (Scheme 21). Using the economical and environmentally friendly photocatalyst Eosin B, a wide range of indolo-[2,1-*a*]-isoquinoline derivatives were obtained in moderate to good yields. Mechanistic studies suggest involvement of a sulfonyl radical pathway initiated by visible-light excitation of Eosin B, which activates persulfate to generate sulfate radical anions that abstract hydrogen from sulfonyl hydrazides to form sulfonyl radicals. These radicals add to substrates, triggering a 6-*endo*-trig cyclization, oxidation, and deprotonation sequence to yield the final products. Compared to previous methods, this protocol avoids metals and bases, uses visible light as a clean energy source, operates under mild conditions, and features simple handling, making it attractive for organic and pharmaceutical applications. Despite existing sulfonation methods,[82,83] often requiring harsh conditions, expensive metals, or excess oxidants, this approach offers a facile, environmentally benign alternative.

In 2024, Lei *et al.*[86] presented an eco-friendly photocatalytic and photo induced strategy for synthesizing fused tetracyclic silylated indolo-[2,1-*a*]-isoquinoline-6-(5*H*)-ones (**65**) from 2-aryl-*N*-acryloyl indoles (**63**) and hydrosilanes (**64**) under mild, metal- and oxidant-free conditions (Scheme 22). The photocatalytic approach employs 9,10-dicyanoanthracene (DCA) with 3-acetoxyquinuclidine as a hydrogen atom transfer (HAT) catalyst, while the photoinduced method uses tris-(trimethylsilyl)-silane ((TMS)$_3$SiH) (**66**) under visible light. Both processes proceed *via* electron-donor–acceptor (EDA) complex formation and radical pathways, yielding products efficiently across a variety of substrates, with yields ranging from 42% to 70%. These methodologies offer significant advantages, including high atom economy, operational simplicity, environmental safety, and hydrogen gas as the only byproduct, making them promising for the sustainable synthesis of functionalized isoquinoline derivatives.

Zhu *et al.*[85] developed a mild and efficient visible-light-induced photocatalytic radical cascade cyclization protocol for the synthesis of indolo-[2,1-*a*]-isoquinoline derivatives (**70**) (Scheme 23). This method employs alkyl 2-mercaptothiazolinium salts (**69**)—easily prepared from inexpensive alkyl halides as alkylating agents under oxidant- and base-free conditions. It enables the coupling of 2-aryl-*N*-acryloyl indoles (**68**) with primary, secondary, and tertiary alkyl groups, yielding products in moderate to good yields. The strategy forms two C–C bonds in a single step, constructing the indolo-[2,1-*a*]-isoquinoline core while introducing aliphatic side chains. Initially, thiazolinium salt (**69**) undergoes single-electron transfer (SET) with photoexcited Ir(III)*, forming radical I and Ir(IV). A β-scission then cleaves the C–S bond, yielding an ethyl radical (**A**) and thione. The ethyl radical undergoes addition and cyclization with substrate (**68**), forming intermediate (**C**) *via* (**B**). Intermediate (**C**) is oxidized in a second SET step, generating cationic species (**D**) and regenerating Ir(III). Final deprotonation of (**D**)



Scheme 24 Synthesis of isoquinolinone by Rawat *et al.*[90]

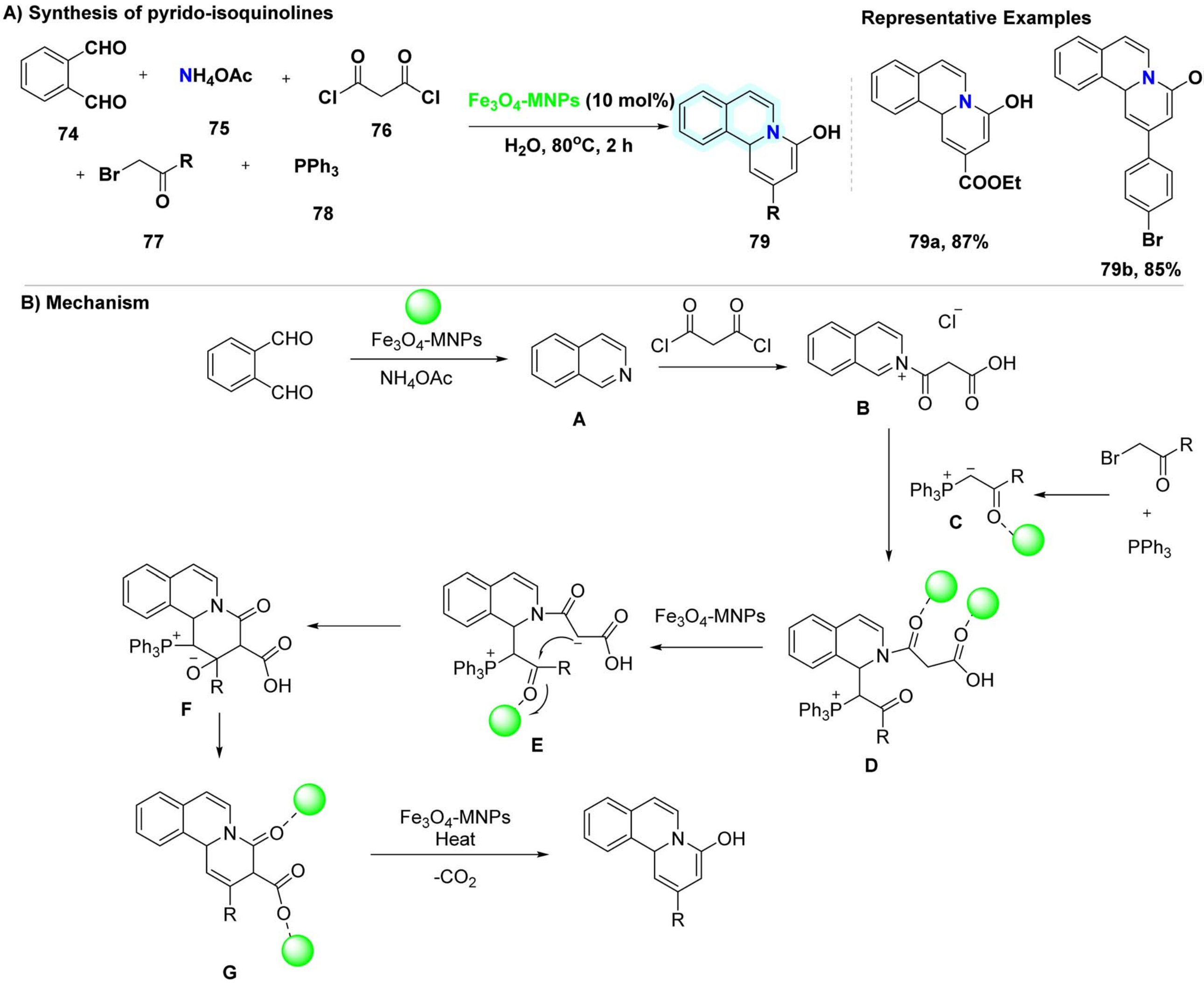
gives the product (**70**). This green and practical approach features broad substrate scope, mild conditions, and avoids costly or sensitive reagents like stoichiometric oxidants, bases, or Katritzky salts.

2.4 Nano catalysts

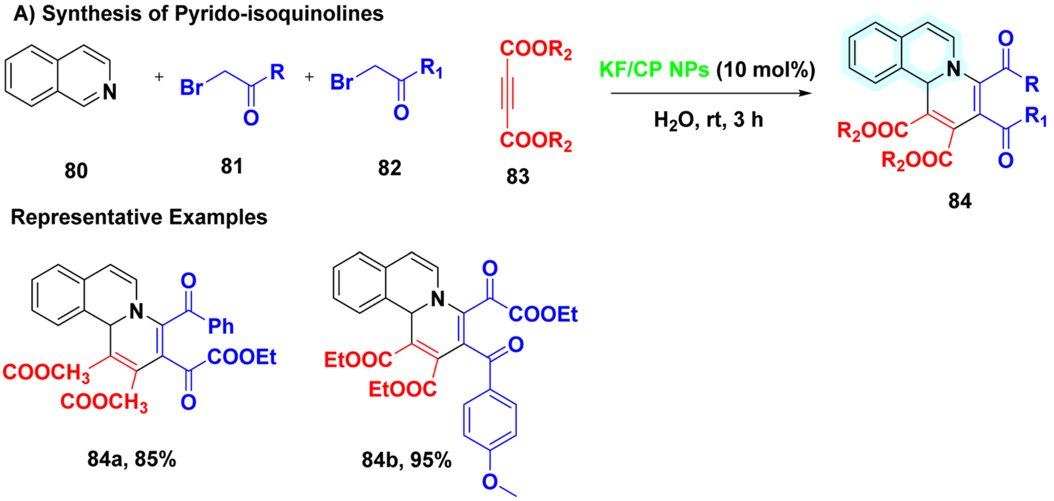
Nanocatalysts have garnered considerable attention as a pivotal component of green chemistry strategies, owing to their unique physicochemical properties and remarkable catalytic efficiencies.[86] Their high surface area-to-volume ratio significantly enhances catalytic activity, enabling reactions to proceed under milder conditions with greater selectivity and reduced energy input compared to conventional catalysts. Furthermore, the facile recovery and recyclability of many nanocatalysts particularly those with magnetic properties contribute to minimizing waste and improving process sustainability.[87] The synthesis of nanocatalysts can often be achieved using environmentally benign methods and renewable resources, further aligning with the principles of green chemistry. Collectively, these attributes position nanocatalysts as promising tools for advancing sustainable and eco-friendly chemical transformations in both academic and industrial contexts.[88,89]

The sustainable synthesis of isoquinolones, key pharmacophores in many natural products and drugs, has gained attention using heterogeneous transition metal-based nanocatalysts. A novel Cu_2O-decorated marigold-like hollow alumina microsphere (Cu_2O@MHAM) nanocatalyst was developed by Rawat *et al.*[90] for the green synthesis of isoquinolones (**73**) from 2-bromobenzonitriles (**71**) and ketones (**72**) under neat conditions (Scheme 24). This method offers significant advantages over previous systems, including excellent yields (up to 92%), broad substrate scope, and superior green chemistry metrics such as a low E-factor, high reaction mass efficiency, and high turnover number. The nanocatalyst was reusable for at least five cycles without loss of activity. Mechanistically, the reaction proceeds through nucleophilic substitution (**B**), electrocyclization (**C**), and nanoparticle-assisted cyclization (**D**). In summary, this Cu_2O@MHAM system provides an efficient, eco-friendly, and reusable catalytic platform for isoquinolone synthesis, demonstrating excellent performance and sustainability.

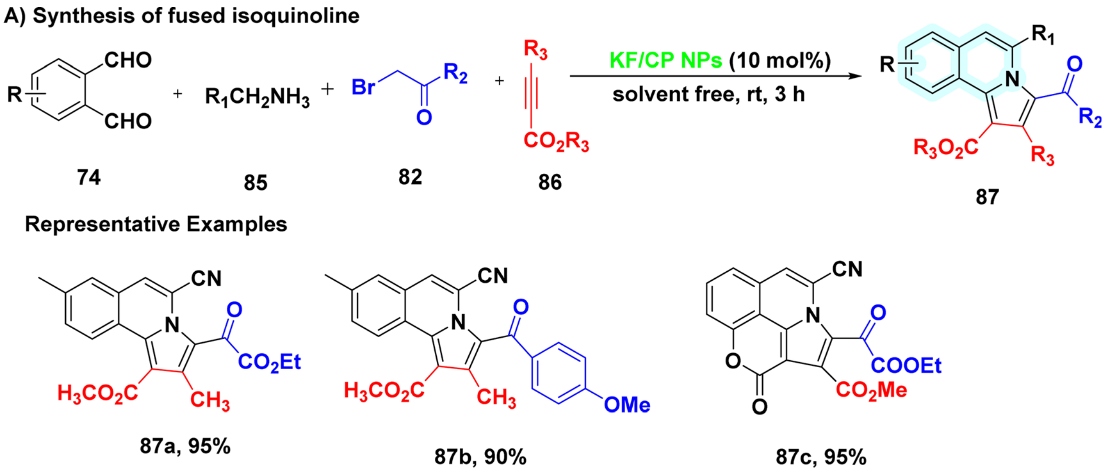
In 2022, Ezzatzadeh *et al.*[91] reported a green and efficient method for synthesizing pyrido-[2,1-*a*]-isoquinolines (**79**) and pyrido-[1,2-*a*]-quinolines in excellent yields *via* multicomponent reactions of pthalaldehyde (**74**), methyl malonyl chloride (**76**), alkyl bromides (**77**), and triphenyl phosphine (**78**) using magnetically recoverable Fe_3O_4 nanoparticles as a catalyst in water at 80 °C (Scheme 25). The Fe_3O_4 nanoparticles were synthesized through a green approach using Clover Leaf extract.



Scheme 25 Synthesis of pyrido isoquinolines by Ezzatzadeh *et al.*[91]



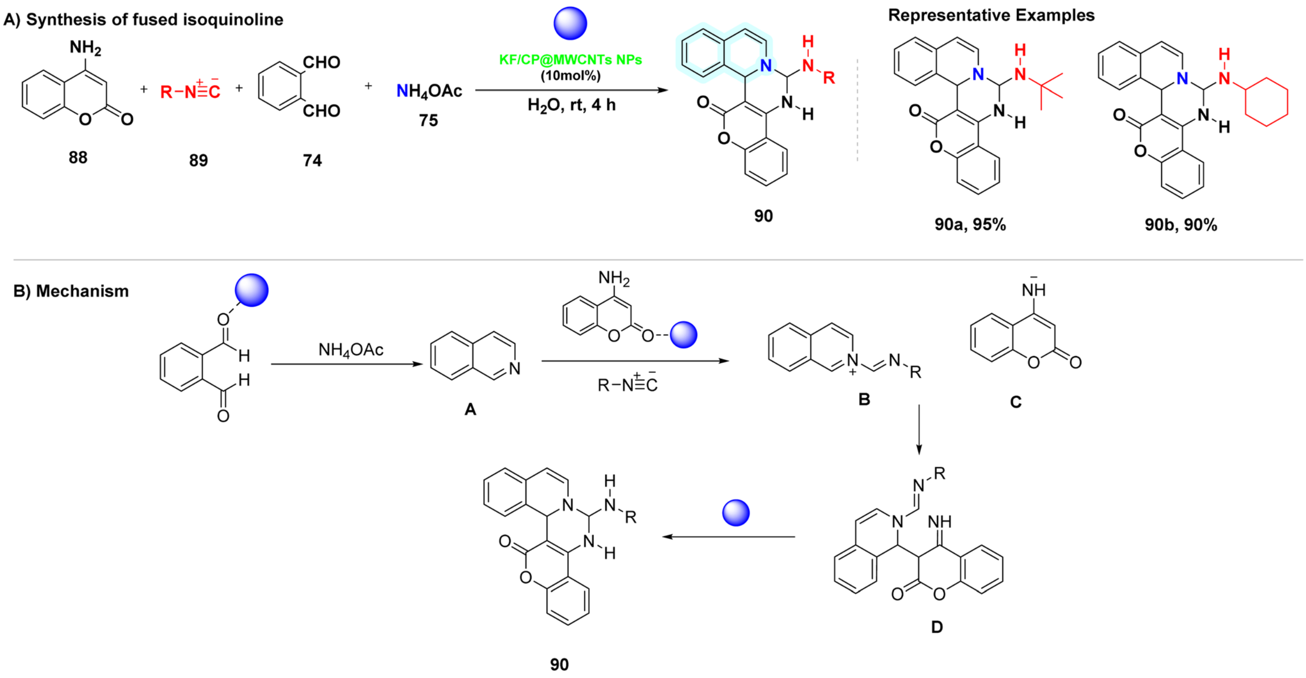
Scheme 26 Synthesis of pyrido-isoquinolines by Hamedani *et al.*[92]



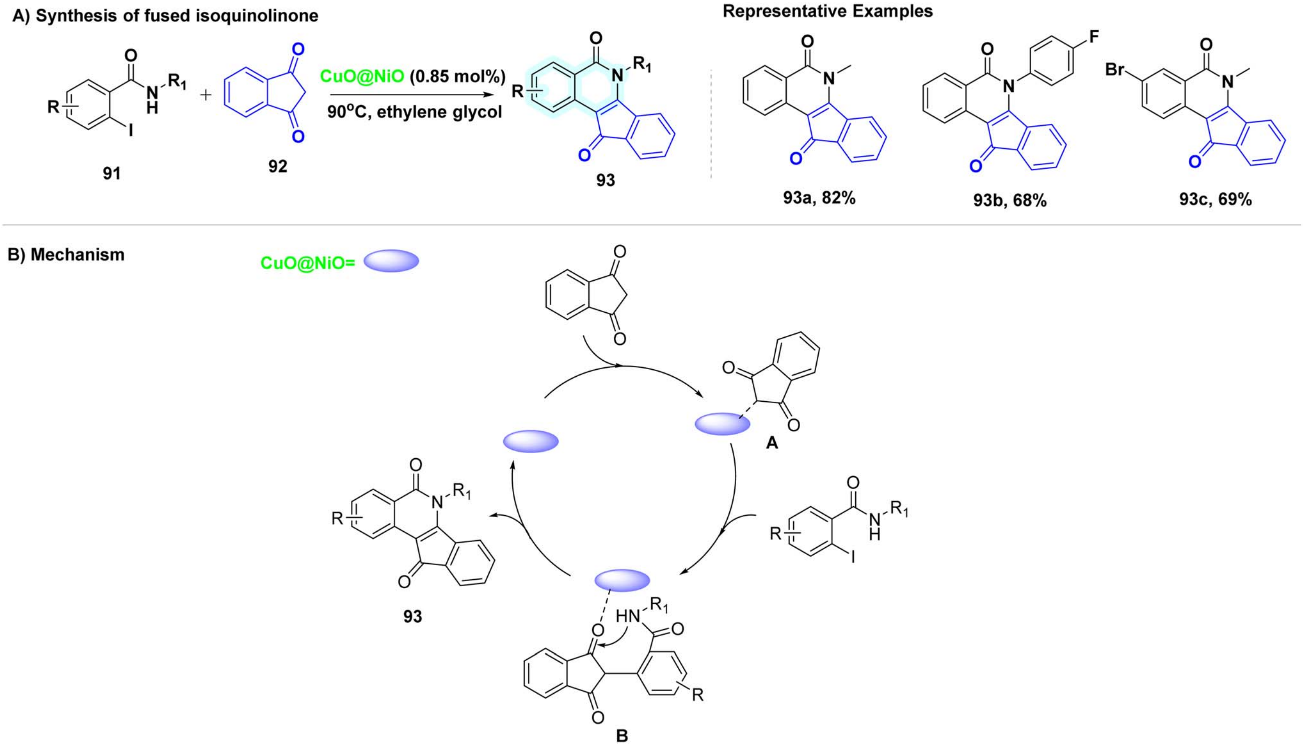
Scheme 27 Synthesis of pyrrolo-fused isoquinolines by S. Amiri *et al.*[93]

Phthalaldehyde and ammonium acetate react in the presence of Fe_3O_4 MNPs to form isoquinoline (**A**), which then couples with malonyl chloride to give an intermediate (**B**). Separately, alkyl bromide and triphenylphosphine form a phosphonium intermediate (**C**), which reacts with the isoquinoline derivative to give (**D**). Cyclization and elimination of triphenylphosphine oxide occur, followed by decarboxylation under heating to yield the final product. The synthesized compounds showed notable ferric ion reducing capacity and minimal DPPH radical scavenging activity, indicating potential antioxidant properties. Additionally, antimicrobial studies revealed that compounds exhibited growth inhibition against both Gram-positive and Gram-negative bacteria. This solvent free, eco-friendly method emphasizes the biological relevance of isoquinoline derivatives and highlights the ease of catalyst recovery using a magnet, better atom economy, and higher yields, aligning well with green chemistry principles.

Hamedani *et al.*[92] also reported a green and efficient method for synthesizing pyrido-[2,1-*a*]-isoquinoline derivatives (**84**) using KF/Clinoptilolite (KF/CP) nanoparticles as a heterogeneous catalyst *via* a four component reaction involving isoquinoline (**79**), two alkyl bromides (**81**, **82**), and electron-deficient internal alkynes (**83**) in water at ambient temperature (Scheme 26). The KF/CP nanocatalyst, composed of natural and inexpensive materials, offers high catalytic activity due to its nanoscale properties and provides free fluoride anions as



Scheme 28 Synthesis of fused isoquinolines by S. Amiri *et al.*[94]

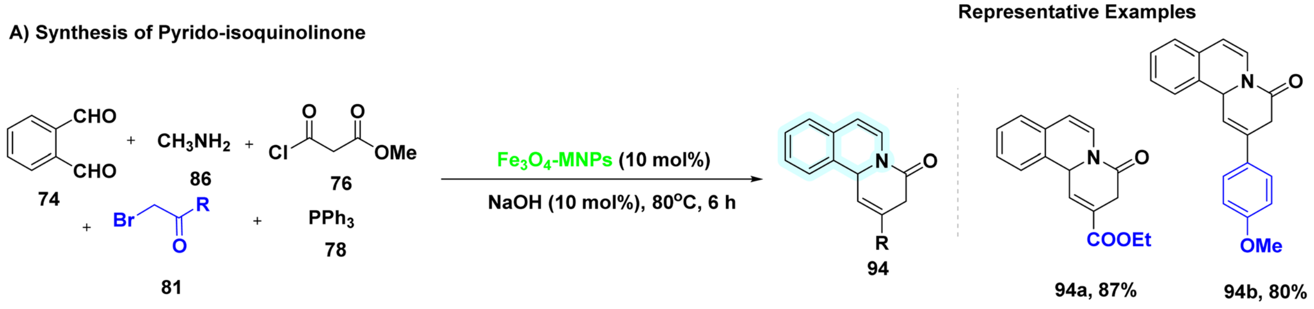


Scheme 29 Synthesis of fused isoquinolinone scaffold by Rawat *et al.*[95]

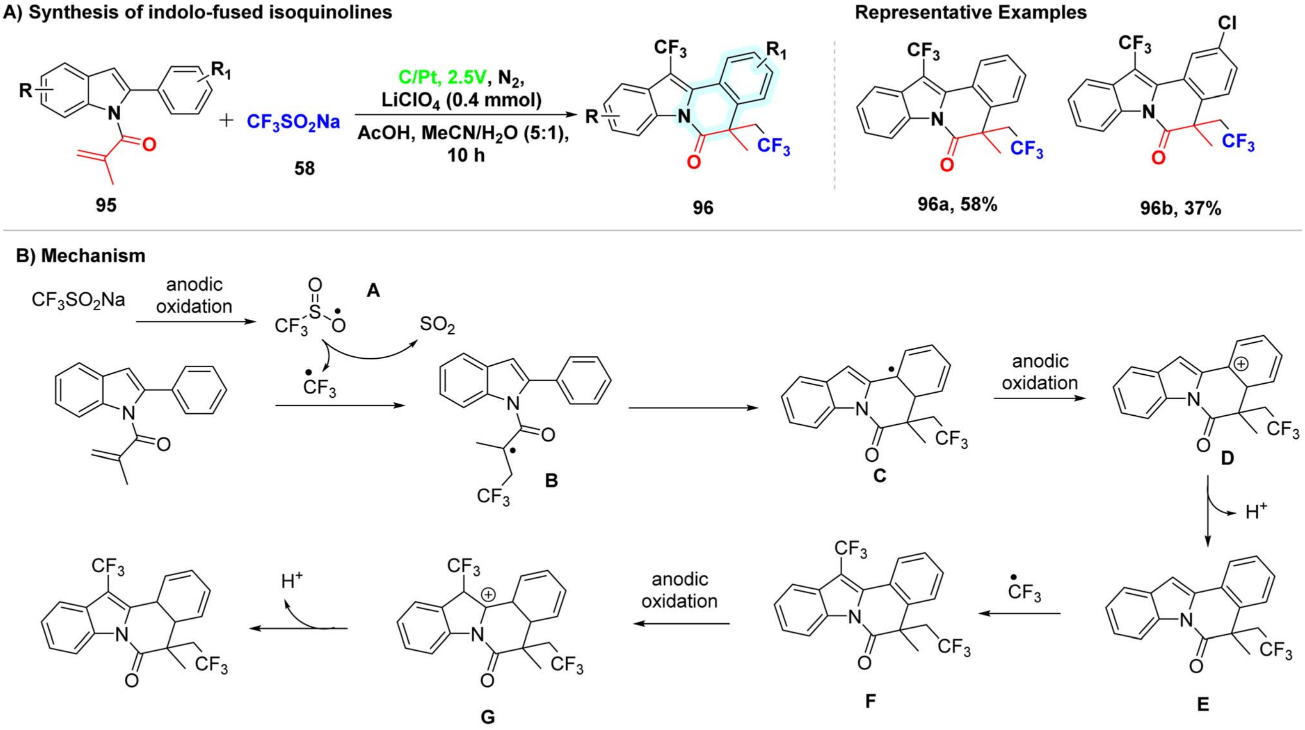
a basic species. The synthesis process is clean, straightforward, and requires no purification steps. Key advantages of this method include high product yields, green solvent usage, catalyst reusability, and ease of product and catalyst separation, making it an attractive and sustainable approach in heterocyclic synthesis.

S. Amiri *et al.*[93] reported a green, solvent-free method for synthesizing pyrrolo-[2,1-*a*]-isoquinoline derivatives (**87**) *via* a four-component reaction involving phthalaldehyde (**74**) or its derivatives, primary amines (**85**), alkyl bromides (**82**), and activated acetylenic compounds (**86**) using KF/Clinoptilolite (KF/CP) nanoparticles as a reusable catalyst at room temperature (Scheme 27). Additionally, Diels–Alder reactions between the synthesized isoquinolines, activated acetylenes, and triphenylphosphine also proceed efficiently under similar conditions. The method demonstrates excellent yields, fast reaction rates, environmental compatibility, and recyclability of the catalyst. Antioxidant evaluations of selected compounds showed promising activity compared to standard antioxidants (BHT and TBHQ), highlighting the biological relevance of the synthesized products.

In 2022, S. Amiri *et al.*[94] also reported a green and efficient method to synthesize pyrimido-isoquinoline derivatives *via* a four-component reaction in water using KF/CP@MWCNTs nanocatalysts at room temperature (Scheme 28). The process offers high yields, short reaction times, and easy catalyst recovery. The compounds showed promising antioxidant and antimicrobial activities, and a mechanism involving isoquinoline intermediate formation was proposed. The reaction starts with the condensation of (**88**) and (**75**) in the presence of KF/CP@MWCNTs nanocatalysts to form isoquinoline intermediate (**A**). Concurrently (**89**), reacts with (**88**), generating



Scheme 30 Synthesis of pyrido-fused isoquinolinones by Hamedani *et al.*[96]

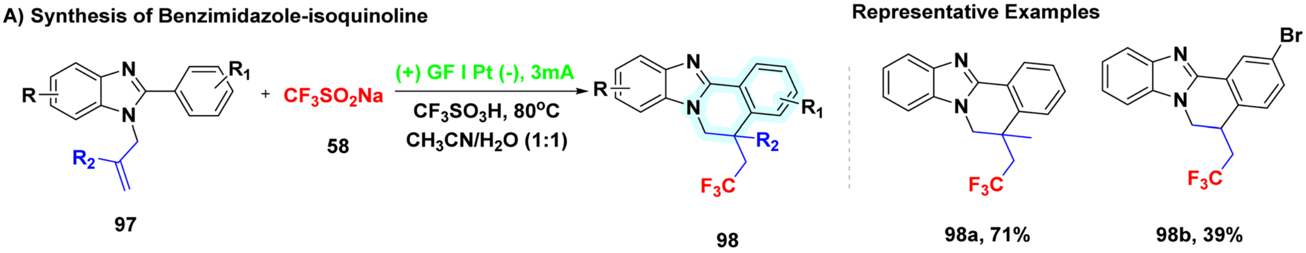


Scheme 31 Synthesis of indolo-fused isoquinolines by Mei *et al.*[100]

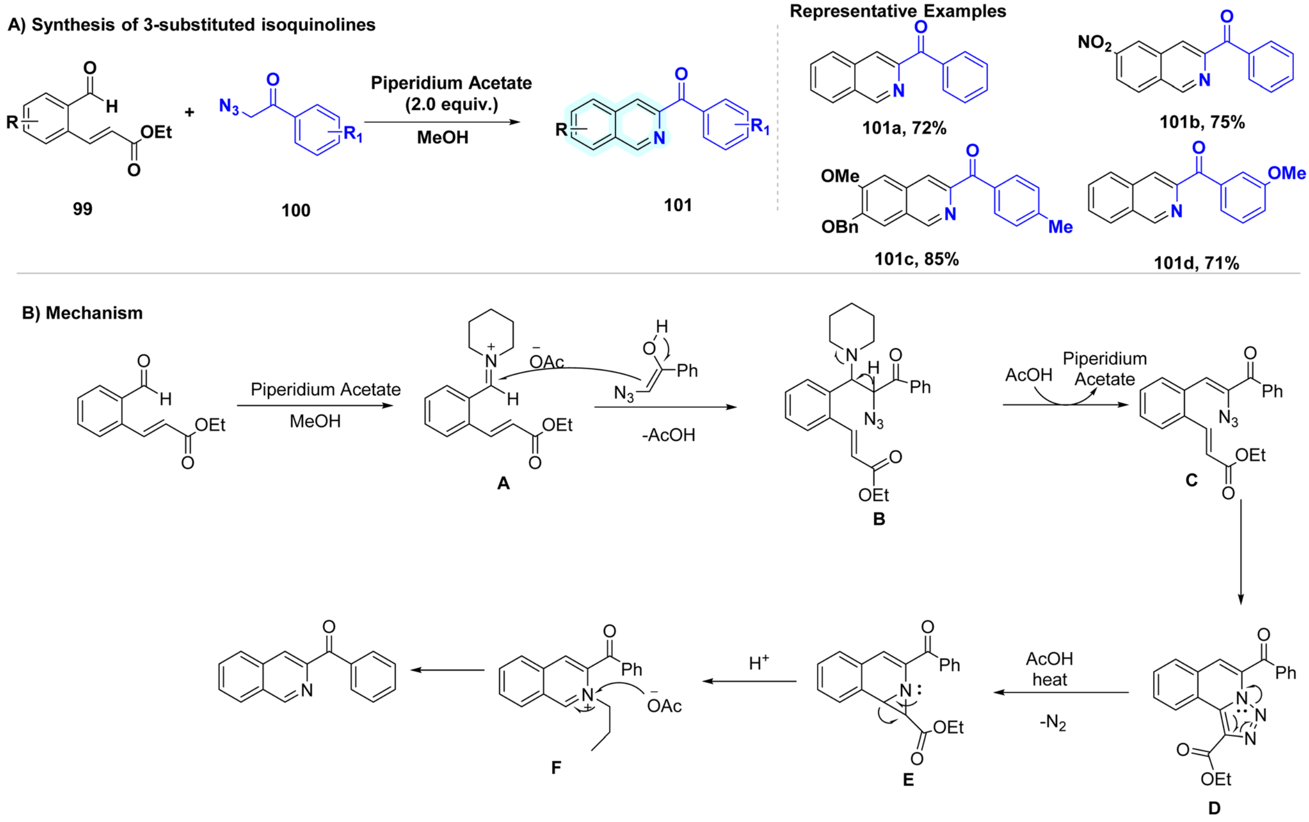
intermediates (**B**) and (**C**). The negatively charged intermediate (**C**) attacks intermediate (**B**), leading to the formation of intermediate (**D**). Finally, intramolecular cyclization of intermediate (**D**), catalyzed by KF/CP@MWCNTs, yields the final product (**90**).

A green and efficient method was developed by Rawat *et al.*[95] for synthesizing indeno-isoquinolinone derivatives (**93**) using a novel CuO@NiO nanocatalyst prepared from malachite and nickel oxalate. The catalyst was characterized using multiple techniques and used in a base/additive-free reaction between 2-iodobenzamide (**91**) and 1,3-indanedione (**92**) in ethylene glycol (Scheme 29). This method offers high yields, broad substrate scope, short reaction time, and excellent green chemistry metrics (low E factor, high reaction mass efficiency, and minimal metal leaching). The catalyst was easily recoverable and reused for six cycles with negligible loss of activity. The reaction begins with the CuO@NiO nanocomposite activating the active methylene group of 1,3-indanedione (**A**), enabling its nucleophilic attack on 2-iodobenzamide to form intermediate (**B**). This is followed by an intramolecular nucleophilic cyclization and subsequent dehydration, ultimately yielding the isoquinoline-based product (**93**).

Hamedani *et al.*[96] reported a green, one-pot synthesis of pyrido-[2,1-*a*]-isoquinolinones (**94**) and pyrido-[1,2-*a*]-quinolinones using a multicomponent reaction of phthalaldehyde (**74**), methylamine (**85**), methyl malonyl chloride (**76**), alkyl bromides (**81**), and triphenylphosphine (**78**) in water at 80 °C, catalyzed by Fe_3O_4 magnetic nanoparticles (Fe_3O_4 MNPs) (Scheme 30). The method offers high yields, short reaction times, and easy catalyst/product separation. A detailed mechanism involving intermediate formation, nucleophilic addition, and cyclization was proposed. The method aligns with green chemistry principles due to high atom economy, water as a solvent, low catalyst loading, and catalyst reusability.



Scheme 32 Synthesis of benzimidazole-fused isoquinolines by Lv *et al.*[101]



Scheme 33 Synthesis of 3-substituted isoquinolines by Prasad *et al.*[102]

2.5 Electrochemical methods

Electrochemical methods are increasingly valued in green chemistry for their ability to drive chemical reactions using electricity instead of hazardous reagents.[97] By employing electrons as clean and efficient reactants, these techniques minimize waste and avoid toxic by-products. Electrochemical synthesis often proceeds under mild conditions and can be powered by renewable energy, making it both sustainable and energy-efficient. As a result, electrochemistry is recognized as a practical and eco-friendly method for modern synthesis.[98,99]

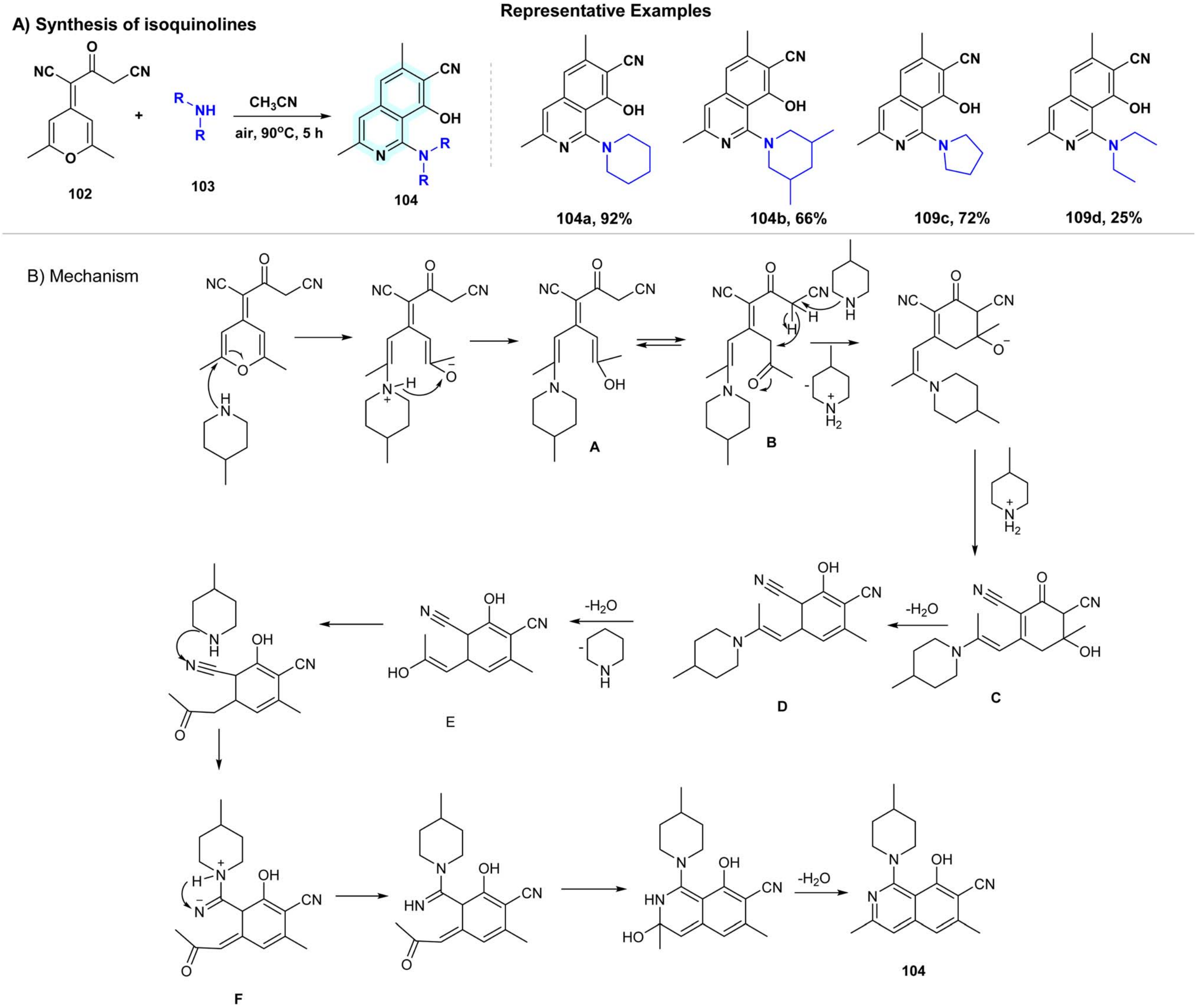
In 2025, an electrochemical method was developed by Mei *et al.*[100] for the green and efficient synthesis of bis-trifluoromethylated indole-[2,1-*a*]-isoquinolines (**96**) using sodium trifluoromethanesulfinate (CF_3SO_2Na) (**58**) as the radical source (Scheme 31). The reaction begins with the anodic oxidation of sodium trifluoromethanesulfinate, generating a trifluoromethanesulfonyl radical (**A**) that releases SO_2 to form a reactive $CF_3^{\bullet}$ radical. This radical adds to the substrate to form radical intermediate (**B**) *via* TS1 (ΔG = 10.5 kcal mol^{-1}), followed by intramolecular cyclization to give radical intermediate (**C**) through TS2 (ΔG = 19.1 kcal mol^{-1}). Subsequent anodic oxidation of (**C**) produces cationic intermediate (**D**), which undergoes deprotonation to yield intermediate (**E**). Another $CF_3^{\bullet}$ radical adds to intermediate (**E**), forming radical intermediate (**F**) *via* TS3 (ΔG = 9.1 kcal mol^{-1}), which is then oxidized to cationic intermediate (**G**). Final deprotonation of (**G**) furnishes the target product (**96**). The strategy enables the efficient construction of bioactive indole-fused tricyclic systems bearing two CF_3 groups, offering a sustainable and versatile platform for the synthesis of fluorinated heterocycles with potential pharmaceutical relevance.

Similarly, Lv *et al.* reported a novel electrochemical radical relay strategy for the direct synthesis of 5-(2,2,2-trifluoro)-ethyl dihydrobenzimidazo-[2,1-*a*]-isoquinoline derivatives (**98**) from benzimidazole-linked unactivated alkenes (**97**), utilizing an undivided electrochemical cell.[101] This approach is compatible with both the Langlois reagent (**58**) as CF_3 source and its difluoro variant, exhibiting broad functional group tolerance including activated sp^3 C–H bonds and eliminates the need for external oxidants (Scheme 32).

2.6 Non-metal-based/metal-free methods

Metal-free approaches in green chemistry offer sustainable alternatives by eliminating the need for toxic and expensive metal catalysts, thus reducing environmental impact and production costs. These methods often provide high selectivity and efficiency under mild conditions, making them attractive for eco-friendly synthesis in pharmaceuticals and fine chemicals.

Prasad *et al.*[102] reported an efficient and transition-metal-free one-pot strategy for the synthesis of 3-ketoisoquinolines (**101**) from easily accessible 2-(formylphenyl)-acrylates (**99**) and phenacyl azides (**100**). The optimized reaction employs piperidinium acetate as a base in methanol at 80 °C and

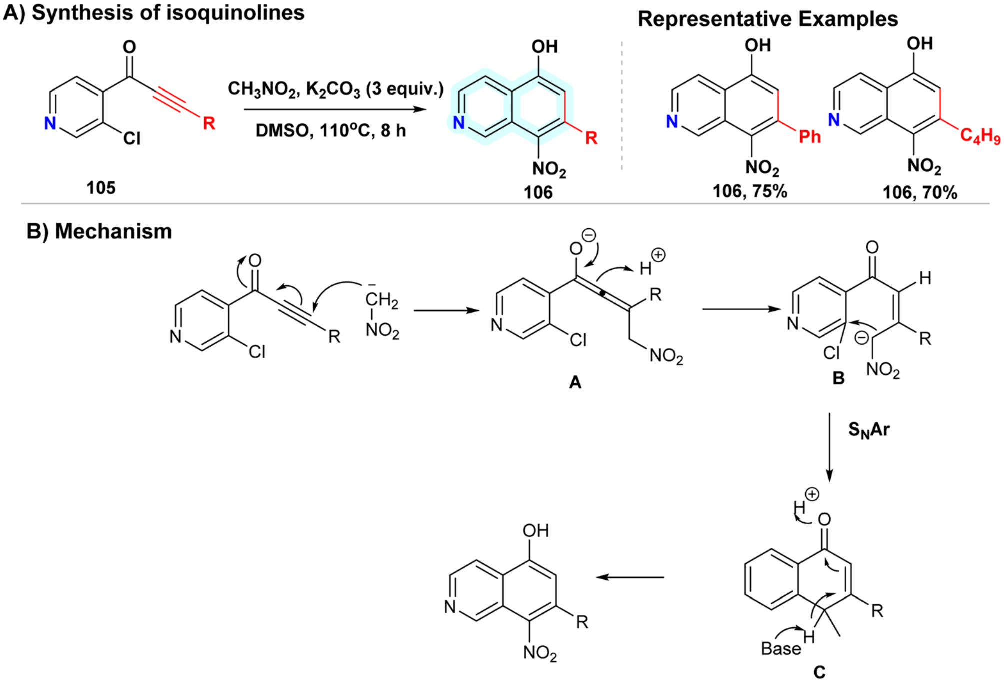


Scheme 34 Synthesis of functionalised isoquinolines by Zhang *et al.*[103]

accommodates a wide range of substrates bearing electron-donating and electron-withdrawing groups, affording the desired products in very good to excellent yields (Scheme 33). Mechanistic studies suggest that the reaction proceeds through a cascade sequence involving iminium ion formation (**A**), nucleophilic addition (**B**), 1,3-dipolar cycloaddition (**D**), thermal denitrogenation to form an aziridine intermediate (**E**), followed by ring opening (**F**) and aromatization to furnish the 3-ketoisoquinoline core. This methodology efficiently integrates Knoevenagel condensation, amination, and elimination steps in a single operation. Furthermore, the synthetic utility of the resulting heterocycles was demonstrated through their successful conversion into pharmacologically relevant derivatives, highlighting the potential of this metal-free protocol for sustainable and practical organic synthesis.

A series of multi-substituted 1-aminoisoquinoline derivatives (**104**) exhibiting dual-state fluorescence emission were synthesized by Zhang *et al.*[103] *via* a metal-free, mild, and efficient reaction between a readily available 4*H*-pyran derivative (**102**) and secondary amines (**103**) (Scheme 34). The reaction likely proceeds *via* ring-opening of compound (**102**) through nucleophilic addition of compound (**103**), forming enol (**A**), which tautomerizes to ketone (**B**). Then, compound (**103**) acts as a base, promoting intramolecular nucleophilic attack of the active methylene on the ketone group in (**B**), yielding intermediate compound (**C**). Dehydration and aromatization of the intermediate compound (**C**) lead to the phenol compound (**D**). Hydrolysis of the enamine unit in (**D**) produces compound (**E**). Subsequent nucleophilic addition forms intermediate compound (**F**), which undergoes intramolecular cyclization and elimination to yield the final product (**104**). The resulting compounds not only demonstrate good yields but also show promising fluorescence properties in both solution and solid states.

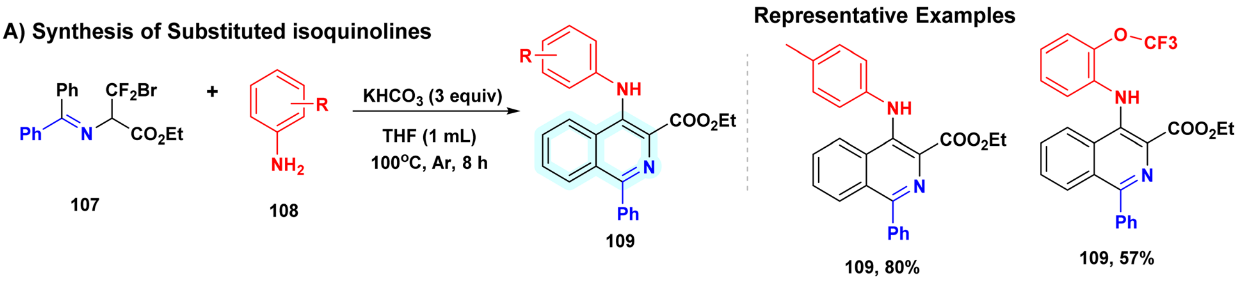
Synthesis of functionalized isoquinolines involving benzannulation of substituted pyridines has also been reported.[104,105]



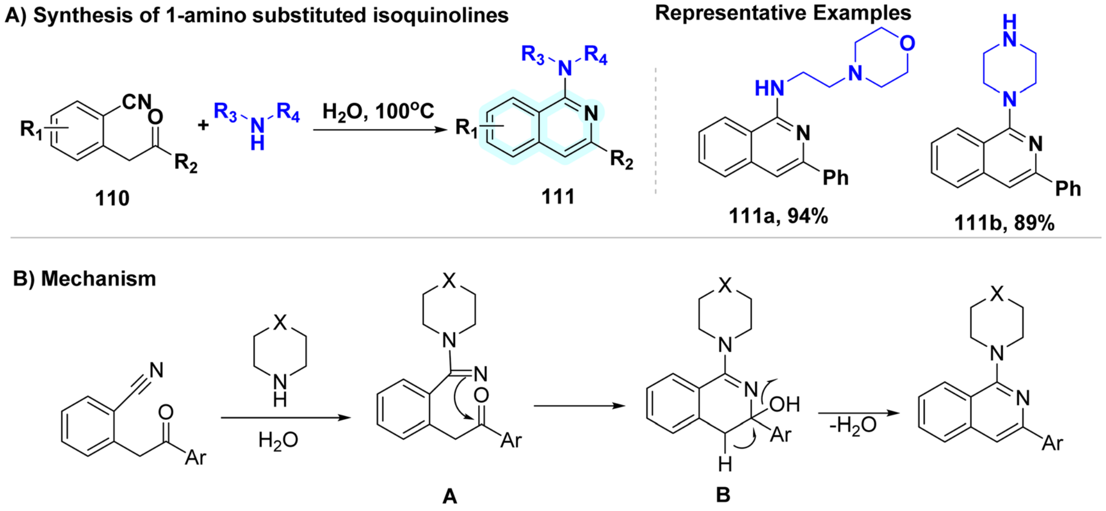
Scheme 35 Synthesis of 5-OH-8-NO_2- isoquinolines by Beesu *et al.*[106]

Although functionally these methods use expensive catalysts, executing the benzannulation through the pyridine precursor takes considerable effort. Beesu *et al.*[106] applying domino Michael- SNAr (Nucleophilic Aromatic Substitution) approach reported a novel, simple to execute, transition metal free, one pot method, that utilized the propensity of nitromethane as an iterative carbanion source, to react with *o*-halopyridinyl-ynones (**105**) for giving nitro isoquinoline derivatives (**106**) (Scheme 35). The proposed domino mechanism begins with a Michael addition of the nitromethane anion to compound (**105**), forming intermediate (**A**), which undergoes tautomerization to yield enone (**B**). The resulting carbanion from (**B**) then performs a nucleophilic aromatic substitution by displacing the aryl chloride, forming intermediate (**C**). Aromatization of (**C**) affords the final product (**106**).

In 2025, Song *et al.*[107] reported a green and efficient synthetic strategy for isoquinoline derivatives (**109**) and benzoxazole-containing amino acids based on fluorinated glycine derivatives (Scheme 36). The key intermediate, ethyl 3-bromo-2-((diphenyl methylene)-amino)-3,3-difluoropropanoate (**107**), was synthesized from glycine and shown to undergo transformation under alkaline conditions to form *gem*-difluoroalkene intermediates, which exhibit both amino acid and reactive *gem*-difluoroalkene properties. When reacted with 2-aminophenol, a benzoxazole-containing amino acid derivative was obtained through a simple, metal-free, and eco-friendly method. Interestingly, using aniline (**108**) as the nucleophile led to the unexpected formation of isoquinoline derivatives (**109**), especially when electron-donating substituents were present on the aniline ring. The yields varied based on the electronic nature of the substituents, with electron-donating groups enhancing product formation. This reaction platform is notable for its operational simplicity, reliance on easily accessible materials, and environmental compatibility, offering a novel route to fluorinated heterocyclic compounds and expanding the scope of *gem*-difluoroalkene-based amino acid chemistry.



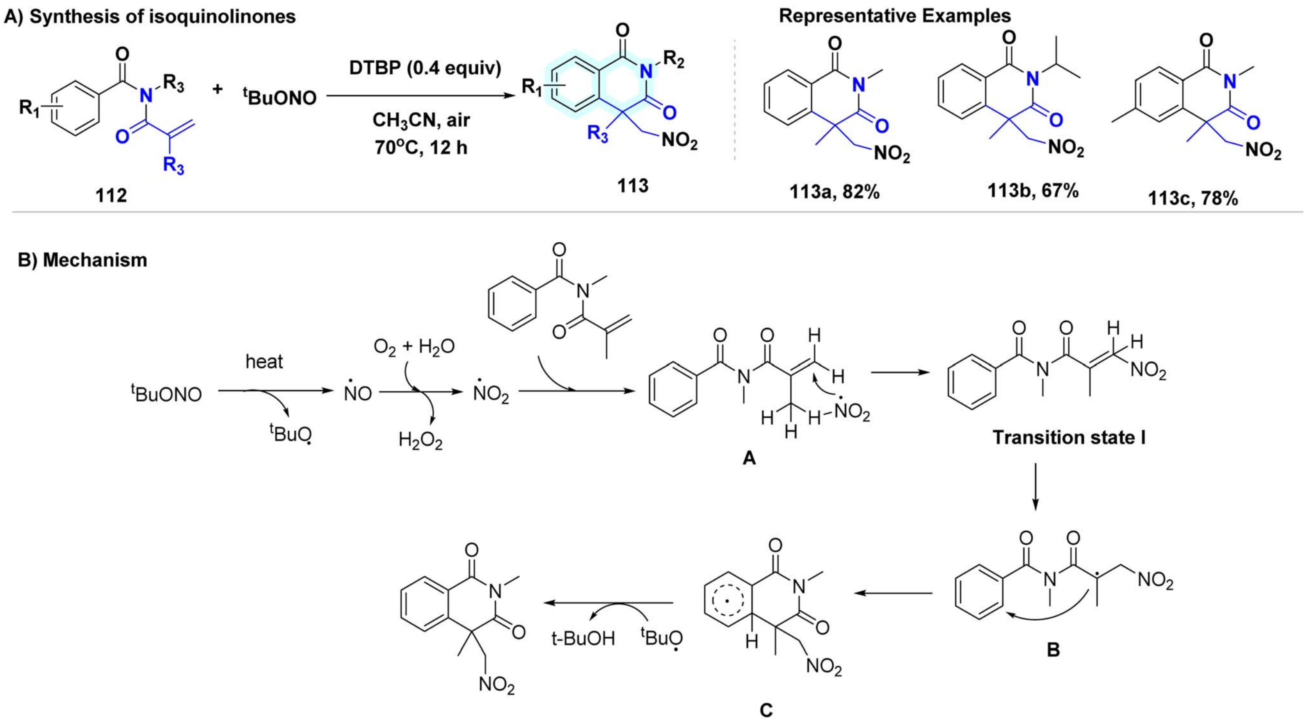
Scheme 36 Synthesis of substituted isoquinolines by Song *et al.*[107]



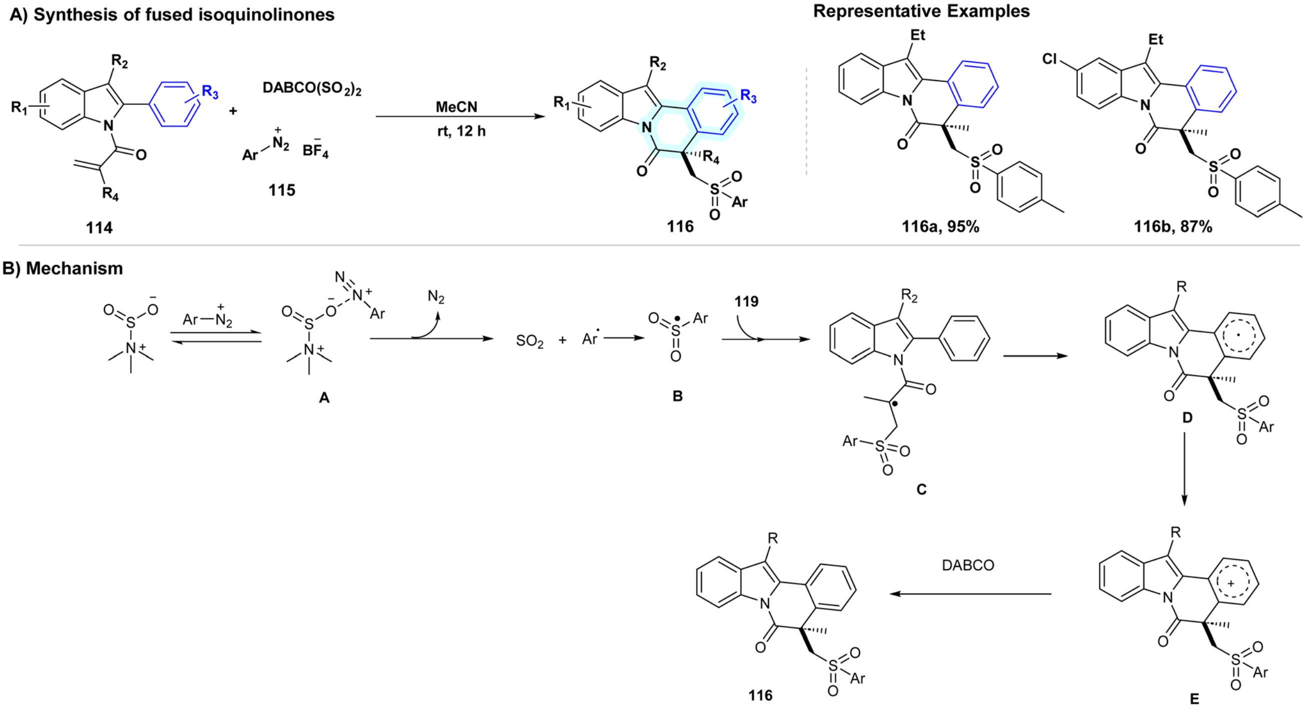
Scheme 37 Synthesis of 1-amino substituted isoquinolines by Sharma *et al.*[108]

Sharma *et al.*[108] reported a novel metal- and additive-free synthetic protocol for the efficient activation of nitriles towards nucleophilic addition and annulation under aqueous conditions, marking the first such report in this context (Scheme 37). This strategy offers a green, atom-economical, and scalable approach to synthesize a diverse range of aminated isoquinolines (**111**) with excellent regioselectivity and functional group tolerance. Utilizing 2-(2-oxo-2-aryl/alkylethyl)-benzonitriles (**110**) and a variety of primary and secondary amines, the method proceeds *via* a mechanism involving nucleophilic attack on the nitrile group, formation of an iminium intermediate (**A**), further intramolecular cyclization gives (**B**), benzylic deprotonation, and final aromatization yields the final product.

A green and efficient metal-free method for synthesizing nitro-substituted isoquinoline-1,3-diones (**113**) has been developed by Ma *et al.*[109] using *tert*-butyl nitrite (*t*BuONO) as a safe and stable nitro source (Scheme 38). This represents the first use of tBuONO in such a transformation, showcasing advantages such as safety, mild reaction conditions, and simple operation. The optimized reaction conducted with *N*-methyl-*N*-methacryloyl benzamide (**112**) in MeCN, using DTBP as an



Scheme 38 Synthesis of isoquinolinones by Ma *et al.*[109]



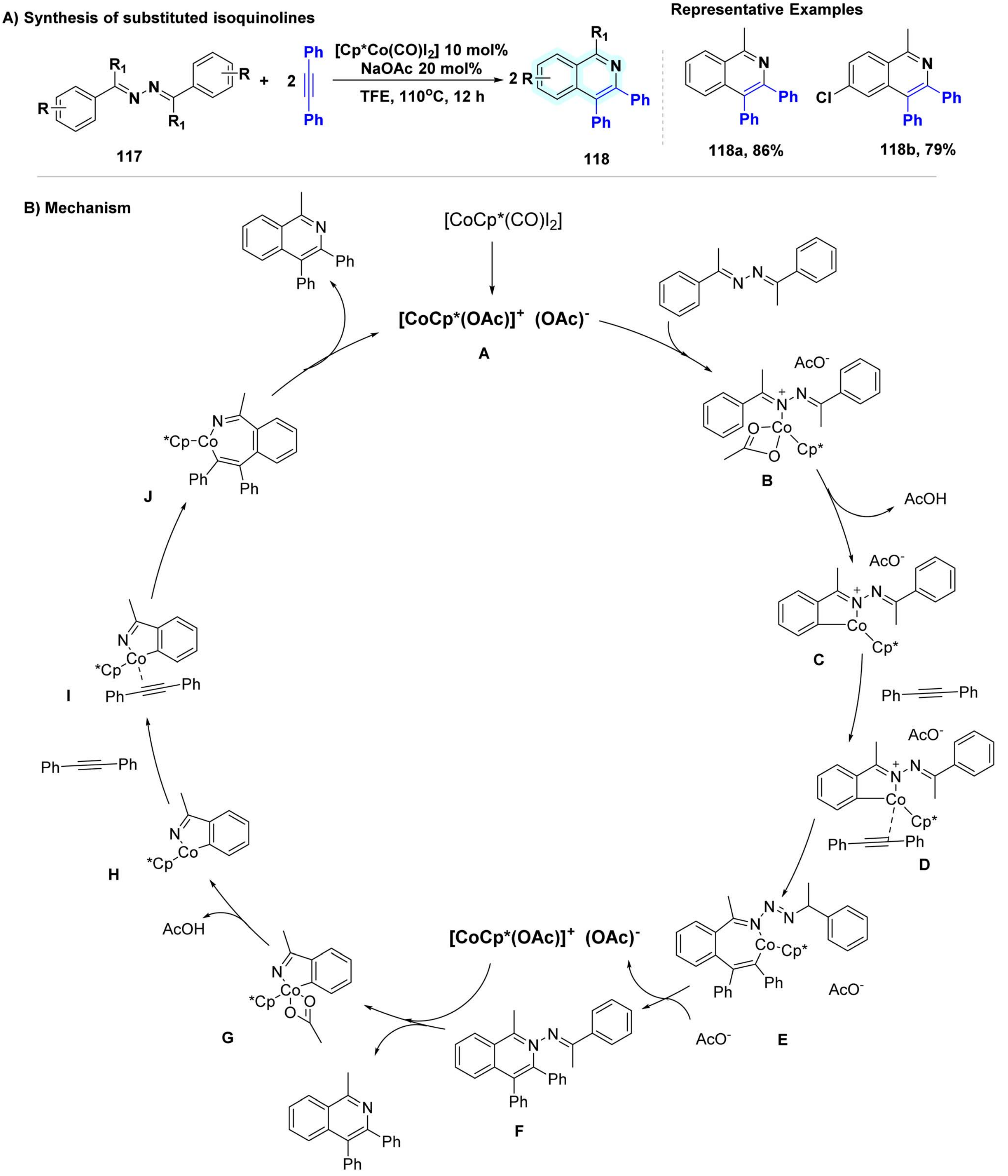
Scheme 39 Synthesis of fused isoquinolinones by Qin et al.[110]

additive under aerobic heating achieved excellent yields (up to 82%). Substrate scope analysis revealed that electron-donating groups on the aromatic ring were well tolerated, while electron-withdrawing groups hindered the reaction due to the sensitivity of the $^{\bullet}NO_2$ radical intermediate. The reaction also tolerated various *N*-substituents, though unprotected NH groups impeded cyclization. Under aerobic conditions, *t*-BuONO decomposes to form *t*-BuO$^{\bullet}$ and NO$^{\bullet}$ radicals. The NO$^{\bullet}$ is further oxidized by trace O_2 and H_2O to generate $NO_2^{\bullet}$, which was confirmed by TEMPO trapping and HRMS analysis. This $NO_2^{\bullet}$ radical adds to the vinyl group of imide (**112**), forming intermediate (**B**) *via* a low-energy transition state. Intramolecular cyclization of (**B**) then yields intermediate (**C**). Finally, *t*-BuO$^{\bullet}$ abstracts a hydrogen atom from C or promotes a redox-deprotonation sequence, delivering the final product (**113**). This method provides a sustainable and scalable route to valuable nitro-functionalized isoquinoline scaffolds, with strong potential for pharmaceutical and synthetic applications.

Qin *et al.*[110] reported an efficient metal-free, three-component reaction for the synthesis of sulfonylated indolo-[2,1-*a*]-isoquinolines (**116**) using 2-aryl-*N*-acryloyl indoles (**114**), aryldiazonium tetrafluoroborates (**115**), and DABCO$^{\bullet}$(SO$_2$)$_2$ as a sulfur dioxide surrogate under mild conditions (Scheme 39). This cascade process involves sulfur dioxide insertion, radical addition, and intramolecular cyclization, delivering a variety of sulfonylated products in moderate to excellent yields. The proposed mechanism includes the generation of aryl radicals, formation of arylsulfonyl radicals *via* SO_2 insertion (**B**), radical addition to the indole substrate gives intermediate (**C**), and cyclization forming (**D**), followed by oxidation and proton abstraction to give the final product. The method offers a sustainable and practical approach to functionalized isoquinoline derivatives, with further biological studies in progress.

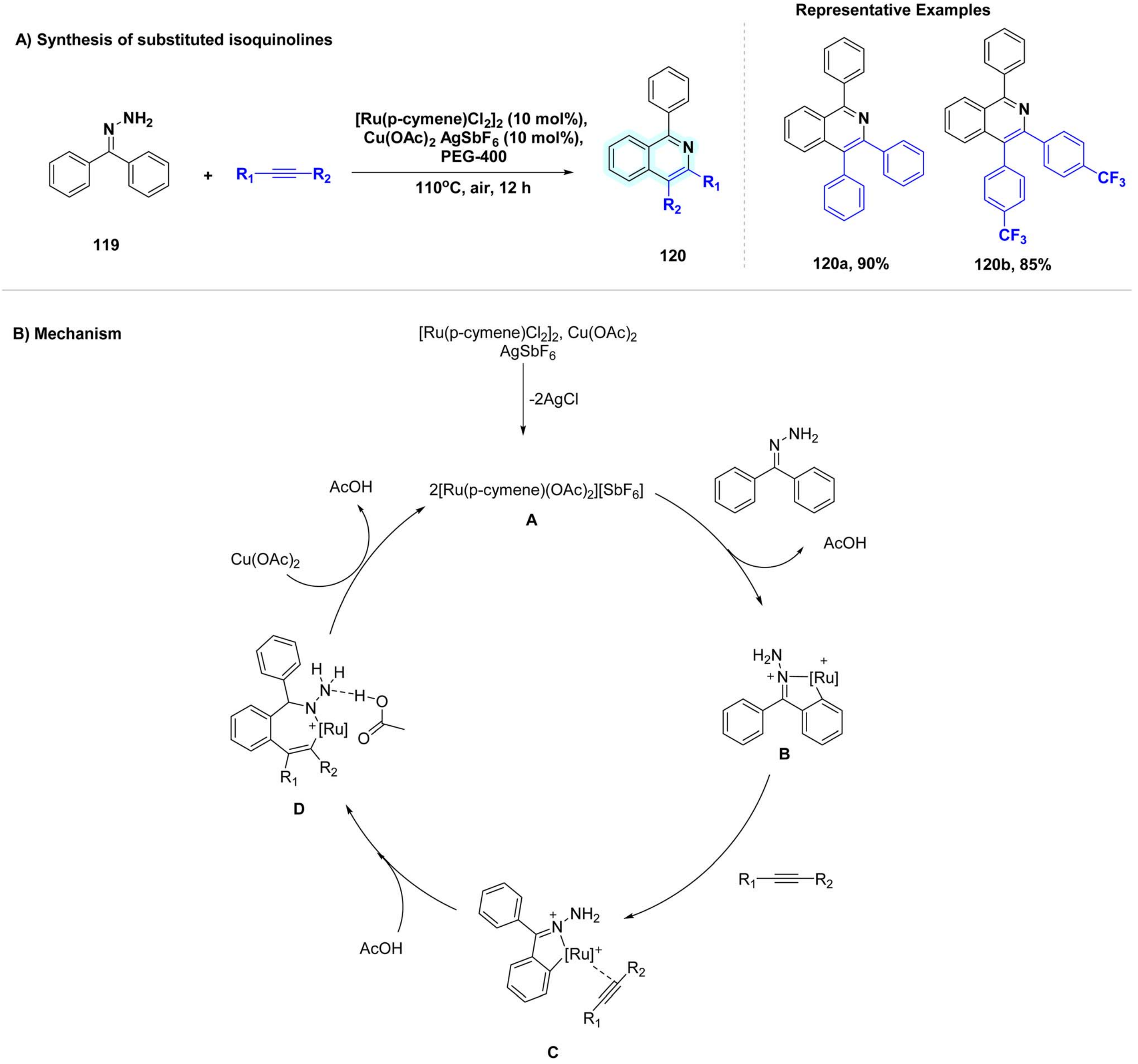
2.7 Metal-catalyzed methods

In 2019, Deshmukh *et al.*[111] reported a novel, efficient, and atom-economical method for the synthesis of isoquinolines (**118**) *via* cobalt-catalyzed annulation of azines (**117**) with alkynes through C–H and N–N bond activation (Scheme 40). The researchers have also reported similar Ru-based, microwave assisted method as previously included in Scheme 3. This protocol eliminates the need for external oxidants and silver salts, setting it apart from traditional approaches that often suffer from low atom economy and reliance on expensive rhodium catalysts or additives. By utilizing azines as both the directing and internal oxidizing groups, the method achieves full incorporation of both nitrogen atoms into the final isoquinoline products, thereby maximizing atom economy. Mechanistic studies suggest that the air-stable cobalt catalyst [Cp*Co(CO)I$_2$], complex undergoes decarbonylation in the presence of NaOAc to form the monocationic active species [CpCo(OAc)]$^+$ (**A**). Initially, the nitrogen atom of ketazine (**117**) coordinates to the Cp*Co center, followed by *ortho* C–H bond activation and cyclometallation, forming a five-membered cobalt acycle (**B**). The π-bond of alkyne then coordinates to cobalt acycle (**C**), and subsequent insertion into the Co–C bond produces a seven-membered cobalt acyclic alkenyl intermediate (**E**). Regeneration of catalyst (**A**) occurs *via* acetate assistance, yielding intermediate (**F**). Complex (**A**) re-engages with intermediate (**D**), facilitating N–N bond cleavage and forming



Scheme 40 Synthesis of substituted isoquinolines by Deshmukh *et al.*[111]

product (**118**) and complex (**G**). Next, acetate-promoted *ortho* C–H activation of arenes and cyclometallation forms a second five-membered cobalt acycle (**H**). Coordination and insertion of another molecule of alkyne into the Co–C bond of intermediate (**I**) produces a second seven-membered cobaltacycle (**J**). Finally, regeneration of catalytic species (**A**) from (**J**) completes the cycle, affording another molecule of product (**118**). The methodology shows broad substrate scope, good functional group tolerance, and scalability to gram-scale synthesis. In summary, this cobalt-catalyzed protocol offers a green, cost-effective, and highly

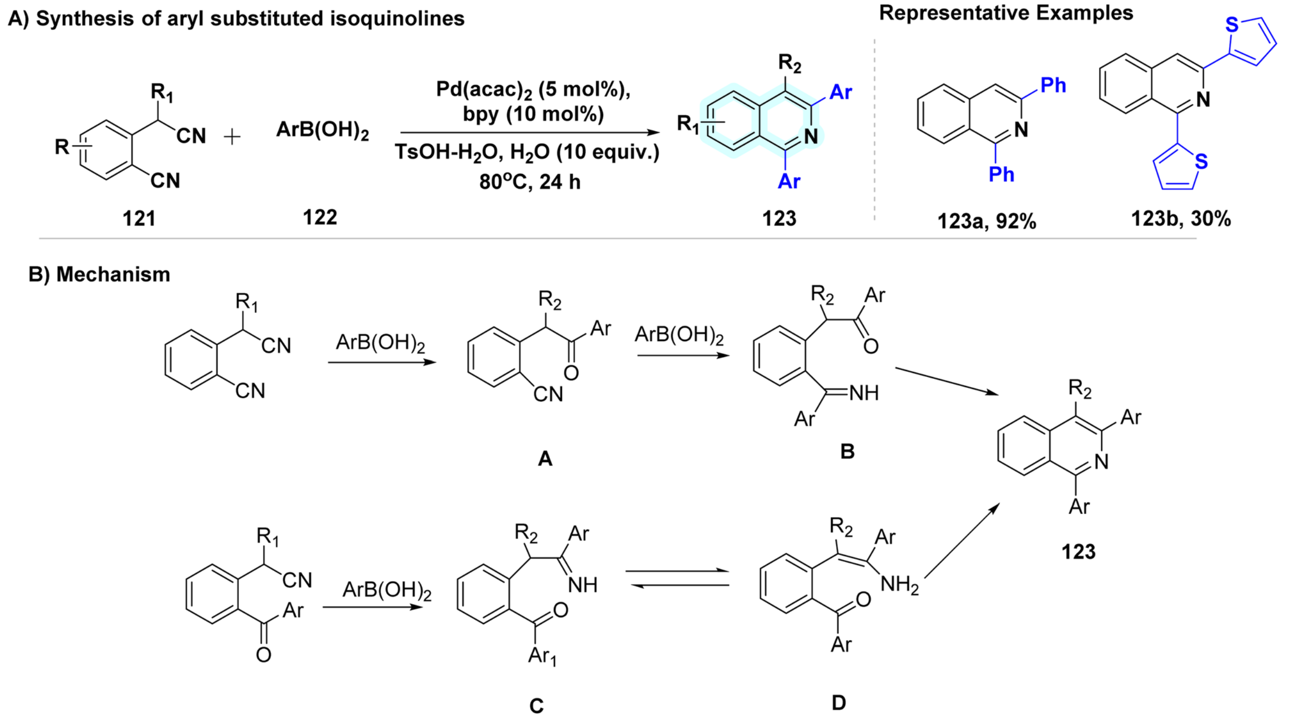


Scheme 41 Synthesis of substituted isoquinoline by Nakkalwar *et al.*[112]

atom-economic route to isoquinolines, addressing several limitations of existing metal-catalyzed annulation reactions.

Similarly, Nakkalwar *et al.*[112] reported that a green and efficient method has been developed for synthesizing 1-phenyl isoquinoline derivatives (**120**) *via* C–H/N–N functionalization of 1-(diphenylmethylene) hydrazine (**119**) and aryl-substituted alkynes (Scheme 41). The reaction employs $[Ru(p\text{-cymene})Cl_2]_2$ as a recyclable homogeneous catalyst, with $Cu(OAc)_2$ and $AgSbF_6$ as oxidant and additive, respectively, in PEG-400 a biodegradable and eco-friendly solvent. Initially, the active Ru(II) catalyst (complex **A**) is formed by the reaction of $[Ru(p\text{-cymene})Cl_2]_2$ with $AgSbF_6$ and $Cu(OAc)_2$. This complex then undergoes cyclometalation with substrate (**124**) to form intermediate (**B**). Insertion of alkyne into (**B**) produces a seven-membered Ru-cyclic intermediate (**C**), which undergoes a proton transfer (assisted by acetic acid) to form (**D**). Finally, intramolecular substitution in (**D**) forms the C–N bond and cleaves the N–N bond, yielding isoquinoline (**125**) and regenerating the active Ru catalyst. This protocol offers advantages such as a simple extraction process, high atom economy, broad substrate scope, excellent yields, and a reusable catalytic system, making it a sustainable approach to isoquinoline synthesis.

In 2017, Hu *et al.* reported a palladium-catalyzed tandem reaction of functionalized nitriles (**121**) with arylboronic acids (**122**) in water as an environmentally friendly and efficient strategy for the synthesis of aryl/alkyl substituted isoquinolines (**123**) (Scheme 42).[113] This approach, utilizing substrates such as



Scheme 42 Synthesis of aryl-substituted isoquinolines Hu *et al.*[113]

2-(cyanomethyl)-benzonitriles or 2-(2-carbonylphenyl)-acetonitriles, demonstrates broad functional group tolerance and operates under mild conditions, with water serving as the green reaction medium. The use of organoboron reagents offers several advantages over traditional organolithium or Grignard reagents, including lower toxicity, greater stability, and compatibility with various functional groups. Mechanistic investigations reveal that the reaction proceeds primarily through carbopalladation of the C(sp^3)-cyano group followed by intramolecular cyclization. Two potential mechanistic pathways have been proposed, involving sequential addition of aryl boronic acids and hydrolysis of the nitrile groups leading to imine intermediates (**B**/**C**) that undergo cyclization to furnish the isoquinoline framework (**123**). This metal-catalyzed tandem protocol not only avoids the limitations of previous methods requiring pre-functionalization or harsh reagents but also provides a versatile and scalable route to synthetically and pharmaceutically important isoquinoline derivatives. Ongoing studies aim to extend this catalytic system to the synthesis of other valuable nitrogen-containing heterocycles.

3 Summary & discussion

A comprehensive evaluation of green synthetic methodologies for isoquinoline analogs construction reveals a fundamental shift toward environmentally responsible practices that directly address the major shortcomings of conventional synthetic strategies. Table 1 summarizes the array of green methods implemented in the synthesis of isoquinoline and its related scaffolds. The breadth of sustainable strategies—encompassing microwave and ultrasound-assisted reactions, visible light photoredox catalysis, nanocatalysis, and metal-free processes—demonstrates both the versatility of green chemistry and its ability to accommodate diverse substrates and reaction types. This review provides a critical analysis of recent developments in the green synthesis of isoquinoline and its derivatives, emphasizing not only the role of energy-efficient technologies—such as microwave, ultrasound, and visible light activation—but also the degree to which individual methods fulfil the twelve principles of Green Chemistry. For each protocol described (Table 1), we systematically annotate its green attributes, considering solvent choice, catalyst recoverability, the use of renewable feedstocks, atom economy, waste reduction, and scalability. This transparent, criterion-based approach allows clear differentiation between truly sustainable methods and those that only partially embody green chemistry principles, thereby informing the design and selection of future synthetic methodologies. Our findings indicate that the most promising approaches for sustainable isoquinoline synthesis are those integrating multiple green chemistry metrics, particularly through the employment of recyclable and non-toxic nanocatalysts (such as Fe_3O_4, CuO@NiO, KF/CP NPs) in environmentally benign solvents or under solvent-free conditions. Specifically, aqueous-phase nanocatalytic protocols (Table 1 entries 25–28) provide outstanding atom economy, high product yields, facile catalyst recovery, and minimal environmental impact, fulfilling several green principles including waste prevention, efficient catalysis, and the use of safe solvents. Conversely, methods that rely solely on non-traditional activation (*e.g.*, microwaves, ultrasound, or

Table 1 Summary of green and sustainable methods for the synthesis of isoquinoline and isoquinoline scaffolds[a]

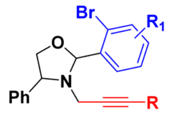
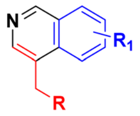
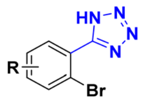
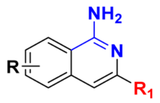
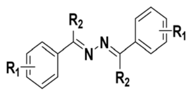
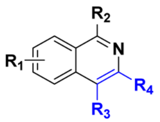
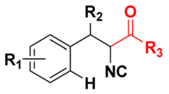
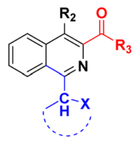
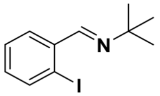
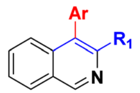
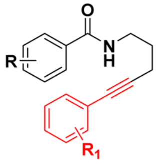
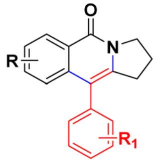
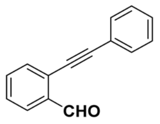
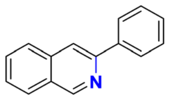
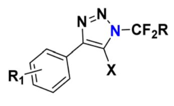
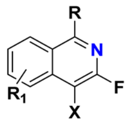
Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
1			$Pd(PPh_3)_4$	HCOONa, DMF/H_2O, 100 °C, MW	30 min	91%	Domino reaction, microwave assisted	Short time, oxidant free, scalable (6,9) Limitation: DMF is toxic	46
2			Fe_3O_4@SiO_2@Cu-MOF-74	K_3PO_4, DMF, 150 °C, N_2, MW	1 h	75%	Microwave assisted, recyclable catalyst	Reusable, broad scope (9,1) Limitation: Uses DMF, excess base	50
3			$[Ru(p\text{-cymene})Cl_2]_2$	KPF_6, PEG 400, 150 °C, MW	10 min	92%	Microwave assisted, Ru/PEG homogenous recyclable catalyst	Atom economy, green solvent, recyclable, scalable (2,5,9,1,6)	52
4			$Fe(acac)_2$	TBHP, DBU, benzene, MW, 120 °C	30 min	91%	Oxidative cascade, microwave assisted	Benign iron catalysis, broad scope (9) Limitation: Benzene is hazardous, TBHP is strong oxidant	53
5			CuI	CS_2CO_3, 2,2′-biimidazole, MW	20 min	76%	Microwave assisted, one-pot	Inexpensive catalyst, improved yields, short time (9,6)	55
6			$[(RuCl_2\ (p\text{-cymene}))_2]$	$Cu(OAc)_2$, H_2O NA_2CO_3, toulene, 100 °C	10 min	90%	Microwave assisted, domino C–C and C–N bond formation	Improved rates, mild conditions (6,5) Limitations: Use of toluene is toxic	56
7			Nafion NR50	HMDS, EtOH,MW 150 ° C	30 min	95%	Microwave acidic catalyst, recyclable	Transition-metal free, better efficiency (3,9,5) Limitation: HDMS is not green	60
8			—	KF, DCE, 165–185 °C, MW	1–5 h	87%	Microwave assisted, one-pot	Broad substrate scope, mild conditions, better yields (6, 1) Limitation: DCE is hazardous solvent, high temperature	61

Table 1 (*Contd.*)

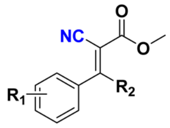
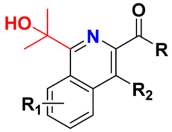
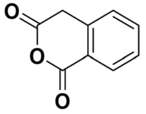
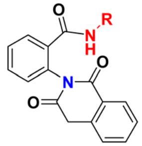
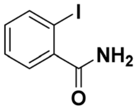
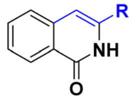
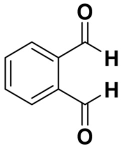
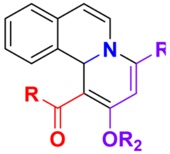
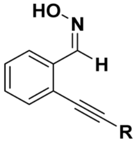
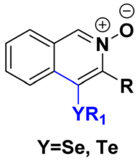
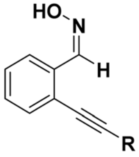
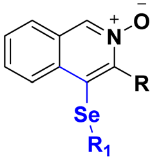
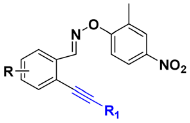
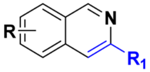
Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
9			—	DBU, TBPB, 120 °C, MW	1 h	94%	Microwave assisted, metal free oxidative cyclization	High atom economy, high efficiency, broad substrate scope (3,2,6) Limitation: TBPB is not green	62
10			—	MW, 700 W	5 min	96%	Microwave assisted	Improved yield, short time, simple (6,1)	63
11			CuI	Cs_2CO_3, DMSO, 80 °C, N_2, US	2–4 h	93%	Ultrasound assisted, one-pot, ligand-free	Mild, additive-free, efficient (1,6,9) Limitations: DMSO is better than DMF, but still not ideal	66
12			—	CH_3NH_2, PPh_3, H_2O, US, rt	1 h	89%	Ultrasound assisted, multi-component reaction	Cataylst free, short time, green media (9,5,6)	67
13			—	Oxone, EtOH, US	10–70 min	93%	Ultrasound assisted, high regio selectivity	Green oxidant, better yield, metal free (3,5,6)	68
14			—	BSA, MeOH, reflux	8 h	96%	Oxidant-free, Se-isoquinoline derivative	Green solvent, mild conditions, scalable (5,6,1,3)	71
15			Eosin Y	CHD, K_2CO_3, anh. DMF, ar, rt, green LED 535 nm	12 h	80%	Visble-light catalysis, N– N-centered radicals	Mild conditions, recyclable catalyst, metal-free (6,9,3) Limitation: DMF	75

Table 1 (*Contd.*)

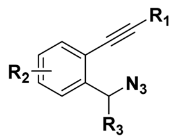
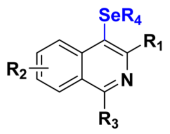
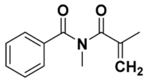
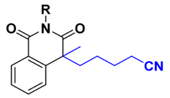
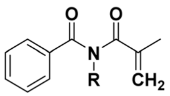
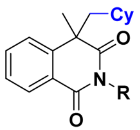
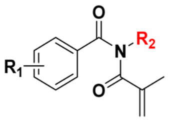
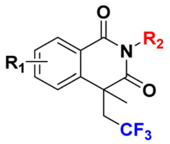
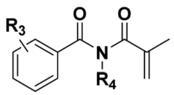
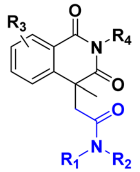
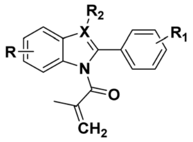
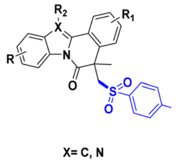
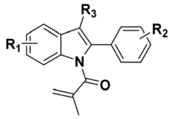
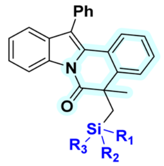
Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
16			—	White LEDs 50 W, HOAc	4 h	83%	Visible light cyclization, radical pathway	Catalyst free, mild (9,6)	76
17			DABCO	DMSO, N_2, 40 °C, 18W, blue LED light	24 h	96%	Visible-light induced, cascade reaction	Metal-free, broad scope (3,9) Limitation: DMSO, long time	77
18			LAILs	EtOH, MeCN/ DCE, 12W purple LED, rt	12 h	73%	Light mediated, metal-free, ionic lquid catalyst	Recyclable catalyst, high atom economy, scalability (9,5,6) Limitation: MeCN/ DCE less green	78
19			Eosin B	Air, 24 W white LED, DMSO, 70 ° C	24 h	75%	Light-mediated, radical cascade reaction	Metal free, additive free, cost effective, simple (3,6) Limitation: DMSO	79
20			—	$(NH_4)_2S_2O_8$, Na_2CO_3, 4CzIPN, blue LEDs 45W, DMSO, ar, rt	10 h	81%	Visible-light photoredox, radical pathway	Mild, scalable, versatile (1,2,6) Limitation: DMSO	80
21			Eosin B	$(NH_4)_2S_2O_8$, 10W blue LED, rt	15 h	84%	Visible-light photoredox, No metals/bases	Mild, broad substrate scope (6)	81
22			Photocatalyst: DCA, HAT catalyst: 3-Acetoxyquinuclidine	MeCN, 10W blue LEDs, N_2, rt	30 h	70%	Visible-light assisted, HAT, EDA complex	Hydrogen gas by-product, atom economy, metal-free (2,3,6) Limitation: MeCN, long time	84

Table 1 (*Contd.*)

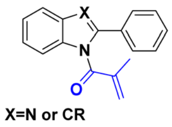
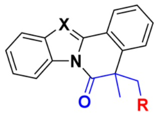
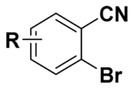
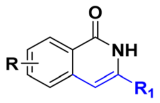
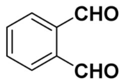
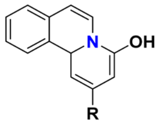
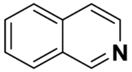
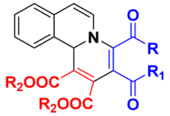
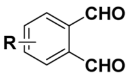
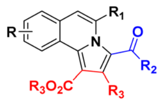
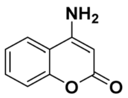
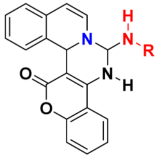
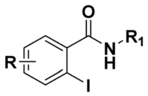
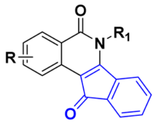
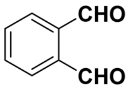
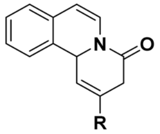
Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
23			[Ir(dtbbpy)(ppy)$_2$]PF$_6$	DMA, blue LED, N_2, rt	12 h	80%	Visible-light assisted, alkyl radical source	Mild, no oxidants/bases, metal free (6,3) Limitation: DMA	85
24			Cu2O@MHAM	Neat, 100 °C	2 h	95%	Nano-catalyst	Low E-factor, recyclable, high mass efficiency, neat (1,6,9)	90
25			Fe_3O_4-MNPs	H_2O, 80 °C	2 h	87%	Nano-catalyst	Green synthesis, magnetic recovery (5,9,1)	91
26			KF/CP NPs	H_2O, rt	3 h	95%	Nano-catalyst	Natural material, reusable (5,9,1,7)	92
27			KF/CP NPs	rt	3 h	95%	Nano-catalyst	Fast, recyclable, solvent-free (6,9,5)	93
28			KF/CP@MWCNTs NPs	H_2O, rt	4 h	95%	Nano-catalyst	Easy recovery, high yield (5,9,1)	94
29			CuO@NiO	90 °C, ethylene glycol (EG)	1 h	92%	Nano-catalyst	Short time, recyclable, low leaching, base/additive-free (6,9) Limitation: EG is only semi green	95
30			Fe_3O_4-MNPs	NaOH, 80 °C	6 h	87%	Nano-catalyst	Atom economy, low loading, reusable (2,9)	96

Table 1 (*Contd.*)

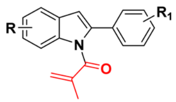
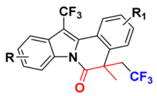
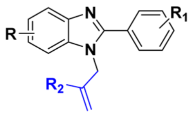
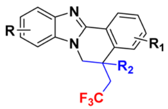
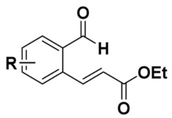
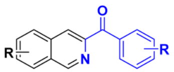
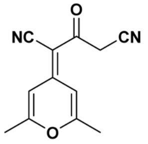
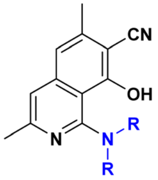
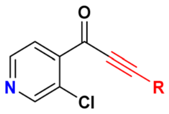
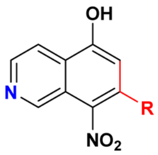
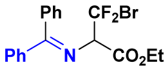
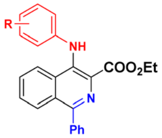
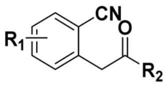
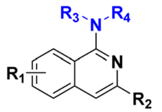
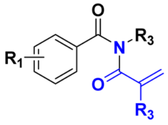
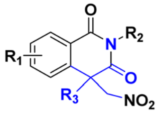
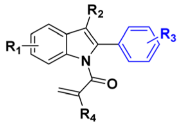
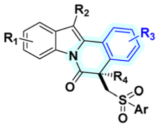
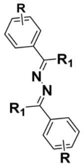
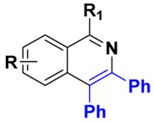
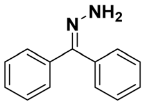
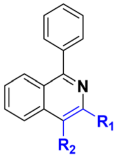
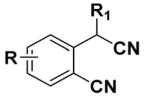
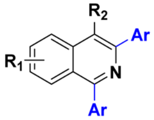
Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
31			—	Langlois reagent, C | Pt, N_2, $LiClO_4$, AcOH, MeCN/H_2O	10 h	56%	Electrochemical, anodic oxidation	Mild, fluorinated, sustainable, metal-free (6,10,1) Limitation: Pt, MeCN	100
32			—	Langlois reagent, (+) GF | Pt (−), 3 mA, CF_3SO_3H, 80 °C, MeCN/H2O	6 h	87%	Electrochemical, undivided cell	Broad scope, no metals, no oxidants (3,6) Limitation: Pt, MeCN	101
33			—	Piperidinium acetate, MeOH	3 h	85%	Metal-free, one-pot	Cascade, broad scope (8,5,1)	102
34			—	MeCN, air, 90 °C	5 h	92%	Metal-free, ring-opening/closing	Dual-state fluorescence, mild (6,3) Limitation: MeCN	103
35			—	CH_3NO_2, K_2CO_3, DMSO, 110 °C	8 h	75%	Metal-free, domino Michael SNAr (nucleophilic aromatic substitution)	One-pot, nitromethane as a carbanion (1,8) Limitation: DMSO	106
36			—	$KHCO_3$, THF, 100 °C, Ar	8 h	80%	Metal-free, *gem*-difluoroalkene intermediates	Simple, eco-friendly (6) THF is okay but not optimal	107
37			—	H_2O, 100 °C	4 h	99%	Metal-free	Regioselective, scalable, no additives (1,3,5)	108
38			—	DTBP, MeCN. Air, 70 °C	12 h	82%	Metal-free	Safe, simple, radical cascade (3,6,10) Limitation: MeCN	109

Table 1 (*Contd.*)

Sch. no.	Substrate	Product	Catalyst	Conditions	Time	Yield (upto)	Key point	Green chemistry aspects/limitations	Ref.
39			—	MeCN, rt	12 h	95%	Metal-free, three-component, sulfoxide insertion	Mild reaction conidtion (6) Limitation: MeCN	110
40			[Cp*Co(CO)I$_2$]	NaOAc, TFE, 110 °C	12 h	93%	Metal-catalyzed	Atom economy, scalable (2,1,9) Limitation: TFE	111
41			[Ru(p-cymene)-Cl$_2$]$_2$ – Cu(Oac)$_2$	AgSbF$_6$, PEG 400, 110 °C, air	12 h	90%	Metal-catalyzed	High atom economy, green solvent, recyclable (2,5,9)	112
42			Pd(acac)$_2$,bpy	TsOH-H$_2$O, H$_2$O, 80 °C	24 h	94%	Metal catalyzed, tandem reaction	Mild, broad tolerance (5) Limitation: Metal, long time	113

[a] Numbers in parentheses indicates the reference of Green Chemistry Principles: 1 (Prevention – waste minimization), 2 (Atom economy), 3 and 4 (Less hazardous synthesis/products), 5 (Safer solvents/auxiliaries), 6 (Energy efficiency), 7 (Renewable feedstocks), 8 (Reduce unnecessary derivatization), 9 (Catalysis/recyclability), 10 (Design for degradation).

photochemistry) are deemed genuinely green only when combined with non-hazardous solvents, minimal reagent excess, and catalyst reusability. Visible light photocatalytic methods employing organic dyes in benign solvents also compare favourably, especially when metals and hazardous solvents are avoided. It is important to note that traditional protocols utilizing solvents such as DMF, DMSO, MeCN, or benzene—despite sometimes offering rapid or high-yielding reactions—do not satisfy green chemistry requirements unless offset by compelling benefits such as high catalyst recyclability or superior atom economy. Furthermore, electrochemical and cascade/cyclization strategies (Table 1 entries 31–34) show promise as sustainable alternatives, provided that non-toxic solvents and electrode materials are employed. Throughout this analysis, both the strengths and weaknesses of individual methodologies (including issues of solvent selection, energy consumption, and byproduct formation) were addressed to provide a balanced perspective on the extent to which these methods fulfil the goals of green chemistry.

Several classical synthetic methods—particularly the Pomeranz-Fritsch, Bischler–Napieralski, and Pictet–Spengler reactions—remain foundational for the commercial and pharmaceutical preparation of isoquinoline derivatives due to their scalability, broad substrate tolerance, and robust yields. Notably, products from Scheme 1 can serve as key intermediates for the synthesis of lamellarin analogues; Scheme 2 highlights that cyclohexanone derivatives may be converted into 6-aminophenanthridines, which are used in *anti*-pyrin drugs; and Scheme 8 demonstrates that the F-product is a valuable precursor for synthesizing valiglurax (potential agent for the treatment of Parkinson's disease) analogues. Moreover, various fused isoquinoline derivatives have exhibited significant antioxidant, antimalarial, and antifungal activities, further underscoring their pharmaceutical relevance.

4 Conclusion

Recent advances in green synthetic chemistry have transformed the assembly of isoquinoline and its derivatives. Newer approaches—such as solvent-free reactions, microwave or ultrasound activation, photoredox and electrochemical strategies, biocatalysis, and continuous flow techniques using green media like water or ionic liquids—offer not only reduced environmental impact, but also superior yields, faster reactions, and improved selectivity. Critically evaluating the breadth, advantages, and limitations of these methods is essential for both research development and industrial application. Looking ahead, the advancement of sustainable isoquinoline and it's derivatives synthesis will depend on the strategic, case-specific integration of several green approaches rather than exclusive reliance on any single technique. Adopting such a flexible, holistic framework ensures that green chemistry concepts are effectively translated into economically sound and environmentally responsible synthesis for these important pharmaceutical targets.

Ultimately, the most effective and environmentally benign methods combine multiple green chemistry principles: employing recoverable, non-toxic catalysts; using sustainable solvents such as water, ethanol, or PEG 400 (or running solvent-free); and maximizing atom economy while minimizing waste and hazards. Methods that focus solely on alternative energy input (like microwaves or ultrasound) without concurrent improvements in reagents or solvent choices do not fully meet the criteria for greenness. Our analysis highlights nanocatalytic systems in water and ruthenium catalysis in PEG-400 as leading examples, offering optimal speed, scalability, catalyst recovery, and minimal environmental impact. Future research should focus on replacing hazardous solvents in photoredox and electrochemical protocols, as well as further minimizing waste and energy use.

Several classical synthetic methods—particularly the Pomeranz-Fritsch, Bischler–Napieralski, and Pictet–Spengler reactions—remain the foundation for commercial and pharmaceutical preparation of isoquinoline derivatives, due to their scalability, substrate tolerance, and robust yields. While modern green chemistry strategies and metal-catalyzed or photoredox methods continue to advance, their full adoption in industrial manufacture awaits further demonstration of cost-effectiveness, environmental benefit at scale, and regulatory approval.

We advocate that further method development should embrace comprehensive green chemistry metrics, including thorough reporting of environmental parameters such as E-factor, solvent recycling, and catalyst reusability. Such transparency will enable meaningful comparisons and guide the progression towards truly sustainable heterocyclic synthesis.

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Acknowledgements

We sincerely express our gratitude to BITS-Pilani, Pilani Campus for providing necessary facilities to do the work.

References

1 A. Y. Khan and G. S. Kumar, Natural isoquinoline alkaloids: binding aspects to functional proteins, serum albumins, hemoglobin, and lysozyme, *Biophys. Rev.*, 2015, **7**, 407–420.
2 C. Mahadeviah, P. K. Nagaraj, T. Y. Pasha and P. Marathi, Exploring the Pharmacological Potential of Isoquinoline Derivatives: A Comprehensive Review, *Int. J. Pharm. Investig.*, 2024, **14**, 1115–1121.
3 D. Yun, S. Y. Yoon, S. J. Park and Y. J. Park, The anticancer effect of natural plant alkaloid isoquinolines, *Int. J. Mol. Sci.*, 2021, **22**, 1653.

4 S. Hu, J. Chen, J.-X. Cao, S.-S. Zhang, S.-X. Gu and F.-E. Chen, Quinolines and isoquinolines as HIV-1 inhibitors: Chemical structures, action targets, and biological activities, *Bioorg. Chem.*, 2023, **136**, 106549.

5 Z.-X. Qing, P. Yang, Q. Tang, P. Cheng, X.-B. Liu, Y. Zheng, Y.-S. Liu and J.-G. Zeng, Isoquinoline alkaloids and their antiviral, antibacterial, and antifungal activities and structure-activity relationship, *Curr. Org. Chem.*, 2017, **21**, 1920–1934.

6 D. Dozio, F. Sacchi, A. Pinto, S. Dallavalle, F. Annunziata and S. Princiotto, Natural Antifungal Alkaloids for Crop Protection: An Overview of the Latest Synthetic Approaches, *Pharmaceuticals*, 2025, **18**, 589.

7 A. Çapcı, M. M. Lorion, H. Wang, N. Simon, M. Leidenberger, M. C. Borges Silva, D. R. M. Moreira, Y. Zhu, Y. Meng, J. Y. Chen, Y. M. Lee, O. Friedrich, B. Kappes, J. Wang, L. Ackermann and S. B. Tsogoeva, Artemisinin–(Iso) quinoline Hybrids by C− H Activation and Click Chemistry: Combating Multidrug-Resistant Malaria, *Angew Chem. Int. Ed. Engl.*, 2019, **58**, 13066–13079.

8 J. Li, Y. Wu, S. Dong, Y. Yu, Y. Wu, B. Xiang and Q. Li, Research progress on neuroprotective effects of isoquinoline alkaloids, *Molecules*, 2023, **28**, 4797.

9 I. S. Marae, M. H. Mahross, B. S. Al-Farhan, M. Abdel-Hakim, E. A. Bakhite and M. M. Sayed, Exploration of Dihydrothieno-[2,3-c]-Isoquinolines as Luminescent Materials and Corrosion Inhibitors, *ACS Omega*, 2022, **7**, 38389–38399.

10 G. Mitchell, E. D. Clarke, S. M. Ridley, D. W. Bartlett, K. J. Gillen, S. K. Vohra, D. T. Greenhow, J. C. Ormrod and P. Wardman, 1, 3, 4 (2*H*)-Isoquinolinetriones: evaluation of amino-substituted derivatives as redox mediator herbicides, *Pest Manag. Sci.*, 2000, **56**, 120–126.

11 J. K. Liu and W. T. Couldwell, Intra-arterial papaverine infusions for the treatment of cerebral vasospasm induced by aneurysmal subarachnoid hemorrhage, *Neurocrit Care*, 2005, **2**, 124–132.

12 S. Ashrafi, S. Alam, A. Sultana, A. Raj, N. U. Emon, F. T. Richi, T. Sharmin, M. Moon, M. N. Park and B. Kim, Papaverine: a miraculous alkaloid from opium and its multimedicinal application, *Molecules*, 2023, **28**, 3149.

13 M. Bleasel and G. Peterson, Emetine, ipecac, ipecac alkaloids and analogues as potential antiviral agents for coronaviruses, *Pharmaceuticals*, 2020, **13**, 51.

14 L. Celio, M. Niger, F. Ricchini and F. Agustoni, Palonesetron in the prevention of chemotherapy-induced nausea and vomiting: an evidence-based review of safety, efficacy, and place in therapy, *Core Evidence*, 2015, **10**, 75–87.

15 J. Kim, J.-H. Park, K. Shah, S. J. Mitchell, K. Cho and H.-S. Hoe, The anti-diabetic drug gliquidone modulates lipopolysaccharide-mediated microglial neuroinflammatory responses by inhibiting the NLRP3 inflammasome, *Front. Aging Neurosci.*, 2021, **13**, 754123.

16 P. Tod, A. Varga, V. Román, B. Lendvai, R. Pálkovács, B. Sperlágh and E. S. Vizi, Tetrabenazine, a vesicular monoamine transporter 2 inhibitor, inhibits vesicular storage capacity and release of monoamine transmitters in mouse brain tissue, *Br. J. Pharmacol.*, 2024, **181**, 5094–5109.

17 H. Kim, S. Park, D. Cheung, Y. Cho, J. Kim, S. Kim, H. Chae, J. Kim and I. Chung, Clinical trial: inhibitory effect of revaprazan on gastric acid secretion in healthy male subjects, *J. Gastroenterol. Hepatol.*, 2010, **25**, 1618–1625.

18 X. Shang, C. Yang, S. L. Morris-Natschke, J. Li, X. Yin, Y. Liu, X. Guo, J. Peng, M. Goto, J. Zhang and K. Lee, Biologically active isoquinoline alkaloids covering 2014–2018, *Med. Res. Rev.*, 2020, **40**, 2212–2289.

19 M. Xu, T. Wagerle, J. K. Long, G. P. Lahm, J. D. Barry and R. M. Smith, Insecticidal quinoline and isoquinoline isoxazolines, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4026–4030.

20 G. Mitchell, E. D. Clarke, S. M. Ridley, D. T. Greenhow, K. J. Gillen, S. K. Vohra and P. Wardman, 1,3,4(2*H*)-isoquinolinetrione herbicides: Novel redox mediators of photosystem I, *Pestic. Sci.*, 1995, **44**, 49–58.

21 A. Diamond and I. Desgagné-Penix, Metabolic engineering for the production of plant isoquinoline alkaloids, *Plant Biotechnol.*, 2016, **14**, 1319–1328.

22 F. Pan, M. Sohail, T. A. Taha, A. G. Al-Sehemi, S. Ullah, H. S. AlSalem, G. A. Mersal, M. M. Ibrahim, A. M. Alenad, O. A. Al-Hartomy, M. A. Amin, Z. Ajmal, A. Palamanit, A. Hayat, A. Zada and W. I. Nawawi, A facile molecular aggregation of isoquinoline based g-C3N4 for high photocatalytic performance under visible light illumination, *Mater. Res. Bull.*, 2022, **152**, 111865.

23 C. Gherasim, A. Airinei, R. Tigoianu, A. M. Craciun, R. Danac, A. Nicolescu, D. L. Isac and I. I. Mangalagiu, Synthesis and photophysical insights of new fused N-heterocyclic derivatives with isoquinoline skeleton, *J. Mol. Liq.*, 2020, **310**, 113196.

24 Ł. Balewski, F. Sączewski, M. Gdaniec, A. Kornicka, K. Cicha and A. Jalińska, Synthesis and Fluorescent Properties of Novel Isoquinoline Derivatives, *Molecules*, 2019, **24**, 4070.

25 V. B. Bojinov and I. K. Grabchev, Novel functionalized 2-(2-hydroxyphenyl)-benzotriazole – benzo[de]isoquinoline-1,3-dione fluorescent UV absorbers, *J. Photochem. Photobiol., A*, 2005, **172**, 308–315.

26 N. W. Kreofsky, M. D. Dillenburg, E. M. Villa and J. T. Fletcher, Ru(II) coordination compounds of N N bidentate chelators with 1,2,3 triazole and isoquinoline subunits: Synthesis, spectroscopy and antimicrobial properties, *Polyhedron*, 2020, **177**, 114259.

27 A. Bischler and B. Napieralski, Zur Kenntniss einer neuen Isochinolinsynthese, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 1903–1908.

28 C. Pomeranz, Über eine neue Isochinolinsynthese, *Monatsh. fur Chem.*, 1893, **14**, 116–119.

29 P. Fritsch, Synthesen in der Isocumarin- und Isochinolinreihe, *Ber. Dtsch. Chem. Ges.*, 1893, **26**, 419–422.

30 A. Pictet and A. Gams, Über eine neue Methode zur synthetischen Darstellung der Isochinolinbasen, *Ber. Dtsch. Chem. Ges.*, 1910, **43**, 2384–2391.

31 A. Pictet and T. Spengler, Über die Bildung von Isochinolin-derivaten durch Einwirkung von Methylal auf Phenyl-

äthylamin, Phenyl-alanin und Tyrosin, *Ber. Dtsch. Chem. Ges.*, 1911, **44**, 2030–2036.

32 S. S. Gupta, D. Parmar, R. Kumar, D. Chandra and U. Sharma, Construction of *N* -heterocycles through group 9 (Co, Rh, Ir) metal-catalyzed C-H activation: utilizing alkynes and olefins as coupling partners, *Catal. Rev.*, 2024, **66**, 713–819.

33 A. S. Santos, D. Raydan, N. Viduedo, M. M. B. Marques and B. Royo, Metal-Catalyzed Synthesis of *N*-Heterocycles *via* Borrowing-Hydrogen Annulation., *More Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, 2022, vol. 1, pp. 281–305.

34 D. R. Mishra, S. Chakroborty, P. Lalitha, B. S. Panda, N. P. Mishra, A. Barik, A. R. Panda, J. Malviya, K. Khatarkar and M. Mukopadhyay, Advances in Metal-Catalyzed Denitrogenative Pathways for N-Heterocycle Synthesis, *Top. Catal.*, 2024, **67**, 246–262.

35 K. C. Majumdar, P. Debnath, N. De and B. Roy, Metal-catalyzed Heterocyclization: Synthesis of five- and six-membered Nitrogen Heterocycles Through Carbon-Nitrogen Bond Forming Reactions, *Curr. Org. Chem.*, 2011, **15**, 1760–1801.

36 X. Zhang, W. Bi, Z. Cao, J. Shen and B. Chen, Recent Developments in the Metal-Catalyzed Synthesis of Nitrogenous Heterocyclic Compounds, *Molecules*, 2024, **29**, 5458.

37 R. A. Sheldon, Atom utilisation, E factors and the catalytic solution, *C. R. Acad. Sci.*, 2000, **3**, 541–551.

38 R. A. Sheldon, Fundamentals of green chemistry: efficiency in reaction design, *Chem. Soc. Rev.*, 2012, **41**, 1437–1451.

39 P. Anastas and N. Eghbali, Green Chemistry: Principles and Practice, *Chem. Soc. Rev.*, 2010, **39**, 301–312.

40 K. R. Danao, P. M. Malghade, D. K. Mahapatra, M. N. Motiwala and U. N. Mahajan, Progressive Insights into the Pharmacological Importance of Isoquinoline Derivatives in Modern Therapeutics, *Int. J. Curr. Res. Rev.*, 2021, **13**, 83–90.

41 C. Luo, M. Ampomah-Wireko, H. Wang, C. Wu, Q. Wang, H. Zhang and Y. Cao, Isoquinolines: Important Cores in Many Marketed and Clinical Drugs, *Adv. Anticancer Agents Med. Chem.*, 2021, **21**, 811–824.

42 R. Gujjarappa, N. Vodnala and C. C. Malakar, Comprehensive Strategies for the Synthesis of Isoquinolines: Progress Since 2008, *Adv. Synth. Catal.*, 2020, **362**, 4896–4990.

43 V. K. Maikhuri, M. Rawat and D. S. Rawat, Recent Advances in the 3 d-Transition-Metal-Catalyzed Synthesis of Isoquinolines and its Derivatives, *Adv. Synth. Catal.*, 2023, **365**, 4458–4494.

44 R. B. N. Baig and R. S. Varma, Alternative energy input: mechanochemical, microwave and ultrasound-assisted organic synthesis, *Chem. Soc. Rev.*, 2012, **41**, 1559–1584.

45 M. B. Gawande, S. N. Shelke, R. Zboril and R. S. Varma, Microwave-Assisted Chemistry: Synthetic Applications for Rapid Assembly of Nanomaterials and Organics, *Acc. Chem. Res.*, 2014, **47**, 1338–1348.

46 X. Xu, H. Feng and E. V. Van der Eycken, Microwave-Assisted Palladium-Catalyzed Reductive Cyclization/Ring-Opening/Aromatization Cascade of Oxazolidines to Isoquinolines, *Org. Lett.*, 2021, **23**, 6578–6582.

47 S. D. Friis, M. T. Pirnot and S. L. Buchwald, Asymmetric Hydroarylation of Vinylarenes Using a Synergistic Combination of CuH and Pd Catalysis, *J. Am. Chem. Soc.*, 2016, **138**, 8372–8375.

48 T. Wakaki, T. Togo, D. Yoshidome, Y. Kuninobu and M. Kanai, Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides *via* C–H Bond Activation, *ACS Catal.*, 2018, **8**, 3123–3128.

49 S. Bera, A. Bera and D. Banerjee, Nickel-Catalyzed Dehydrogenation of N-Heterocycles Using Molecular Oxygen, *Org. Lett.*, 2020, **22**, 6458–6463.

50 P. D. Q. Dao, S. W. Lee, H.-J. Lim and C. S. Cho, Recyclable Magnetic MOF-Catalyzed Synthesis of 1-Aminoisoquinolines and 6-Aminophenanthridines from 5-(2-Bromoaryl)-tetrazoles and 1,3-Diketones under Microwave Irradiation, *J. Org. Chem.*, 2024, **89**, 18556–18564.

51 S. W. Lee, P. D. Q. Dao, H.-J. Lim and C. S. Cho, Recyclable Magnetic Cu-MOF-74-Catalyzed C(sp$_2$)-N Coupling and Cyclization under Microwave Irradiation: Synthesis of Imidazo[1,2- c]quinazolines and Their Analogues, *ACS Omega*, 2023, **8**, 16218–16227.

52 D. S. Deshmukh, N. Gangwar and B. M. Bhanage, Rapid and Atom Economic Synthesis of Isoquinolines and Isoquinolinones by C–H/N–N Activation Using a Homogeneous Recyclable Ruthenium Catalyst in PEG Media, *Eur. J. Org. Chem.*, 2019, **2019**, 2919–2927.

53 Y. Xu, H. Chen, W. Li, Q. Xie, L. Yu and L. Shao, Microwave-Assisted Radical Insertion/Cyclization of Vinyl Isocyanides for the Synthesis of Multi-Substituted Isoquinolines, *ChemistrySelect*, 2017, **2**, 8033–8038.

54 R. Fu, X. Xu, Q. Dang and X. Bai, Synthesis of Novel Tricyclic Pyrimido[4,5- *b*][1,4]benzothiazepines *via* Bischler-Napieralski-Type Reactions, *J. Org. Chem.*, 2005, **70**, 10810–10816.

55 Z. Hu, L.-L. Ou, S.-D. Li and L. Yang, Efficient copper(I)-catalyzed, microwave-assisted, one-pot synthesis of 3,4-diaryl isoquinolines, *Res. Chem. Intermed.*, 2015, **41**, 3461–3469.

56 T. Swamy, B. Maheshwar Rao, J. S. Yadav, V. Ravinder, B. Sridhar and B. V. Subba Reddy, Microwave-assisted, ruthenium-catalyzed intramolecular amide-alkyne annulation for the rapid synthesis of fused tricyclic isoquinolinones, *RSC Adv.*, 2015, **5**, 68510–68514.

57 N. Guimond, S. I. Gorelsky and K. Fagnou, Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies, *J. Am. Chem. Soc.*, 2011, **133**, 6449–6457.

58 X. Xu, Y. Liu and C. Park, Rhodium(III)-Catalyzed Intramolecular Annulation through C-H Activation: Total Synthesis of (±)-Antofine, (±)-Septicine, (±)-Tylophorine, and Rosettacin, *Angew Chem. Int. Ed. Engl.*, 2012, **51**, 9372–9376.

59 L. Ackermann, Metal-catalyzed direct alkylations of (hetero) arenes *via* C–H bond cleavages with unactivated alkyl halides, *Chem. Commun.*, 2010, **46**, 4866.

60 T.-C. Lin, C.-K. Chan, Y.-H. Chung and C.-C. Wang, Environmentally friendly Nafion-catalyzed synthesis of 3-substituted isoquinoline by using hexamethyldisilazane as a nitrogen source under microwave irradiation, *Org. Biomol. Chem.*, 2023, **21**, 7316–7326.

61 A. Kubíčková, S. Voltrová, A. Kleman, B. Klepetářová and P. Beier, One-pot multistep synthesis of 1-fluoroalkylisoquinolines and fused fluoroalkylpyridines from *N* -fluoroalkyl-1,2,3-triazoles, *Org. Chem. Front.*, 2024, **11**, 4442–4448.

62 D. Xue, H. Chen, Y. Xu, H. Yu, L. Yu, W. Li, Q. Xie and L. Shao, Microwave-assisted synthesis of hydroxyl-containing isoquinolines by metal-free radical cyclization of vinyl isocyanides with alcohols, *Org. Biomol. Chem.*, 2017, **15**, 10044–10052.

63 M. H. Hekal and F. S. M. Abu El-Azm, Efficient MW-Assisted Synthesis of Some New Isoquinolinone Derivatives With *In Vitro* Antitumor Activity, *J. Heterocycl. Chem.*, 2017, **54**, 3056–3064.

64 P. Cintas, Ultrasound and green chemistry – Further comments, *Ultrason. Sonochem.*, 2016, **28**, 257–258.

65 M. Lupacchini, A. Mascitti, G. Giachi, L. Tonucci, N. d'Alessandro, J. Martinez and E. Colacino, Sonochemistry in non-conventional, green solvents or solvent-free reactions, *Tetrahedron*, 2017, **73**, 609–653.

66 V. R. Sangepu, D. Sharma, R. Venkateshwarlu, R. D. Bhoomireddy, K. K. Jain, R. Dandela and M. Pal, Ultrasound Assisted α-Arylation of Ketones: A Rapid Access to Isoquinolinone Derivatives, *ChemistrySelect*, 2022, **7**, e202202710.

67 S. Sharafian, Z. Hossaini, F. Rostami-Charati and M. A. Khalilzadeh, Ultrasound-promoted Green Synthesis of pyrido[2,1-a]isoquinoline Derivatives and Studies on their Antioxidant Activity, *Comb. Chem. High Throughput Screening*, 2021, **24**, 119–128.

68 D. R. Araujo, H. A. Goulart, A. M. Barcellos, R. Cargnelutti, E. J. Lenardão and G. Perin, Oxone-Promoted Synthesis of 4-(Chalcogenyl)isoquinoline- *N* -oxides from Alkynylbenzaldoximes and Diorganyl Dichalcogenides, *J. Org. Chem.*, 2021, **86**, 1721–1729.

69 G. Perin, L. K. Soares, P. S. Hellwig, M. S. Silva, J. S. S. Neto, J. A. Roehrs, T. Barcellos and E. J. Lenardão, Synthesis of 2,3-bis-organochalcogenyl-benzo-[*b*]-chalcogenophenes promoted by Oxone®, *New J. Chem.*, 2019, **43**, 6323–6331.

70 P. S. Hellwig, J. S. Guedes, A. M. Barcellos, G. Perin and E. J. Lenardão, Synthesis of 3,4-Bis(Butylselanyl) Selenophenes and 4-Alkoxyselenophenes Promoted by Oxone®, *Molecules*, 2021, **26**, 2378.

71 J. M. Anghinoni, S. S. Ferreira, J. C. Kazmierczak, G. Perin, F. Penteado and E. J. Lenardão, Synthesis of Selenium-Decorated *N* -Oxide Isoquinolines: Arylseleninic Acids in Selenocyclization Reactions, *J. Org. Chem.*, 2024, **89**, 11272–11280.

72 P. Li, J. A. Terrett and J. R. Zbieg, Visible-Light Photocatalysis as an Enabling Technology for Drug Discovery: A Paradigm Shift for Chemical Reactivity, *ACS Med. Chem. Lett.*, 2020, **11**, 2120–2130.

73 M. H. Shaw, J. Twilton and D. W. C. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.*, 2016, **81**, 6898–6926.

74 S. P. Pitre and L. E. Overman, Strategic Use of Visible-Light Photoredox Catalysis in Natural Product Synthesis, *Chem. Rev.*, 2022, **122**, 1717–1751.

75 Y. Yuan, C. Faure, D. Menigaux, M. Berthelot, P. Belmont and E. Brachet, Synthesis of Isoquinolines and Related Heterocycles under Visible-Light Conditions, *J. Org. Chem.*, 2023, **88**, 15750–15760.

76 X.-R. Gong, S.-S. Sun, M.-L. Ren, Q.-Y. Wu, Y.-Y. Chen and Y.-L. Xu, Visible-Light-Promoted Selenylation/Cyclization of *o* -Alkynyl Benzylazides/*o* -Propargyl Arylazides: Synthesis of Seleno-Substituted Isoquinolines and Quinolines, *J. Org. Chem.*, 2024, **89**, 4176–4184.

77 D.-L. Zhang, Z.-G. Le, Q. Li, Z.-B. Xie, W.-W. Yang and Z.-Q. Zhu, Visible-light-driven EDA complex-promoted cascade cyclization to construct 4-cyanoalkyl isoquinoline-1,3-diones, *Chem. Commun.*, 2024, **60**, 2958–2961.

78 T. Zhang, X. Ren, J. Li, Y. Wang, B. Wang, Z. Chen, Y. Xia, S. Wu, C. Liu and Y. Zhang, Lewis Acidic Ionic-Liquid-Catalyzed Radical-Cascade Alkylation/Cyclization of *N* -Alkyl- *N* -methacryloyl Benzamides with Alkanes *via* Visible-Light-Induced Ligand-to-Metal Charge Transfer: Access to Alkylated Isoquinoline-1,3(2 *H* ,4 *H*)-diones, *Org. Lett.*, 2024, **26**, 10259–10266.

79 S. Wang, P. Dai, Z. Yan, Y. Wang, J. Shao, Y. Wu, C. Deng and W. Zhang, Metal-free, Visible-Light-Induced Radical Trifluoromethylation/Cyclization of N-benzamides with CF_3SO_2Na to Synthesize CF_3 -Containing Isoquinoline-1,3-diones, *ChemistrySelect*, 2019, **4**, 10329–10333.

80 W. Niu, Y. Liu, E. Dai, J. Sun, Y. Dai and X. Xu, Synthesis of amide-functionalized isoquinoline derivatives by photo-induced carbamoyl radical cascade amidation/cyclization, *Org. Biomol. Chem.*, 2025, **23**, 5533–5541.

81 Y. Tang, J. Duan, B. Yang, Y. He, C. Du and X. Zhang, Visible-light-promoted organic-dye-catalyzed sulfonylation/cyclization to access indolo-[2,1- *a*]-isoquinoline derivatives, *Org. Biomol. Chem.*, 2023, **21**, 8152–8161.

82 J. Zhang, Z. Yang, J.-T. Yu and C. Pan, Three-component synthesis of arylsulfonyl-substituted indolo-[2,1- *a*]-isoquinolinones and benzimidazo-[2,1- *a*]-isoquinolin-6(5*H*)-ones by SO_2 insertion and radical cascade cyclization, *Org. Biomol. Chem.*, 2022, **20**, 3067–3071.

83 Y. Pan, X. Gong, R. Hao, S. Zeng, Z. Shen and W. Huang, The synthesis of anticancer sulfonated indolo-[2,1- *a*]-isoquinoline and benzimidazo-[2,1- *a*]-isoquinolin-6(5 *H*)-ones derivatives *via* a free radical cascade pathway, *RSC Adv.*, 2022, **12**, 9763–9772.

84 Z. Lei, F. Xue, B. Wang, S. Wang, Y. Xia, Y. Zhang, W. Jin and C. Liu, Radical cascade cyclization for the green and simple synthesis of silylated indolo-[2,1-a]-isoquinoline derivatives

via visible light-mediated Si–H bonds activation, *Chin. Chem. Lett.*, 2024, **35**, 108633.

85 C.-F. Zhu, F. Li, J.-J. Mai, X.-J. Li, X. Dong, M. Shi, M.-H. Shen and H.-D. Xu, Visible-light-promoted synthesis of alkylated Indolo-[2,1-α]-isoquinolines using 2-Mercaptothiazolinium salts as alkyl radical source, *Tetrahedron Lett.*, 2025, **154**, 155397.

86 N. Agarwal, V. S. Solanki, B. Pare, N. Singh and S. B. Jonnalagadda, Current trends in nanocatalysis for green chemistry and its applications- a mini-review, *Curr. Opin. Green Sustainable Chem.*, 2023, **41**, 100788.

87 M. zach, C. hagglund, D. chakarov and B. kasemo, Nanoscience and nanotechnology for advanced energy systems, *Curr. Opin. Solid State Mater. Sci.*, 2006, **10**, 132–143.

88 J. M. Campelo, D. Luna, R. Luque, J. M. Marinas and A. A. Romero, Sustainable Preparation of Supported Metal Nanoparticles and Their Applications in Catalysis, *ChemSusChem*, 2009, **2**, 18–45.

89 X.-J. Liang, A. Kumar, D. Shi and D. Cui, Nanostructures for medicine and pharmaceuticals, *J. Nanomater.*, 2012, **1**, 921897.

90 M. Rawat and D. S. Rawat, Cu_2O-Decorated Marigold Hollow Alumina Microsphere Nanoparticles as a Robust and Efficient Catalyst for the Synthesis of Isoquinolones, *ACS Sustain. Chem. Eng.*, 2022, **10**, 10014–10023.

91 E. Ezzatzadeh, F. Z. Hargalani and F. Shafaei, Bio-Fe_3O_4 -MNPs Promoted Green Synthesis of pyrido-[2,1- *a*]-isoquinolines and pyrido-[1,2- *a*]-quinolines: Study of Antioxidant and Antimicrobial Activity, *Polycyclic Aromat. Compd.*, 2022, **42**, 3908–3923.

92 N. F. Hamedani, M. Ghazvini, F. Sheikholeslami-Farahani and M. T. B. Jamnani, KF/Clinoptilolite Nanoparticles as a Heterogeneous Catalyst for Green Synthesis of pyrido-[2,1-a]-isoquinolines using Four-Component Reaction of Alkyl Bromides, *Comb. Chem. High Throughput Screening*, 2020, **22**, 728–739.

93 S. Soleimani Amiri, Green production and antioxidant activity study of new pyrrolo-[2,1-a]-isoquinolines, *J. Heterocycl. Chem.*, 2020, **57**, 4057–4069.

94 S. S. Amiri, M. Ghazvini, S. Khandan and S. Afrashteh, KF/Clinoptilolite@MWCNTs Nanocomposites Promoted a Novel Four-Component Reaction of Isocyanides for the Green Synthesis of Pyrimidoisoquinolines in Water, *Polycyclic Aromat. Compd.*, 2022, **42**, 4736–4751.

95 M. Rawat and D. S. Rawat, CuO@NiO Nanocomposite Catalyzed Synthesis of Biologically Active Indenoisoquinoline Derivatives, *ACS Sustain. Chem. Eng.*, 2020, **8**, 13701–13712.

96 N. Faal Hamedani, M. Ghazvini, L. Azad and A. Noushin, Green synthesis of pyrido-[2,1- *a*]-isoquinolines and pyrido-[1,2- *a*]-quinolines using Fe_3O_4-MNPs as efficient nanocatalyst: Study of antioxidant activity, *J. Heterocycl. Chem.*, 2020, **57**, 337–345.

97 S. Z. Hashmi, D. Bareth, J. Dwivedi, D. Kishore and P. A. Alvi, Green advancements towards the electrochemical synthesis of heterocycles, *RSC Adv.*, 2024, **14**, 18192–18246.

98 K. T. Chen, Electrochemical Synthesis: Empowering Green Chemistry and Sustainable Future, Insights Anal, *Electrochem*, 2023, **9**, 17.

99 S. Garg, H. S. Sohal, D. S. Malhi, M. Kaur, K. Singh, A. Sharma, V. Mutreja, D. Thakur and L. Kaur, Electrochemical Method: A Green Approach for the Synthesis of Organic Compounds, *Curr. Org. Chem.*, 2022, **26**, 899–919.

100 H. Mei, Y. Zhang, J. Liu, J. Escorihuela, L. Kiss and J. Han, Electrochemical Dual Trifluoromethylation/Cyclization of 2-Aryl-N-acryloyl Indoles Enabling Assembly of Indole-[2, 1-a]-isoquinolines, *Adv. Synth. Catal.*, 2025, **367**, e202401225.

101 Y. Lv, J.-Y. Dai, Z.-X. Zhao, J. Liu, Z.-W. Li, C.-H. Lu, Y.-F. Zhang, W.-D. Liu and J.-S. Li, Electrochemical synthesis of 5-trifluoroethyl dihydrobenzimidazo-[2,1-a]-isoquinolines from pendent unactivated alkenes *via* radical relay, *Tetrahedron Lett.*, 2023, **119**, 154410.

102 B. Prasad, M. Phanindrudu, D. K. Tiwari and A. Kamal, Transition-Metal-Free One-Pot Tandem Synthesis of 3-Ketoisoquinolines from Aldehydes and Phenacyl Azides, *J. Org. Chem.*, 2019, **84**, 12334–12343.

103 X. Zhang, Y. Zhou, M. Wang, Y. Chen, Y. Zhou, W. Gao, M. Liu, X. Huang and H. Wu, Metal-Free Facile Synthesis of Multisubstituted 1-Aminoisoquinoline Derivatives with Dual-State Emissions, *Chem.–Asian J.*, 2020, **15**, 1692–1700.

104 T. Takahashi, Y. Li, P. Stepnicka, M. Kitamura, Y. Liu, K. Nakajima and M. Kotora, Coupling Reaction of Zirconacyclopentadienes with Dihalonaphthalenes and Dihalopyridines: A New Procedure for the Preparation of Substituted Anthracenes, Quinolines, and Isoquinolines, *J. Am. Chem. Soc.*, 2002, **124**, 576–582.

105 A. E. Morrison, J. J. Hrudka and G. B. Dudley, Thermal Cycloisomerization of Putative Allenylpyridines for the Synthesis of Isoquinoline Derivatives, *Org. Lett.*, 2016, **18**, 4104–4107.

106 M. Beesu and G. Mehta, Synthesis of Quinolines and Isoquinolines *via* Site-Selective, Domino Benzannulation of 2- and 3-Chloropyridyl Ynones with Nitromethane, *J. Org. Chem.*, 2019, **84**, 8731–8742.

107 Y. Song, Z. Liu, C. Liu, J. Zhang and Y. Zhao, Construction of Benzoxazole and Isoquinoline Compounds *via* Base-Mediated Cyclization of Amino Acid Derivatives, *Org. Lett.*, 2025, **27**, 3060–3065.

108 H. Sharma, M. Kumar, A. Sethi, Poonam and B. Rathi, Metal-free construction of aminated isoquinoline frameworks from 2-(2-oxo-2-arylethyl) benzonitrile in an aqueous medium, *Green Chem.*, 2023, **25**, 167–171.

109 H. Ma, T. Yu, S. You, M. Zhang and C. Deng, Synthesis of nitro-containing isoquinoline-1,3-diones with tert-butyl nitrite, *J. Heterocycl. Chem.*, 2024, **61**, 331–335.

110 B. Qin, S. Huang, J.-Q. Chen, W. Xiao and J. Wu, Metal-free synthesis of sulfonylated indolo-[2,1- *a*]-isoquinolines from sulfur dioxide, *Org. Chem. Front.*, 2022, **9**, 3521–3526.

111 D. S. Deshmukh, P. A. Yadav and B. M. Bhanage, Cp* Co (III)-catalyzed annulation of azines by C–H/N–N bond activation for the synthesis of isoquinolines, *Org. Biomol. Chem.*, 2019, **17**, 3489–3496.

112 S. L. Nakkalwar, H. M. Kasralikar, N. S. Kaminwar, S. B. Patwari and V. B. Jadhav, A green synthesis of isoquinolines using Ru(II)/peg-400 as homogeneous recyclable catalyst *via* C-H/N-N bond activation, *Indian J. Chem., Sect. B:Org. Chem. Incl. Med. Chem.*, 2020, **59**, 842–849.

113 K. Hu, L. Qi, S. Yu, T. Cheng, X. Wang, Z. Li, Y. Xia, J. Chen and H. Wu, Efficient synthesis of isoquinolines in water by a Pd-catalyzed tandem reaction of functionalized alkylnitriles with arylboronic acids, *Green Chem.*, 2017, **19**, 1740–1750.