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Recent advancement in the synthesis of quinoline derivatives *via* multicomponent reactions†

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The synthesis of quinoline derivatives through multicomponent reactions (MCRs) has emerged as an efficient and versatile strategy in organic synthesis. MCRs offer the advantage of constructing complex molecular architectures in a single step, utilising multiple starting materials in a convergent manner. This review provides an overview of recent advancements in the field of quinoline synthesis *via* MCRs. Various MCRs, such as the Povarov reaction, the Gewald reaction, and the Ugi reaction have been successfully employed for the synthesis of diverse quinoline scaffolds. These methodologies not only showcase high atom economy but also allow the incorporation of structural diversity into the final products. The versatility of MCRs enables the introduction of functional groups and substitution patterns tailored to specific applications. This review highlights the significance of quinoline derivatives in medicinal chemistry, materials science, and other interdisciplinary areas. The continuous innovation and development of novel MCR-based approaches for quinoline synthesis hold great promise for the rapid and efficient generation of valuable compounds with a wide range of biological and physicochemical properties.

1. Introduction

The realm of organic chemistry never ceases to captivate scientists and researchers with its boundless complexity and diversity. Among its vast collection of chemical compounds, quinolines have long been recognized for their intriguing structural motifs and versatile applications.[1–4] They are some of the most important naturally occurring compounds and have various applications in pharmaceutical and other industries. It is also a widely studied molecule in synthetic organic chemistry, and there are numerous papers in the literature reporting a wide variety of synthesis procedures for the creation of this scaffold for its importance in biological and medicinal chemistry.

Quinoline was first obtained from coal tar by the German scientist Runge[5] in 1834, and later it was extracted from cinchonine by French chemist Gerhardt[6] in 1842. It took some years before pure quinoline was available for synthesis and other studies. The main sources of quinoline include petroleum, coal processing, wood preservation and shale oil. However, numerous synthetic processes have been developed for various quinoline derivatives, such as transition metal catalysts, Brønsted acid/base catalysts and even catalyst-free synthesis. Some of the well-known synthetic techniques are Friedländer, Pfitzinger, Povarov, Skraup, Doebner and Conrad–Limpach–Knorr synthesis. The nitrogen source will depend on the specific reaction conditions and the desired quinoline derivative. The most commonly used starting material is aniline; however, ammonia, hydrazine, nitriles, and nitroso compounds are also utilized in numerous syntheses. Nevertheless, the majority of these approaches entail severe reaction conditions, elevated temperatures, acid catalysts, harmful solvents and limited selectivity in terms of the desired reaction outcome. Therefore, more recently, several alterations to these reactions involving photocatalytic, electrocatalytic, microwave and ultrasound-mediated synthesis using organo and transition metal-catalysed synthesis have been reported.

Basic types of quinoline derivatives have various applications in the production of dyes, paints, insecticides and antibacterial compounds. However, the quinoline structure is also a crucial building block for many natural products, serving as a fundamental framework in medicinal chemistry.[7,8] A quinoline ring is typically found in numerous synthetic antimalarial, antibacterial, antifungal and anti-inflammatory drugs, and natural substances with potent properties in inhibiting the growth of parasites[9–13] such as quinine, chloroquine and amodiaquine have been employed in the treatment of malaria. Certain quinoline derivatives have demonstrated antibacterial properties, particularly against *Mycobacterium tuberculosis*, the causative agent of tuberculosis. Quinolines have also shown antifungal activity against various fungal pathogens.[14] Styrylquinoline derivatives for instance, have been identified as effective agents against *Candida albicans*, a common fungal pathogen responsible for various infections.

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† Celebrating the 100th birthday of Prof Sukh Dev.

Not only this, quinoline derivatives have typically been explored for their potential as anticancer agents as well.[15] Compounds like lenvatinib act as kinase inhibitors, interfering with cell signaling pathways involved in cancer growth and progression (Fig. 1).[16,17] Many of these compounds showed PDE4 inhibitory properties *in vitro*. Quinoline-based drugs, like pitavastatin, are employed to reduce cholesterol levels, aiding in the management of cardiovascular diseases.[18] Quinoline derivatives have been investigated for their potential in treating neurodegenerative disorders like Alzheimer's and Parkinson's diseases due to their ability to interact with certain neurotransmitter systems and receptors.[19] Some quinoline derivatives possess anti-inflammatory properties and modulate immune responses, suggesting potential applications in autoimmune and inflammatory conditions. The diverse pharmacological activities of quinoline compounds make them valuable candidates for drug development across a wide spectrum of therapeutic areas, from infectious diseases to cancer and neurological disorders.

Multicomponent reactions (MCRs) are synthetic processes that yield a single product from three or more reactants in a single reaction, achieved through a series of simple reactions. They are vital in organic chemistry for their efficiency, enabling the synthesis of complex molecules in one step from multiple starting materials. They enhance diversity, atom economy, and synthetic versatility, accelerating drug discovery and materials science while uncovering new reactivity. MCRs facilitate the rapid generation of compound libraries for screening purposes in drug discovery. This acceleration of lead optimization can significantly shorten the time required to identify potential drug candidates. Beyond drug discovery, MCRs have applications in materials science for the synthesis of polymers, dendrimers, and other complex materials with tailored properties. They differ from traditional sequential two-component synthesis methods by utilising as many as seven initial components and yielding higher quantities of products compared with classical chemical processes. In an optimal scenario, all reaction equilibria within the intricate MCR mixture are reversible, with the final step of product formation being irreversible. This irreversible step acts as the driving force, pushing all intermediates towards the formation of a single product.[20] The simplicity and adaptability of the experimental methods that provide access to a wide range of goods through the myriad reagent combination options are the driving forces behind MCRs' success. Multicomponent reactions are a recently developed strategy for eco-friendly synthesis that enables the rapid production of intricate products from basic reagents, without requiring additional purification steps. An excellent illustration of this is the synthesis of 2,3-disubstituted quinolines using aniline, aldehydes, and acetylene derivatives, which can be catalysed using organic or metal catalysts.

In view of potential applications, there are several established methods available for creating the quinoline ring, which can be easily adapted to produce a variety of quinolines with different substitutions. MCR is one of the most promising

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Dr Arnab Mandal was born on 19th February 1992 in West Bengal, India. After graduating from the University of Burdwan, he obtained his M.Sc. (Chemistry) degree in 2015 from the Indian Institute of Technology, Kanpur. He completed his PhD thesis work in 2021 under the supervision of Professor Debasis Das at the University of Calcutta. He has been pursuing his postdoctoral research work with Professor Abu Taleb Khan at the Indian Institute of Technology, Guwahati, since December 2022. His current research interests include multicomponent reactions, synthesis of heterocycles, reaction mechanism and newer synthetic methodologies in organic chemistry.

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Professor Abu Taleb Khan was born on 20th November, 1961, in West Bengal. He obtained his PhD degree (1990) in Synthetic Organic Chemistry from Kalyani University under the supervision of Professor K. C. Majumdar. He carried out his first postdoctoral research work for a period of two and half years with Professor G. Mehta at the School of Chemistry at Hyderabad Central University. He was awarded the prestigious AvH fellowship in 1992 to pursue his second postdoctoral research post with Professor Richard R. Schmidt, University of Konstanz, Germany. After working as a Scientist Fellow at RRL-Jorhat, he joined as an Assistant Professor at IIT Guwahati on 23rd December, 1996. He was promoted to full Professor on 20th March 2004 and has been serving as HAG Professor since April 2010. He also served as the Vice-Chancellor of Aliah University, Kolkata from October 2013 to September 2017. His current research interests are green chemistry, new synthetic methodology, new brominating reagents, synthesis of heterocycles using MCRs, carbohydrate chemistry, reaction mechanism and total synthesis of natural products.

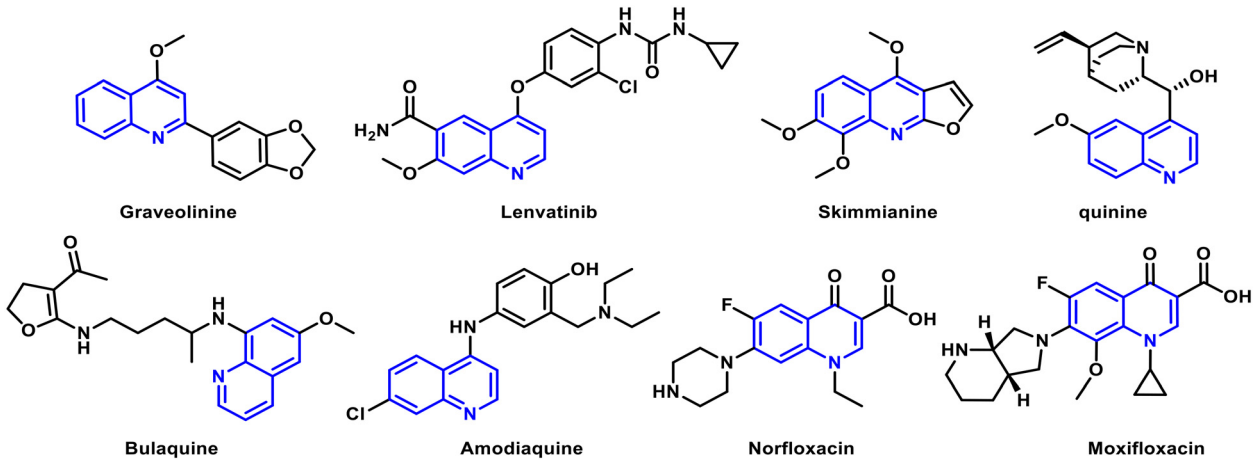


Fig. 1 Some quinoline-based natural products, antimalarial and anti-bacterial drugs.

techniques for synthesising the complicated framework of quinoline in a single step. So far, a huge number of review articles have covered the synthesis of quinoline. However, we focus specifically on the recent multicomponent approach towards the synthesis of quinoline analogues, which has not been covered in the previous reports. This review includes the literature from 2012 to date and focusses on the synthesis of quinolines.

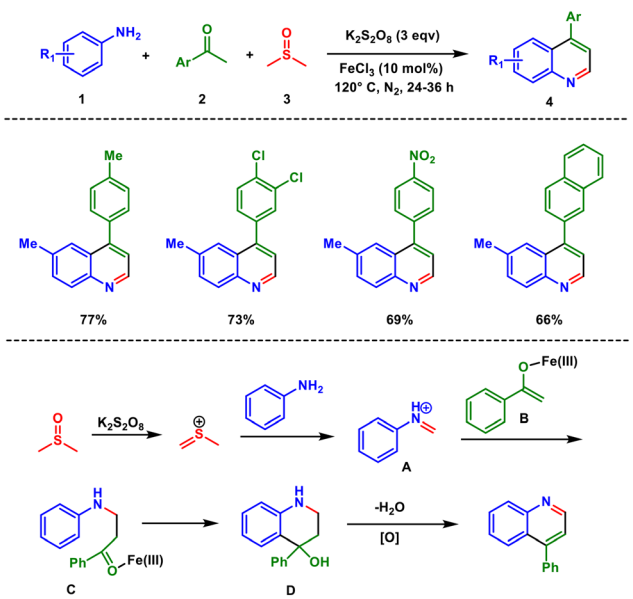
2. Metal-catalysed reactions

Over the last few decades, transition-metal-catalysed methods have played a dominant role in the synthesis of complex quinoline-based heterocycles, particularly in organic and medicinal chemistry. This is because transition metals and their complexes possess excellent catalytic abilities, allowing for the generation of lead drug candidates. This has provided an advantage over traditional synthetic methods, as it allows for the construction of complex compound libraries from readily available starting materials. Furthermore, these metals and their complexes can serve as a cost-effective and less hazardous alternative to other catalysts for the preparation of therapeutic molecules based on quinoline from easily accessible materials.

2.1. Iron(III) catalyst

Iron catalysis plays a pivotal role in modern chemical synthesis, offering a sustainable and cost-effective alternative to more expensive and less abundant transition metals. Iron catalysis has revolutionized the synthesis of quinoline, a vital structural motif in pharmaceuticals and materials. This field has gained significant attention due to iron's ability to facilitate a wide range of reactions, ranging from cross-coupling reactions to asymmetric transformations and even more complex processes like cycloisomerizations and C–H functionalizations.[21,22] Iron-catalysed reactions have profound implications for green chemistry as iron is abundant, inexpensive, and non-toxic compared with other transition metals like palladium or rhodium. As a result, these catalytic processes contribute to minimizing the environmental impact and cost of chemical synthesis, aligning with the principles of sustainability.

In 2017, Singh and coworkers reported a $FeCl_3$-catalysed oxidative annulation reaction toward the synthesis of 4-aryl quinoline involving anilines **1**, aryl ketone **2** and dimethyl sulfoxide (DMSO) **3** promoted by $K_2S_2O_8$ (Scheme 1).[23] The reaction readily accommodated a wide range of substituents, both electron-donating and electron-withdrawing, as well as halides. These substituents were easily converted into their corresponding quinolines with consistently high yields. Here, DMSO serves as a methine source that reacts with $K_2S_2O_8$ in



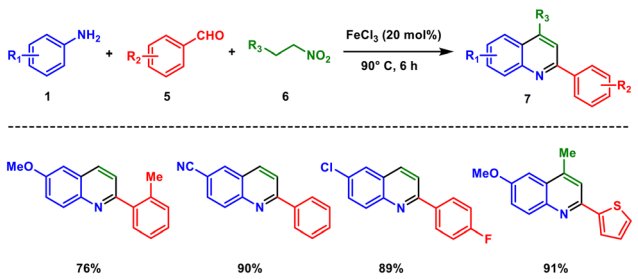
Scheme 1 $FeCl_3$-catalysed reaction of anilines and aryl amine involving DMSO.

the presence of aniline to produce the intermediate **A**. This iminium intermediate reacts with enolate **B** to generate C, which undergoes cyclization by C–N bond formation. Dehydration followed by oxidation affords the desired quinoline **4**.

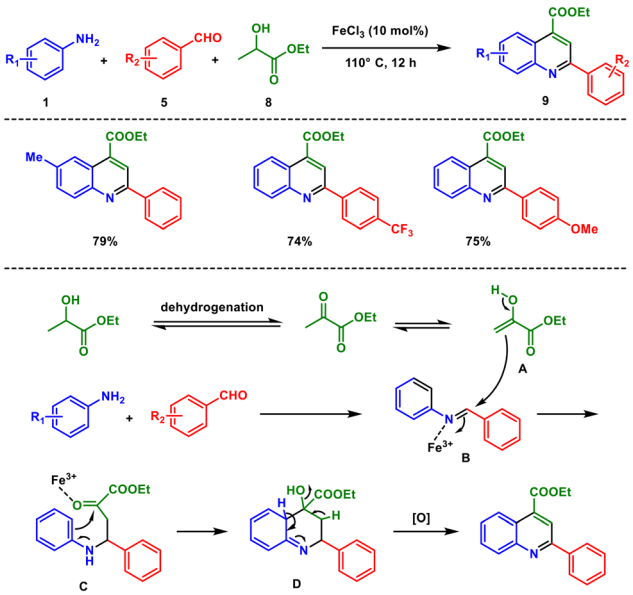
Likewise, Majee and coworkers in the year 2019 developed a one-pot methodology for the synthesis of 2-arylquinolines catalysed by $FeCl_3$ under ambient conditions.[24] This protocol involves three-component coupling of simple anilines **1**, aldehydes **5**, and nitroalkanes **6** at 90 °C for 6 hours (Scheme 2). After optimization of the different reaction parameters, a library of compounds was synthesized. This synthetic procedure possesses a broad scope, and more than 55 derivatives were synthesized along with gram-scale synthesis in good yield.

The reaction most likely occurs *via* imine formation followed by a sequential aza-Henry cyclization. By rearrangement of the nitro group, the aza-Henry intermediate produces a dihydroquinoline carbene, which on rearrangement and subsequent oxidation produces the desired 2,4-substituted quinoline **7**. This method has several advantages, including the use of easily accessible chemicals as starting materials, a low-cost metal catalyst, the ability to carry out the reaction in the presence of oxygen, and the ability to tolerate a wide range of functional groups.

Shortly afterwards, Yang and Wan reported a three-component reaction catalysed by $FeCl_3$ that shows high efficiency allowing access to 2,4-disubstituted quinoline.[25] The reaction involves anilines **1**, aryl aldehyde **5** and ethyl lactate **8** *via* simple iron(III) chloride catalysis under neat reaction conditions. This approach is very sustainable and environmentally friendly because it utilises biomass, alcohol dehydrogenation, and diversity-oriented synthesis to produce quinoline derivatives **9** (Scheme 3). Firstly, ethyl pyruvate **A** is formed from ethyl lactate through dehydrogenation. On the other hand, an imine **B** is generated from aniline and the aldehyde. Then the ethyl pyruvate attacks the imine facilitated by the ferric ion. The adduct **C** subsequently undergoes an intramolecular addition where the nucleophilic aryl C–H bond reacts with the ketone carbonyl, leading to the formation of intermediate **D**. Dehydration-induced elimination of this intermediate, followed by aromatization, results in the formation of the desired product.



Scheme 2 Three-component reaction *via* aza-Henry cyclization.



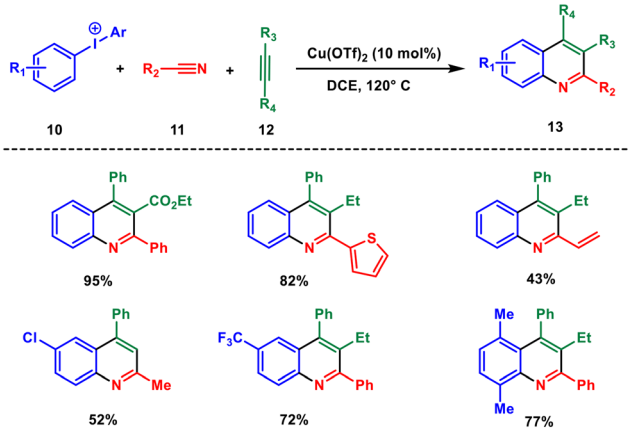
Scheme 3 Fe-catalysed reaction of ethyl pyruvate with aryl amine and aryl aldehyde.

The iron-catalysed synthesis of quinolines offers a versatile and efficient method for generating these important heterocyclic compounds. This approach leverages the unique reactivity of iron catalysts to facilitate the formation of quinolines from readily available starting materials. Overall, this method stands as a promising strategy in the synthesis of quinolines, showcasing the potential for further developments and applications in organic synthesis.

2.2. Copper catalysts

The synthesis of quinolines through copper catalysis offers a powerful tool for chemists to access a wide range of structurally diverse quinoline derivatives. Here, we delve into various multicomponent approaches of copper-catalysed quinoline synthesis, reaction conditions, catalytic systems, and key steps involved in this synthetic process catalysed by copper.

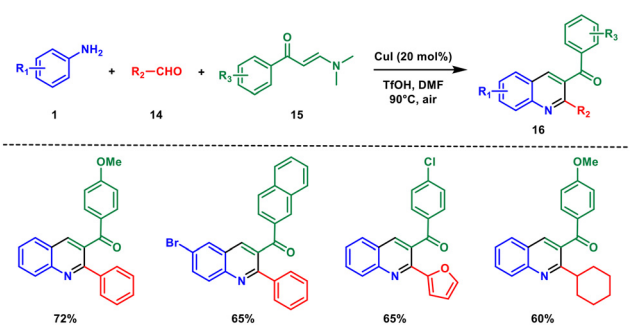
Anilines are the most used starting materials for quinoline synthesis, but nitriles and azides are also introduced as a source of the nitrogen atom. Nitriles can form anilide through an iminium cation which acts as an electron acceptor. In this regard, the Chen group in the year 2013 proposed a new route to forge a wide range of poly-substituted quinolines *via* diaryliodonium salts **10**, nitriles **11** and alkynes **12**, as environmentally benign reagents with low toxicity.[26] This three-component regioselective cyclisation is catalysed by $Cu(OTf)_2$ and the aryl group of the diaryliodonium acts as a C2 building block (Scheme 4). This approach represents a notable departure from the established methods relying on condensation chemistry and enables wide variation in the substitution patterns on the quinolines **13**. The cascade annulation involved a series of cationic intermediates, thus ensuring an efficient process and high regioselectivity.



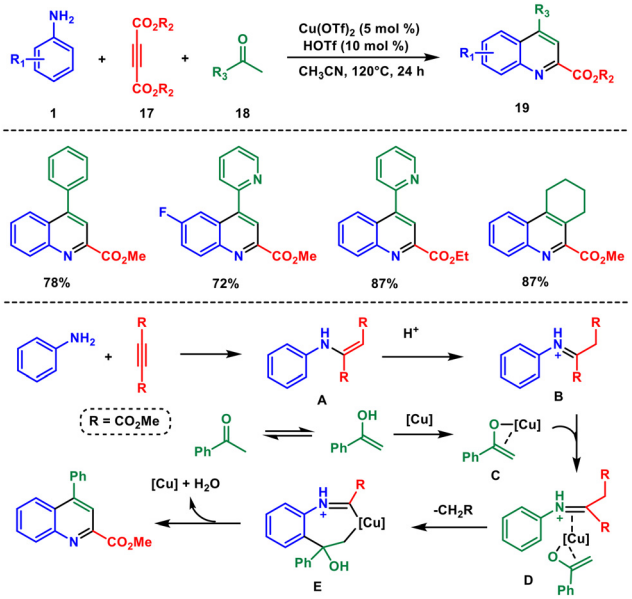
Scheme 4 Synthesis of quinolines from iodonium salts.

In 2017, Wan and colleagues developed a copper(I)-catalysed three-component regioselective synthesis of functionalised quinolines using anilines **1**, aldehydes **14**, and enaminones **15**.[27] In contrast to many alternative approaches, Povarov-type reactions stand out due to their benefits, such as the convenient accessibility of initial compounds and the swift creation of a wide range of products through multi-component processes (Scheme 5). In light of this, the development of Povarov-type three-component reactions that allow for the specific production of quinolines displaying varied substitution arrangements going beyond the traditional Povarov reaction, holds great importance.

Yi and co-workers in 2018 reported the synthesis of 2,4-disubstituted quinolines in a single step by using a copper triflate catalyst[28] to combine simple anilines **1**, alkyne esters **17** and (hetero)aryl/cycloalkyl ketone **18** in acetonitrile. The reaction has excellent tolerance for various functional groups and produces the desired quinolines **19** with exclusive regioselectivity (Scheme 6). Initially, an enamine **A** is generated rapidly from *in situ* nucleophilic addition of aniline to the alkyne ester. Subsequently, the enol form **B** coordinates with the Cu(II) catalyst, leading to the formation of intermediate **C**. This is succeeded by additional coordination with **B**, giving rise to intermediate **D**. The regioselective migratory insertion of the enol form results in the formation of intermediate **E**,



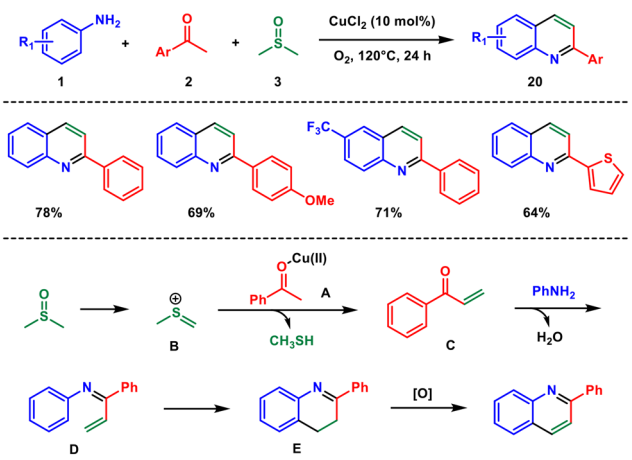
Scheme 5 Povarov-type synthesis of quinoline.



Scheme 6 $Cu(OTf)_2$-catalysed synthesis of 2,4-disubstituted quinoline.

involving a comparable C–C bond cleavage. Protonolysis of **E** produces the final product and restores the active Cu(II) catalyst, accompanied by the expulsion of a water molecule.

Shortly afterwards, Guo and co-workers reported a method for synthesising 2-aryl quinolines using a copper catalyst, O_2 as an oxidant, and DMSO as a carbon source.[29] This method involves a cyclization reaction of simple anilines **1** and aryl ketones **2** under aerobic conditions in a DMSO **3** medium. A variety of electron-donating and electron-withdrawing groups in aryl ketone and aniline participated in the reaction and converted to the respected quinolines **20** with moderate to good yields (Scheme 7). The protocol is atom-efficient and straightforward, as a variety of ketones and anilines can be used to directly generate 2-aryl quinolines. Initially, DMSO gets activated to form **B**. This intermediate **B** can react with the enolate



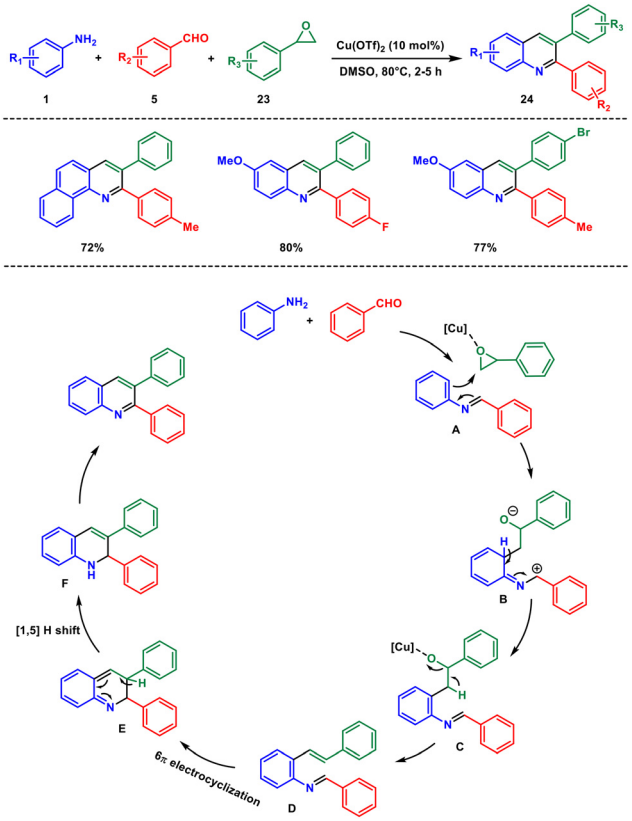
Scheme 7 Cu-catalysed synthesis of 2-substituted quinoline.

A and undergo demethylthioation to produce species **C**. Aniline then condenses with **C** to produce imine **D**, which further undergoes annulation followed by aromatization to yield the final product, **20**. It can be noted that the starting materials are the same as for Scheme 1, but the product is 4-substituted quinolines for the iron(III)-catalysed reaction whereas it is 2-substituted for the copper(II)-catalysed reaction. This is because in the presence of $K_2S_2O_8$ and Fe(III) DMSO reacts with aniline and produces an imine which attacks the enolate. But here in the presence of Cu(II), DMSO reacts with the aryl ketone to produce a vinyl ketone which reacts with aniline to produce 2-arylquinoline.

In the same year, Lin *et al.* proposed a new A^3 coupling reaction which involves an amine, aldehyde and alkyne to construct a 4-hydroxyalkyl quinoline derivative *via* Cu(I) and Au(I) sequential catalysis.[30] The reaction involves cyclization of anilines **1**, aldehydes **14** and aliphatic/aromatic alkynes **21**, respectively (Scheme 8). This protocol provides easy access to various 2,4-substituted quinolines that contain an aliphatic chain substituent at the 2,4-position in high yields. The reaction entails a sequence of events starting with domino imine formation, followed by imine addition to propargyl amine, cyclization, oxidation, and ultimately, the alkynyl–Cu(I) complex undergoes nucleophilic decomposition of the metal complex, resulting in the formation of the final product **22**. The authors provided DFT calculations to investigate the proposed mechanism by transition state searches by computation.

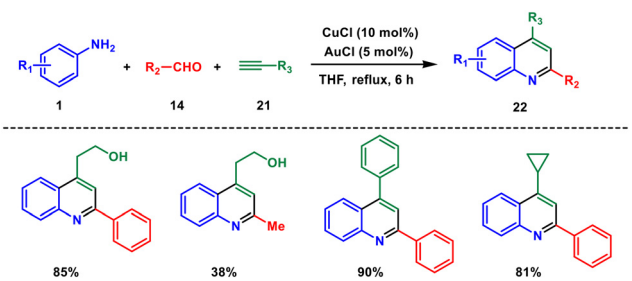
In 2021, our group devised an efficient method to synthesize 2,3-diarylquinoline derivatives using easily accessible aryl amines **1**, aryl aldehydes **5**, and styrene oxides **23**.[31] This process relies on 10 mol% copper(II) triflate in a three-component reaction (Scheme 9). By combining the *in situ*-formed imine with styrene oxide, we successfully generated the desired products. Our approach offers multiple benefits, including high atom efficiency, precise regioselectivity, sequential creation of one C–N and two C–C bonds, shorter reaction times, a wider range of applicable starting materials and good yields.

Mechanistically the reaction between the amine and aldehyde forms a Schiff's base intermediate **A**. Subsequently, intermediate **A** reacts with styrene oxide to yield intermediate **B**, which, upon aromatization, produces **C**. Then, elimination of water from intermediate C results in the formation of **D**, which undergoes 6π-electrocyclic ring closure to generate intermediate **E**. Intermediate **E** experiences a [1,5] hydrogen shift,[32] leading to dihydroquinoline **F**, followed by aerial oxidation to furnish the desired quinoline.



Scheme 9 $Cu(OTf)_2$-catalysed synthesis of 2,3-diaryl quinoline.

The copper-catalysed synthesis of quinolines represents a valuable and robust approach in organic synthesis. This method harnesses the catalytic power of copper to facilitate the construction of quinoline structures from diverse starting materials. It offers notable advantages such as mild reaction conditions, high efficiency and excellent functional group tolerance. The versatility and reliability of copper catalysis in quinoline synthesis underscores its significance in accessing these important heterocyclic compounds.



Scheme 8 Cu and Au dual-catalysed A^3 coupling reaction.

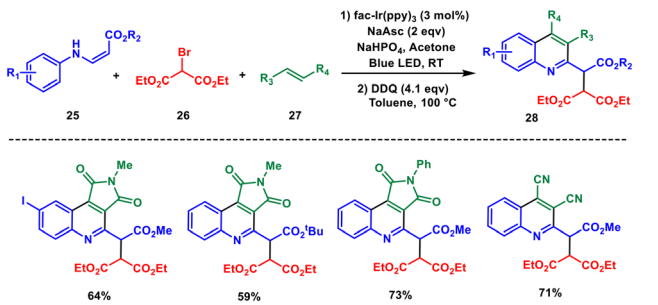
2.3. Metal photocatalyst

Metal photocatalysts are a promising class of materials with unique properties that enable them to harness light energy for various catalytic processes, typically in the presence of oxygen or another oxidizing agent. Metal-based coordination complexes which strongly absorb in the visible light region such as *fac*-Ir(ppy)$_3$ and $[Ru(bpy)_3]^{2+}$ are the most used photocatalysts in recent years, as they provide novel routes to access various diverse organic scaffolds.[33,34] In this context, the synthesis of quinoline compounds using photocatalysis has gained signifi-

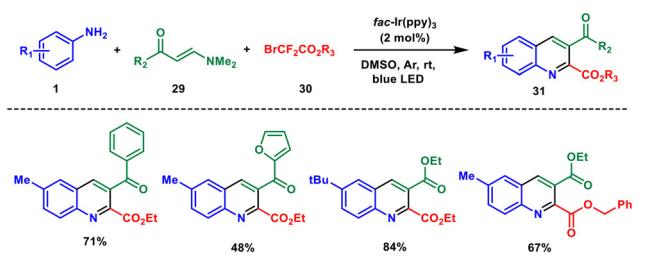
cant attention in recent years as a green and sustainable method.[35]

For instance, Choi and Park in 2018 constructed highly substituted quinolines based on a three-component radical cascade reaction of β-aminoacrylate **25** with diethyl bromomalonate **26** and an alkene (mostly *N*-methyl maleimide) **27** in acetonitrile. The cyclization was carried out using 3 mol% Ir(ppy)$_2$(dtbbpy)PF$_6$ and base under 12 W blue LED lamp at room temperature (Scheme 10).[36] Under optimised conditions, a tandem coupling reaction exhibits excellent chemoselectivity due to the distinct electronic characteristics of the reacting components. When electron-rich β-aminoacrylates are combined with electron-deficient halides and alkenes, quinolines are produced in favourable yields. The final step involves the *in situ* oxidation of tetrahydroquinolines using DDQ at 100 °C, resulting in the formation of quinolines.

Recently in 2022, Wang and coworkers developed an iridium-catalysed photoinduced multicomponent reaction. A mixture of aryl amine **1**, enaminone **29**, ethyl bromodifluoroacetate **30** and *fac*-Ir(ppy)$_3$ (2 mol%) was irradiated under 6 W blue LED irradiation under an argon atmosphere for 5 h.[37] The authors synthesized a library of compounds of alkyl, aryl, electron-donating and electron-withdrawing substituents in moderate yields (Scheme 11). The crucial steps involving the sequential cleavage of C–Br and C–F bonds were the decisive steps in this reaction, followed by intermolecular [3 + 3] cyclization between *in situ*-generated 1,3-vinylimine ions and arylamines. This strategy features broad functional group tolerance and wide substrate scope that enables further synthetic applications of the obtained products.



Scheme 10 Blue LED-induced generation of substituted quinoline using Ir-photocatalyst.



Scheme 11 Blue LED-promoted synthesis of quinoline *via* vinylimine ions.

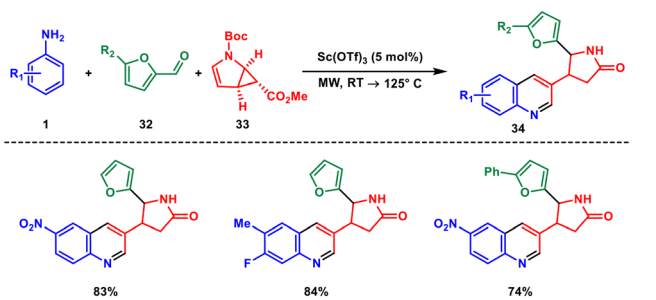
2.4. Other metal catalysts

Various other transition and post-transition metals such as scandium, cobalt, zinc or silver can serve as catalysts, enabling the formation of quinolines through different catalytic cycles and enabling the creation of diverse quinoline derivatives.

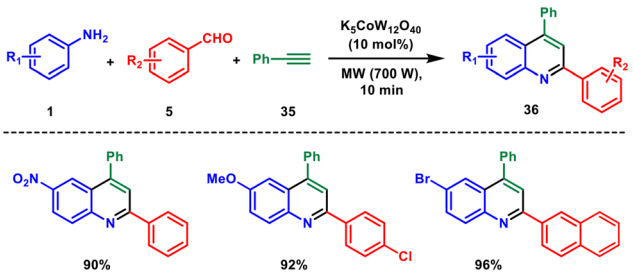
Back in 2012, the Reiser group reported a scandium triflate-mediated multicomponent stereoselective synthesis of 3-pyrrolidinone-substituted quinolines under microwave irradiation using aryl amine **1**, furancarbaldehyde **32** and pyrrole derivatives **33** (Scheme 12). This is a Povarov-type reaction which combines donor–acceptor-induced cyclopropane ring opening, 1,4-furan ring migration and formation of the quinoline ring.[38] A variety of modified *cis*-pyrrolidinones were successfully synthesised with a high degree of stereoselectivity, resulting in excellent yields. These compounds hold significance as fundamental building blocks in biologically significant compounds with pharmaceutical relevance. The reaction proceeds through an intermediate having *endo* and *exo* epimers with respect to the stereochemistry of the furan substituent which can be separable on silica. Interestingly the *endo* isomer is arranged in such a way that it gives the desired product **34** while the *exo* epimer yields a ring-opened polycyclic imine.

Polyoxometalates (POMs), known for their versatile molecular and electronic structural variations, play a crucial role in a wide range of academic fields due to their unique structure. After Chester's research was published in 1970,[39] $Co^{III}W_{12}^{5-}$ and similar POM anions have been employed as precise agents for outer-sphere electron transfers. Conversely, the potential efficacy of various POM anions as electron-transfer agents has been harnessed in the selective catalytic oxidation of both inorganic and organic substrates.

In this context, in 2012 Mohammadpoor-Baltork *et al.* reported a microwave-assisted one-pot three-component reaction using aromatic amines **1**, aromatic aldehydes **5**, and phenylacetylene **35** catalysed by POM.[40] They used a small amount of catalytic potassium dodecatungstocobaltate trihydrate to produce 2,4-substituted quinolines **36** in high yields. This method is notable for its ability to selectively convert aromatic aldehydes over aliphatic ones, making it valuable for synthesising quinoline derivatives (Scheme 13). The reaction



Scheme 12 Microwave-assisted synthesis using Sc(OTf)$_3$.

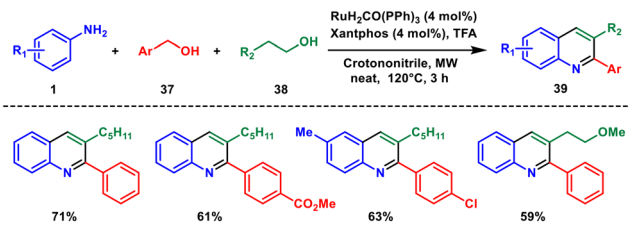


Scheme 13 Co-POM-catalysed synthesis of 2,4-diaryl quinoline.

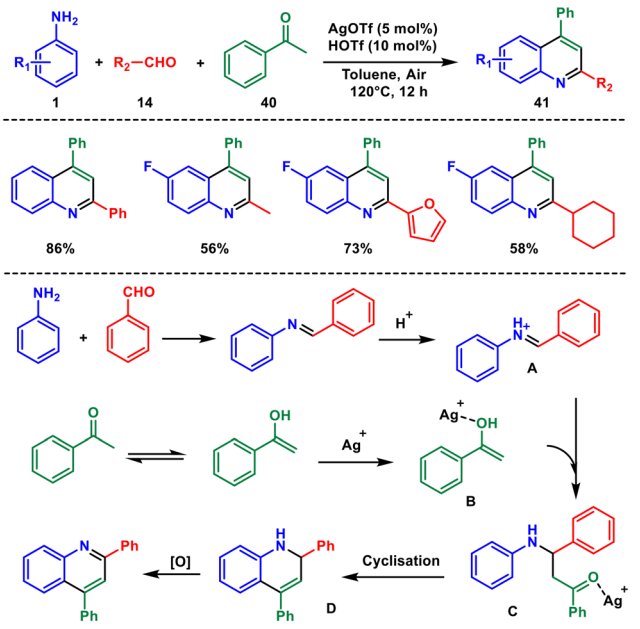
proceeds through a Co(II) radical cation generated from an electron transfer from the phenyl acetylene moiety. Additionally, the catalyst could be reused multiple times without significant loss of activity.

In 2015, Porcheddu *et al.* presented an innovative method for synthesising diverse substituted quinolines through a ruthenium-catalysed dehydrogenative cross-coupling of primary alcohols and imines.[41] This transformative process utilised trifluoroacetic acid (TFA) and a ruthenium catalyst to facilitate the *in situ* generation of imines from various anilines **1** and benzyl alcohols **37**, employing a hydrogen-transfer procedure (Scheme 14). Notably, the same catalyst was employed throughout the process, allowing for the introduction of various primary alcohols **38** *via* a telescopic approach, resulting in the formation of quinolines **39** in satisfactory to commendable yields. This methodology offers several advantages, such as the utilization of alcohols as starting materials, the absence of potent oxidizing agents, and the wide array of potential precursor compounds. In comparison with conventional quinoline synthesis methods, this contemporary adaptation of the Skraup reaction stands out due to its enhanced efficiency and versatility.

Shortly after that, Zhang and co-worker reported a new method for synthesising a range of polysubstituted quinolines using silver triflate as a catalyst.[42] It emerged as an important catalyst for the construction of many architecturally intriguing molecules, including quinoline. This method involves combining arylamines **1**, aldehydes **14**, and acetophenone **40** (Scheme 15). The technique works well with a broad range of substrates, allowing for greater flexibility in the creation of the heterocyclic framework using a single catalytic system to facilitate multiple chemical transformations. It is an important step toward developing more efficient and environmentally friendly



Scheme 14 Ru-catalysed reaction with alkyl and aryl alcohol.

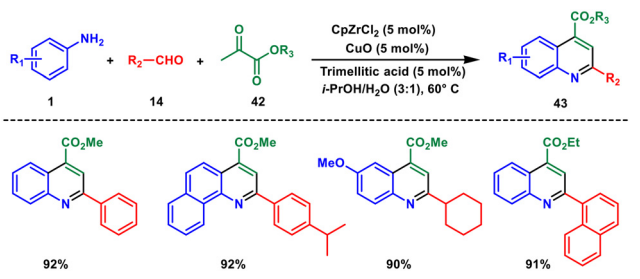


Scheme 15 Silver triflate-mediated three-component synthesis of 2,4-substituted quinoline.

synthesis strategies for complex molecules from simple starting materials.

Mechanistically, the equilibrium between acetophenone and its enol form is highly inclined toward the enol **B** in the presence of the silver catalyst. The generated enol immediately reacts with imine **A**, forming intermediate **C** which *via* intramolecular cyclization produces **D**. Oxygen in the air serves as a potent oxidizing agent for the aromatization of **D** to the final quinoline **41** product.

Later in 2017, Gao and coworkers introduced a new system for catalysis that involves three types of cooperation and relays. The system is used to trigger the Mannich addition, followed by C–C construction and oxydehydrogenation.[43] This triple cooperative and relay catalytic system used aryl amines **1**, aldehydes **14** and ketones **42** for the synthesis of polysubstituted quinoline **43** under mild conditions The catalytic system is composed of zirconocene dichloride and trimellitic acid that forms a new zirconocene species $Cp_2Zr(OOC)_2PhCOOH$ which promotes the Mannich addition and C–C bond construction reactions (Scheme 16). Additionally, the system features



Scheme 16 Zr-catalysed Mannich-type reaction leading to quinoline.

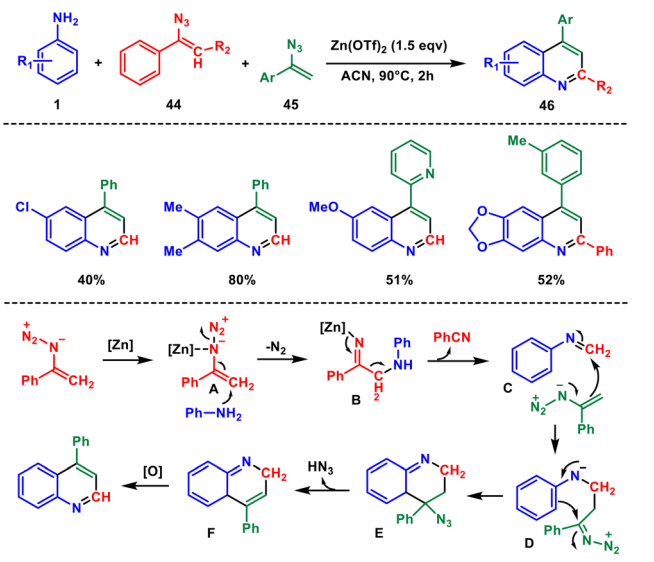
copper oxide (CuO) that allows for relay catalysis for oxydehydrogenation. The use of this system was shown to be highly effective in synthesising substituted quinolines from commercially available anilines, aldehydes, and ketones. The substrate and the product of this reaction are similar to those in Scheme 3. However, the yield of this reaction is much higher, despite using much milder reaction conditions.

In the same year, Jiang and co-worker found an unprecedented $Zn(OTf)_2$-promoted selective cleavage of vinyl azides **44** and **45** with aryl amine **1** for the synthesis of 4-substituted quinolines **46**,[44] where vinyl azides operate as a dual synthon by undergoing simultaneous cleavage of the C=C and C–N bonds, leading to the formation of two C=C bonds and one C=N bond in a single-step process (Scheme 17). However, various anilines with electron-withdrawing substituents did not effectively participate in the reaction. Control experiments revealed that the methylene end of the vinyl azide is important because the reaction does not take place with methyl-substituted vinyl azide. Mechanistically, intermediate **A** is formed through the coordination of zinc with the nitrogen in the azide group, which enhances the electrophilic nature of the olefin. Following that, aniline initiates a nucleophilic attack, resulting in intermediate **B**, accompanied by the removal of nitrogen. Subsequently, intermediate **B** transforms into imine intermediate **C** by breaking a C–C bond,[45] resulting in the production of benzonitrile as a by-product. Following this, intermediate **C** undergoes an intramolecular cyclization, specifically a [4 + 2]-annulation with compound **45**, leading to the formation of intermediate **E**. This, in turn, gives rise to intermediate **F** with the elimination of HN_3. Finally, **F** undergoes aromatization when exposed to O_2 in the air, yielding the desired quinoline **46**.

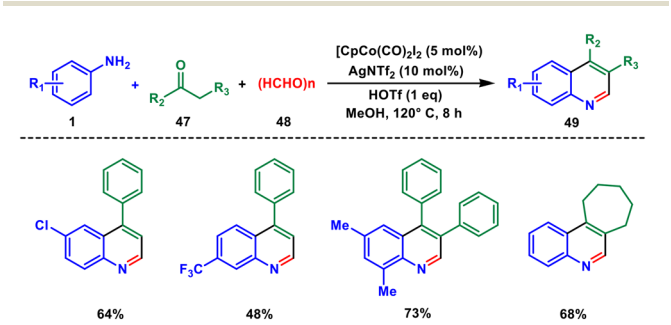
In 2017, the Yi group developed a new method for the synthesis of diverse quinolines using a Co(III) catalyst for the first time. This method involves the one-pot synthesis of 3,4-substituted quinolines **49** from simple aryl amines **1** and ketones **47** with paraformaldehyde **48**.[46] The yield of the reaction is good to excellent, and there is excellent tolerance for different functional groups (Scheme 18). The only by-products of the reaction are water and hydrogen gas. The method also shows exclusive site- or/and region-selectivity when unsymmetrical ketones and *meta*-substituted anilines are used. This method has significant potential for the synthesis of biologically important quinoline frameworks in an environmentally friendly and atom-economical manner with exclusive site selectivity.

The same group in 2018 reported C–H activation of anilines with alkynes for synthesis of quinolines with exclusive regioselectivity.[47] The same Co(III)-catalyst is used in this DMSO-involved cyclization of simple anilines **1** with alkynes **21** for direct and highly efficient synthesis of privileged quinolines **50** with broad substrate tolerance and in good to excellent yields (Scheme 19). Here DMSO served the dual role of solvent and the C1 building block for the synthesis of quinoline products.

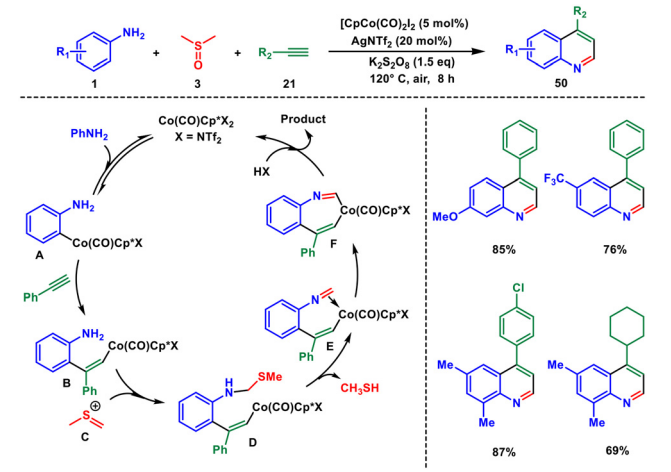
In terms of the mechanism, the process begins with the formation of the active cationic Co(III) catalyst. This catalyst then coordinates with aniline, leading to the EAS pathway and sub-



Scheme 17 Zinc triflate-mediated three-component synthesis of 2,4-substituted quinoline.



Scheme 18 Co-catalysed three-component reaction of aryl amine and ketone with formaldehyde.



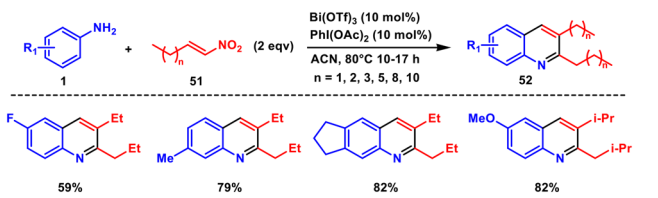
Scheme 19 Co-catalysed synthesis of 2-substituted quinoline.

sequent *ortho*-metalation, resulting in the formation of intermediate **A**. The increased polarization of the carbon–cobalt bond in intermediate **A** promotes the 1,2-regioselective insertion of an alkyne,[48] yielding intermediate **B**. In the presence of $K_2S_2O_8$, DMSO is activated, producing compound **C**, which combines with **B** to generate intermediate **D**. Subsequently, **D** undergoes oxidation, leading to the formation of an imine species **E** and the elimination of CH_3SH. Subsequently, Co–C migratory insertion occurs, yielding intermediate **F**. Ultimately, protonolysis of **F** yields the final product **50**, concurrently releasing the active Co(III) catalyst.

In 2020, we investigated the reaction behaviour of aryl amines **1** with nitroalkenes **51** in the presence of bismuth(III) triflate and diacetoxyiodobenzene.[49] This approach offers advantages including consecutive formation of a C–N bond and two C–C bonds, high regioselectivity, broad substrate scope, and favourable yields. Instead of the anticipated 3-alkylindole derivatives, we obtained 2,3-dialkylquinoline derivatives **52**. This reaction provides a new route to synthesize 2,3-dialkylquinoline derivatives under more gentle conditions (Scheme 20). Mechanistic understanding determined through theoretical calculations revealed a preference for the conventional aza-Michael reaction over the Michael addition. The aza-Michael adduct formed leads to an imine by water elimination, which may tautomerize to the corresponding amine. Subsequent reactions between the resulting imine and enamine intermediates led to the desired quinoline derivatives.

Metal–organic frameworks (MOFs) represent a novel category of porous materials formed through the combination of metal ions and organic building blocks. MOFs have a unique porous structure with organic and inorganic active sites, and their structural flexibility makes them excellent heterogeneous catalysts. Compared with homogeneous transition-metal catalysts, MOF-based catalysts offer advantages such as a large internal surface area, microporosity, and well-organized porous structures. The choice of MOF, its structure, and the specific metal ions or ligands used can greatly influence its catalytic activity and selectivity. Researchers continue to explore and design MOFs with tailored properties to address various challenges in organic synthesis and catalysis.

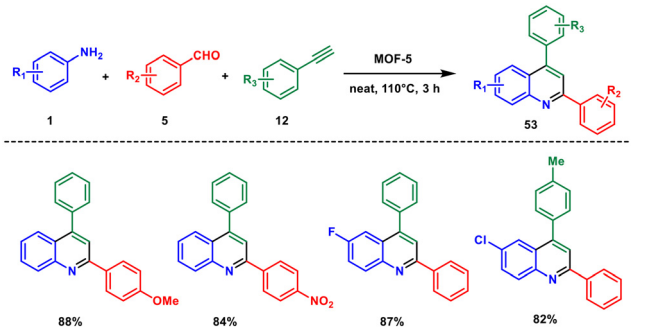
In view of developing another MOF-catalysed reaction, Zhang and coworkers in 2020 developed a new zinc-based MOF-catalysed three-component coupling reaction for the synthesis of 2,4-disubstituted quinoline derivatives. They used aromatic amines **1**, aldehydes **5** and alkynes **12** reacted neat at 110 °C to produce quinoline **53** in excellent yields.[50]



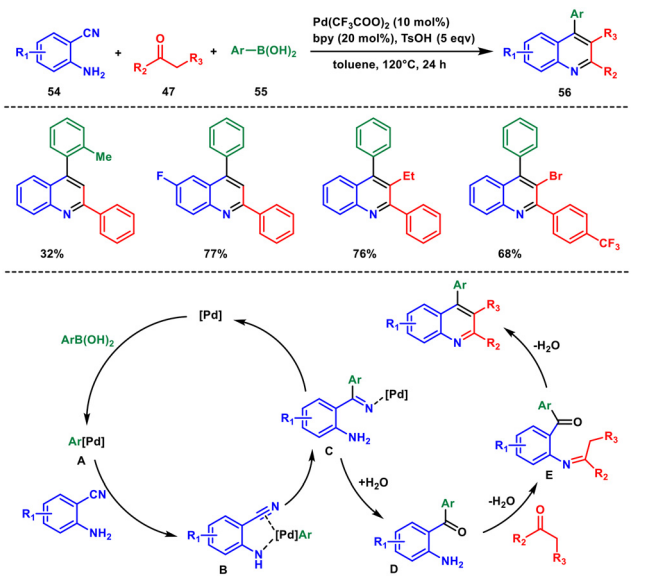
Scheme 20 $Bi(OTf)_3$-catalysed synthesis of 2,3-dialkyl quinoline.

The advantages of the method are easy recovery and reusability of the catalyst, broad substrate scope, short reaction time, and solvent-free conditions (Scheme 21). The reaction proceeds *via* generation of an imine which is coordinated by the MOF-5 and enhances its electrophilicity. Then the addition of alkyne to imine forms a propargylamine intermediate, which then undergoes an intramolecular hydroarylation, followed by oxidative aromatization with oxygen to afford the desired product. This reaction bears significant similarities to Scheme 13, including similar starting materials, products, and being a solvent-free reaction. However, the yields with the POM catalyst are slightly higher than with the MOF catalyst.

Recently, Chen and co-workers proposed a new approach for the synthesis of poly-substituted quinolines through a three-component tandem reaction of 2-aminobenzonitriles **54**, arylboronic acids **55** and ketones **47**.[51] The method utilises easily accessible materials, employing straightforward palladium-catalysed conditions and a wide range of functional groups (Scheme 22) giving good yield. The authors synthesized



Scheme 21 MOF-catalysed A^3 coupling reaction to construct 2,4-diaryl quinoline.



Scheme 22 Pd-catalysed coupling reaction leading to quinoline.

a library of alkyl, aryl and halide-substituted quinolines in moderate to good yields. Moreover, a variety of aryl groups placed at the C-4 position, alkyl and aryl groups at the C-2 position and halide groups at the C-3 position were found to be compatible under the given conditions.

To begin, the Pd(II) catalyst engages in transmetalation with an arylboronic acid, forming arylpalladium intermediate **A**. This species can potentially bind with 2-aminobenzonitrile, creating an N-bound intermediate labeled as **B**. Following this, the intramolecular carbopalladation of the cyano group leads to the generation of an imine palladium complex **C**. Subsequently, in the presence of water, complex **C** undergoes hydrolysis to yield intermediate **D**. From there, intermediate **D** takes part in a series of reactions involving condensation and cyclization, ultimately resulting in the formation of poly-substituted quinolines **56**.

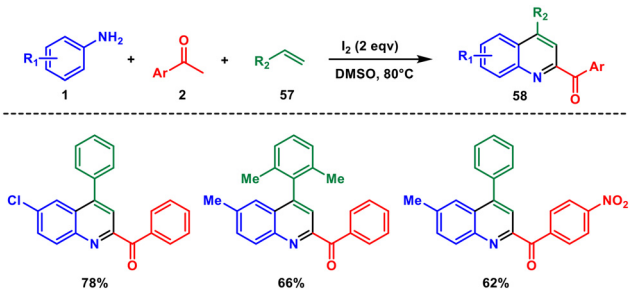
3. Non-metal-catalysed reactions

Non-metal catalysis is considered an important development in green chemistry due to the mild reaction conditions and eco-friendly catalysts that can be used in organic synthesis. Green chemistry principles have spurred the innovation of using organocatalysts instead of metal catalysts for synthesizing quinoline derivatives, aligning with sustainability goals.[52] They have several benefits, including their insensitivity to moisture and oxygen, low cost, easy accessibility, and low toxicity. These advantages make them particularly useful in the production of pharmaceutical compounds when compared with metal catalysts.

3.1. Iodine-catalysed MCR of quinolines

Iodine can act as a catalyst in various chemical reactions. It is used extensively in a variety of chemical reactions and is a green alternative to transition metals in organic chemistry.[53] The most common method for quinoline synthesis involving iodine as a catalyst is the Friedländer synthesis. The specific mechanism and conditions under which iodine serves as a catalyst can vary depending on the reaction. The choice of iodine as a catalyst is often influenced by factors such as reaction selectivity and efficiency.

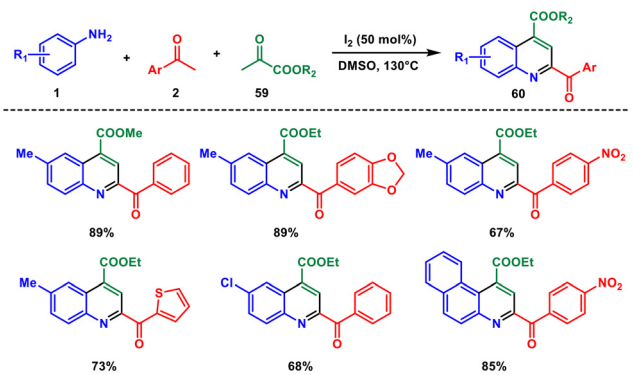
In 2014, Wu and co-workers introduced an efficient method for synthesising 2,4-disubstituted quinolines **58** directly from aryl amines **1**, aryl ketones **2** and styrenes **57**.[54] This new approach utilised molecular iodine as a catalyst and involved a unique variant of the Povarov reaction (Scheme 23). Instead of the usual carbonyl carbon, the methyl group of the methyl ketone was found to participate in the reaction. The authors proposed a mechanistic pathway involving a series of sequential reactions, namely iodination, Kornblum oxidation, Povarov reaction, and aromatization. This self-sequenced cascade reaction, driven by molecular iodine, allowed for the sequential occurrence of three distinct reactions within a single reactor. Furthermore, this catalytic process was straightforward to carry out and offered significant advantages.



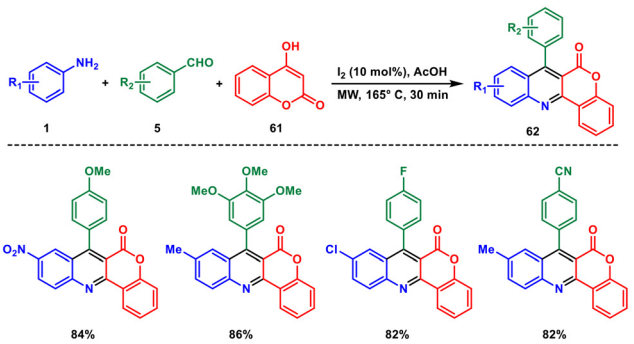
Scheme 23 Iodine-catalysed three-component synthesis of quinoline.

In the next year, the same research group published a significant finding on the use of iodine as a catalyst in a Povarov-type reaction involving the same arylamines **1** and aryl ketones **2** along with α-ketoesters **59**.[55] This approach demonstrated high efficiency by employing a catalytic amount of hydrogen iodide (HI), which was generated *in situ* through iodination and Kornblum oxidation steps (Scheme 24). The generated HI acted as a promoter for the subsequent Povarov step, eliminating the need for additional additives. The outcome was the synthesis of substituted quinolines **60**, showcasing a simple and intriguing procedure with excellent compatibility for various functional groups. This reaction introduces a novel reactivity pathway for the Povarov reaction, offering promising possibilities in terms of functional group tolerance.

In the same year, Sashidhara and coworkers introduced a straightforward and efficient method for selectively synthesising chromeno[4,3-*b*]quinolin-6-one **62** derivatives.[56] This process, conducted under microwave irradiation, utilised molecular iodine as the sole catalyst. The reaction involved a three-component tandem annulation of aromatic amines **1**, aromatic aldehydes **5** and 4-hydroxycoumarin **61** resembling a Povarov-type reaction (Scheme 25). The reaction proceeds through formation of a Knoevenagel intermediate between the aldehyde and coumarin followed by rearrangement and 1,3-H shift to afford the product. The authors supported the mechanism by control experiments. The method offered high yields and proved to be a valuable approach for generating diverse libraries of hybrid drug-like scaffolds. By employing this strat-



Scheme 24 Iodine-catalysed synthesis through Kornblum oxidation.



Scheme 25 Microwave-assisted Povarov-type reaction with coumarin.

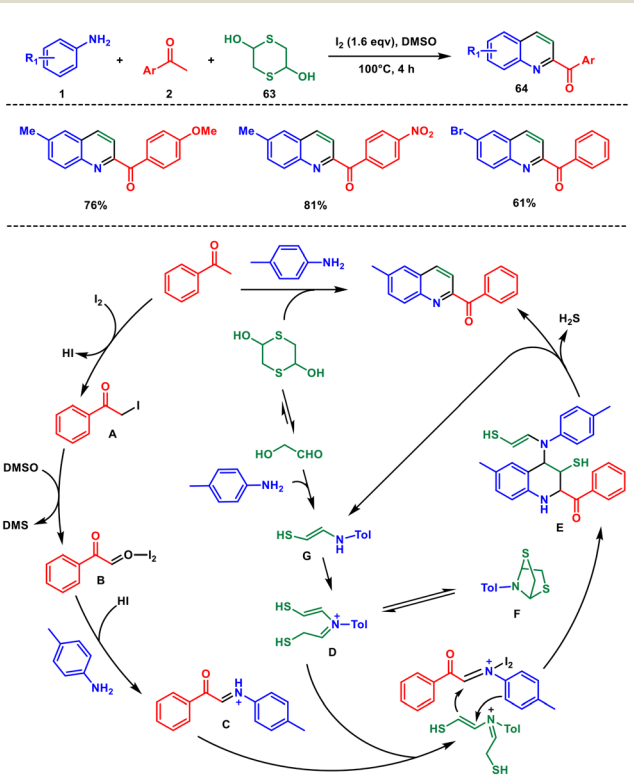
egy, a complex central structure could be constructed in a single step using readily available starting materials and environmentally friendly oxidants, contributing to a greener and more sustainable synthetic approach.

In a 2017 study, again Wu *et al.* introduced a highly efficient method for synthesising 2-acylquinolines through a [4 + 2] cycloaddition reaction.[57] They utilised I_2 as a catalyst and employed 1,4-dithiane-2,5-diol **63** as a substitute for ethylene. It is the first example where an arylamine **1** substrate played a crucial role in activating 1,4-dithiane-2,5-diol for participation in the Povarov reaction (Scheme 26). In this process, 1,4-dithiane-2,5-diol acted as an ethylene surrogate. Furthermore, this method presented a novel approach for utilizing 1,4-dithiane-2,5-diol as a C2 building block in the synthesis of nitrogen-containing heterocycles, instead of its typical use in constructing sulfur-containing heterocycles through desulfurization.

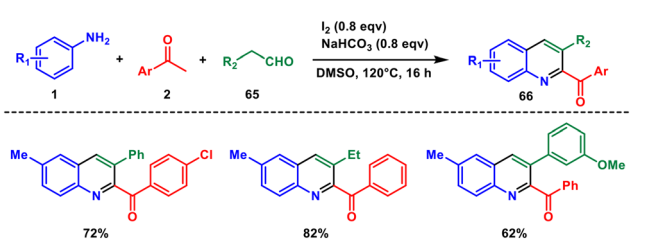
In the initial step, acetophenone is converted into phenylglyoxal **B** through a process involving the release of HI and DMS, achieved through an iodination/Kornblum oxidation sequence. Intermediate **B** then undergoes a dehydration reaction with *p*-toluidine to form the iminium ion **C**. Meanwhile, mercapto acetaldehyde, produced from 1,4-dithiane-2,5-diol under equilibrium conditions, gets initiated by *p*-toluidine to create enamine intermediate **D**, which subsequently reacts with **C** to generate intermediate **E**. It's worth noting that intermediate **D** can also undergo intramolecular nucleophilic attack independently to produce **F** when intermediate **C** is absent. The transformation between intermediate **D** and compound **F** is reversible, with compound **F** readily converting back to intermediate **D**, which then promptly combines with intermediate **C** to yield the desired product **64**. Intermediate **E** then goes through an oxidative aromatization process, resulting in the final product **64** *via* desulfurization and deamination steps.[58] Enamine intermediate **G** continues to participate in the reaction throughout this mechanistic sequence.

In the same year, they also developed a novel approach involving iodine–amine synergistic promotion for a formal [4 + 2] cycloaddition reaction. This reaction involved the use of arylamines **1**, methyl ketones **2** and aldehydes **65**. The authors used the aryl(alkyl)aldehydes as alkene surrogates in a DMSO solvent.[59] Unlike previous methods that mainly yielded 2-substituted quinolines, this protocol enabled the modular synthesis of diverse 2-acyl-3-aryl(alkyl)quinolines (Scheme 27). Consequently, it expanded the scope of Povarov-type reactions. The arylamines played dual pivotal roles in this process. They not only acted as reactants but also served as essential catalysts for promoting enamine formation. Furthermore, the mechanistic investigation suggested that the reaction proceeded through an iodination/Kornblum oxidation/Povarov/aromatization sequence.

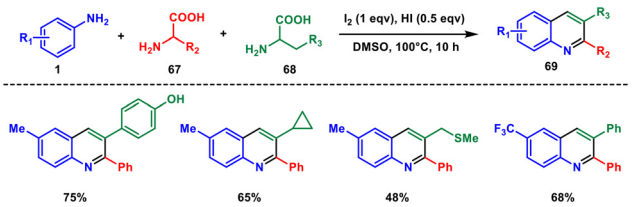
Later that year, they developed a novel method for generating a wide range of 2,3-disubstituted quinolines. This time they used aryl amine **1** and two distinct amino acids **67** and **68** with high efficiency and diversity that facilitates the creations of pharmaceutical derivatives, photochemical active compounds, and challenging scaffolds (Scheme 28).[60] Using this



Scheme 26 Iodine-mediated synthesis of quinoline involving 1,4-dithiane.



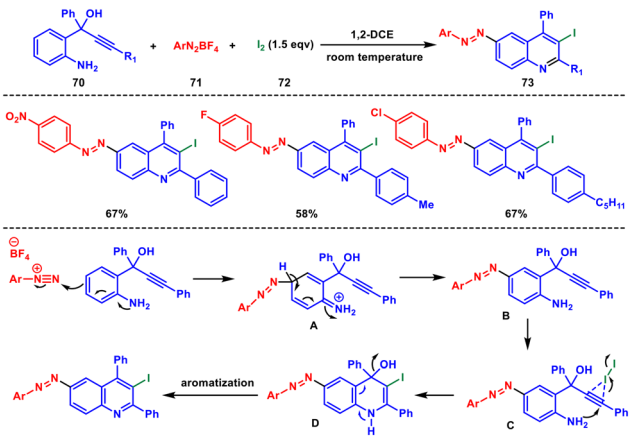
Scheme 27 Iodine-promoted synthesis through [4 + 2] cycloaddition reaction.



Scheme 28 Synthesis of quinoline involving aniline and amino acids.

method, challenging fused rings and biquinolines which have never been prepared before can be readily reached. They introduced the concept of using two amino acids as heterocyclic precursors for the first time. Utilising renewable resources like amino acids and operating under metal-free conditions render this reaction environmentally friendly, potentially valuable in pharmaceutical exploration, photochemical applications, and industrial manufacturing. Mechanistically, an I_2-facilitated decarboxylation and deamination process activate two separate amino acids *in situ*. Subsequently, I_2 facilitates the formation of new C–N and C–C bonds as a terminal oxidant.

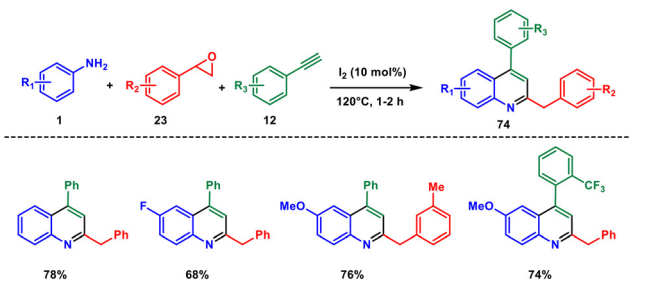
In 2018, Yaragorla and coworkers developed a comprehensive and diverse approach to synthesize quinoline derivatives. They employed a sequential process involving azo-coupling and electrophilic cyclization reactions to prepare 6-(aryldiazenyl)-3-iodoquinolines **73**.[61] This one-pot, three-component method utilised 2-aminoaryl propargyl alcohols **70**, aryldiazonium salts **71** and molecular iodine **72**. The reaction proceeded through a series of steps including azo-coupling, regioselective iodocyclization, and aromatization, resulting in the formation of the desired quinoline derivatives **73** (Scheme 29). The reaction begins with the azo-coupling reaction of aniline and diazonium salts to produce **B** through the intermediate **A**. Then the triple bond of the amino propargyl alcohol attaches with the iodine to generate intermediate **C**. This species then undergoes iodocyclization followed by aromatization to produces the desired quinoline product.



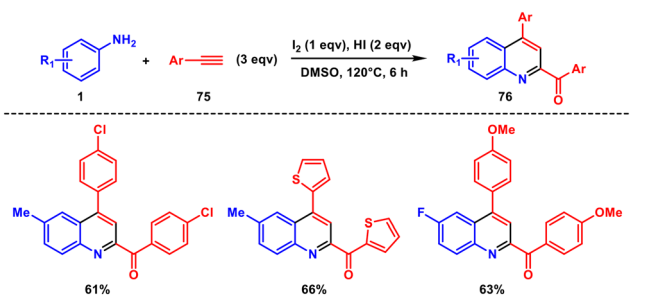
Scheme 29 Room temperature synthesis of 3-iodoquinoline involving 2-aminoaryl propargyl alcohol.

In 2021, our group reported a metal- and solvent-free synthesis of 2-benzyl-4-arylquinoline derivatives from aryl amines **1**, styrene oxides **23** and aryl acetylenes **12** in the presence of 10 mol% molecular iodine (Scheme 30).[62] This reaction occurs at 120 °C, which sidesteps the need for metal catalysts, reducing metal waste. Unlike the [4 + 2] imino-Diels–Alder route, our process involves an alternative pathway where an activated imine is captured by a terminal alkyne, forming a benzylic vinylic cation. This cation then undergoes intramolecular cyclization, followed by a [1,3] H shift and oxidation, resulting in the desired quinoline **74**. Key aspects of this methodology include employing uncomplicated starting materials, achieving high regioselectivity, shorter reaction times, maximizing atom economy, generating one C–N and two C–C bonds in a single step, and accommodating a broad spectrum of functional groups.

In the same year, Wu and coworkers introduced a new approach to the Povarov reaction using iodine and HI as a mediator.[63] This method enables the synthesis of 2,4-substituted quinolines **76** by utilizing anilines **1** and arylacetylenes **75**. Notably, arylacetylenes serve a dual role as both diene precursors and dienophiles. The C(sp)–H bond in arylacetylenes undergoes oxidation to form an aldehyde by the I_2/DMSO system (Scheme 31). Subsequently, the aldehyde reacts with aniline *in situ*, generating a diene C–acylimine. This innovation in the Povarov reaction expands the range of applicable diene precursors and broadens the substrate scope to include compounds beyond carbonyl compounds.



Scheme 30 Solvent-free synthesis of 2-benzyl-4-ayl quinoline.



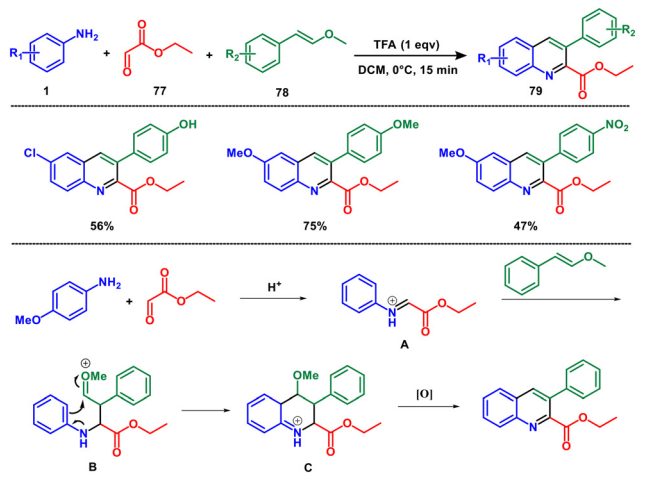
Scheme 31 Iodine-catalysed synthesis of 2,4-substituted quinoline in DMSO.

The iodine-catalysed synthesis of quinolines stands as a valuable and practical method in organic chemistry. Leveraging iodine as a catalyst enables the efficient construction of quinoline frameworks from diverse starting materials. This approach offers distinct advantages, including mild reaction conditions, operational simplicity, and broad substrate compatibility. The effectiveness of iodine catalysis in quinoline synthesis highlights its significance as a versatile and environmentally friendly strategy. Continued exploration and optimization of iodine-catalysed methods holds promise for further enhancing the scope, efficiency, and applicability of quinoline synthesis in various synthetic endeavours.

3.2. Acid-catalysed reactions

Acid catalysts play an important role in the chemical and pharmaceutical industries, catalysing various process such as esterification, hydrolysis, dehydration, polymerization, and many organic synthesis reactions. They serve as a proton source thereby lowering the activation energy required for the reaction to occur.

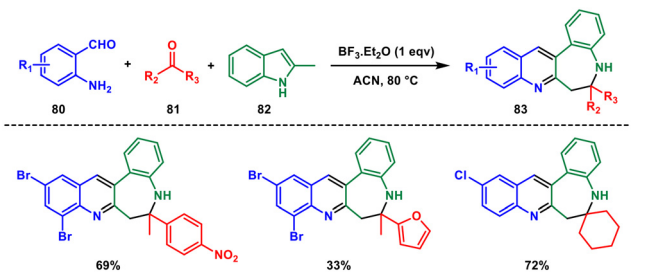
For instance, in 2016, McNulty *et al.* introduced a novel three-component coupling reaction for the preparation of 2-carboxyl-3-aryl quinoline derivatives from anilines **1**, ethyl glyoxalate 77 and enol ethers **78** as phenylacetaldehyde surrogates. The reaction takes place quickly and in dichloromethane, catalysed by trifluoroacetic acid (TFA) under mild conditions and delivers quinolines with good to high yields.[64] This method provides a more straightforward route to obtain 3-aryl quinolines, avoiding complications encountered with phenylacetaldehyde derivatives (Scheme 32). When aniline reacts with ethyl glyoxylate, it forms an imine, which upon protonation yields intermediate **A**. The reaction progresses through a stepwise Mannich-aldol-type process progressing through intermediate **B** which upon rearrangement leading to intermediate **C**. Loss of a proton to restore aromaticity followed by elimination of methanol and spontaneous oxidation results in the desired product **79**. By using aryl enol ethers, it is also possible to obtain products with reversed regioselectivity compared with standard Povarov products. This chemistry has been successfully employed to synthesize a wide range of 3-aryl quinolines, as well as a more limited selection of vaulted diaryl ether analogues.



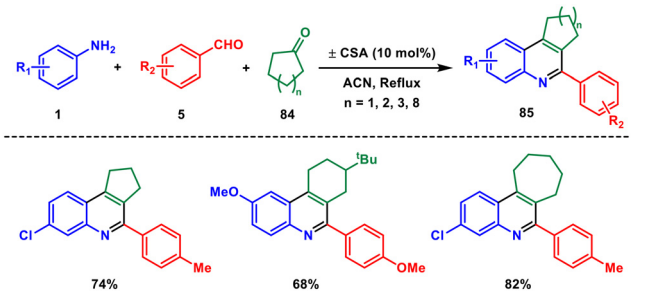
Scheme 32 TFA-catalysed synthesis of quinoline involving enol ether under mild conditions.

In 2016, Gu and coworkers developed a boron trifluoride-catalysed three-component Mannich-type reaction involving *o*-amino benzaldehyde **80**, ketone **81** and 2-methylindole **82**.[65] This reaction provided a straightforward route to diverse quinoline-fused 1-benzazepine derivatives **83** using a Lewis acid in acetonitrile solvent under mild conditions (Scheme 33). The key intermediate in this process was a previously unreported C,N-1,6-bisnucleophile, formed through an indole-to-quinoline transformation between *o*-aminobenzaldehyde and 2-methylindole. A variety of keto- or aldocarbonyl-containing compounds can serve as electrophiles to engage with this bisnucleophile, leading to a considerable enhancement in product diversity. Nevertheless, the reaction yields obtained were generally moderate in the majority of cases.

In 2017, our research group published a study presenting a straightforward and efficient method for synthesising various fused quinoline, benzoquinoline, and naphthoquinoline derivatives.[66] This method involved a one-pot three-component reaction using aryl amines **1**, aromatic aldehydes **5** and cyclic ketones **84**, with camphorsulfonic acid serving as the catalyst (Scheme 34). The protocol offered numerous advantages, including the use of a readily available and inexpensive catalyst, short reaction times, mild reaction conditions, easy isolation procedures, a wide range of applicable substrates, and



Scheme 33 Lewis acid-catalysed synthesis of fused quinoline.

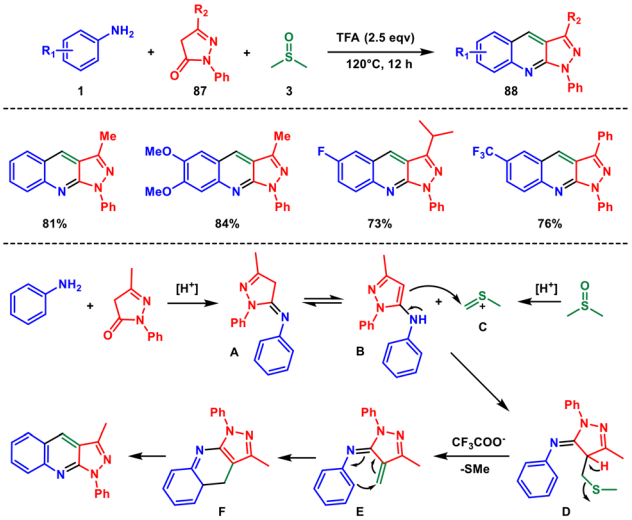


Scheme 34 (±)CSA-catalysed synthesis of quinoline derivatives.

an environmentally friendly approach with high atom efficiency. First, the cyclic ketone reacts with CSA to form an active intermediate which reacts with the imine formed from the aldehyde and ketone followed by an intramolecular Michael addition, and subsequent oxidation produces the desired product **85**. We also explored the application of pregnenolone acetate and terephthalaldehyde in the synthesis of steroid-substituted benzo[*f*]quinoline and bis-benzo[*f*]quinoline, respectively. These novel quinoline and benzoquinoline derivatives represented the first instances of their synthesis using camphorsulfonic acid as a catalyst.

In 2019 Sharma and coworkers developed a rapid microwave-assisted Povarov-type multicomponent synthesis of 4-aryl quinolines.[67] The reaction involves anilines **1**, alkynes **12** and paraformaldehyde **48** and proceeds through [4 + 2] cycloaddition of imine and alkynes in the presence of camphor sulphonic acid (CSA), without any metal catalyst. The Povarov reaction, which involves a [4 + 2] cycloaddition of imines and olefins, has traditionally been a highly anticipated method for producing substituted N-heterocycles (Scheme 35).[68] However, when it comes to the synthesis of 4-substituted quinolines, terminal alkynes and paraformaldehyde are seldom employed in Povarov-type reactions. Instead, inorganic Lewis acids are typically used to catalyze this reaction, while the potential of organic acids in this context remains largely unexplored.[69,70] The reaction proceeds through the formation of *in situ*-generated imine from condensation of aniline and paraformaldehyde. This imine then undergoes Povarov-type cyclisation with the alkyne, which on spontaneous oxidation yields the final product.

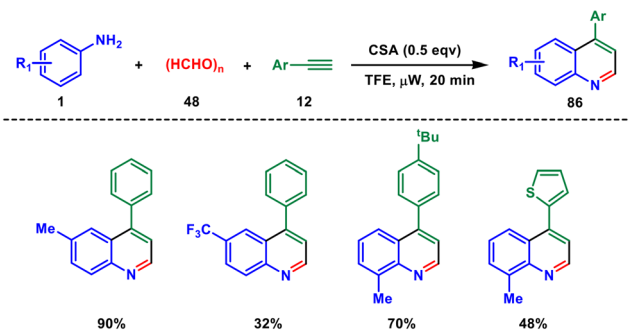
In 2021, Tiwari and colleagues presented a novel method for synthesising 3-substituted-1-aryl-1*H*-pyrazolo-[3,4-*b*]quinoline compounds using an acid-mediated and DMSO-assisted one-pot tandem synthesis.[71] This approach allows for the selective formation of these valuable heterocycles without the need for transition metals or oxidants, making it an environmentally friendly process. The reaction involves the use of various substituted aryl amines **1** and pyrazolones **87**, which undergo a cascade mechanism to produce a series of pyrazolo [4,3-*c*] quinolines **88**. This is the first example of DMSO activation in pyrazolone (Scheme 36). Here DMSO not only acts as a solvent but also serves as the source of methine to the quinoline moiety.



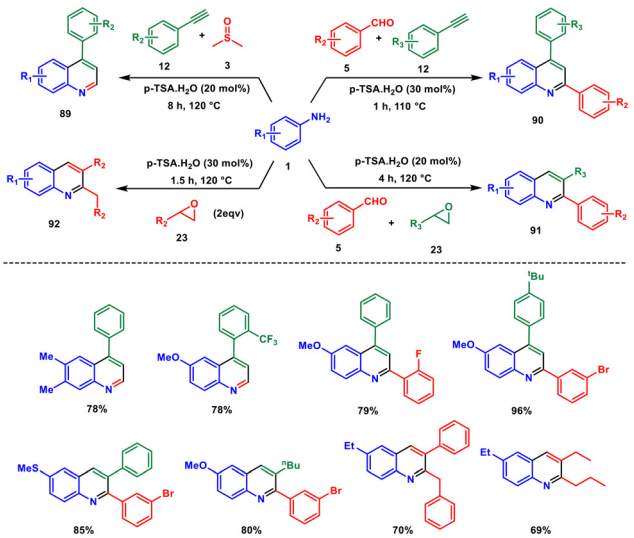
Scheme 36 TFA-catalysed synthesis of pyrazole quinoline using DMSO as a carbon source.

Initially the process begins with the condensation of aniline and pyrazolone in the presence of TFA, leading to the formation of an imine **A** that undergoes isomerization to a more stable pyrazole **B**. However, in the presence of acid, DMSO is activated and generates an electrophilic thionium ion **C** that reacts with pyrazole **B** to form an intermediate **D**. Through the elimination of CH_3SH, the intermediate **D** generates an azadiene intermediate **E**. This azadiene intermediate then undergoes annulation to produce an intermediate **F**, which ultimately undergoes aromatization to yield the desired product.

Recently our group has developed several three-component metal-free methods for the synthesis of differently substituted quinolines using *p*-TSA as catalyst. Firstly, we adopted a green and non-metallic approach to creating 4-arylquinoline **89** utilizing easily accessible arylamine **1**, arylacetylene **12** and DMSO **3** with 20 mol% *p*-TSA.[72] In this method, DMSO serves both as a reactant, contributing the C2 carbon atom to the quinoline structure, and as a solvent. Importantly, this process demonstrates high effectiveness and efficiency, all without requiring metal catalysts, ligands, co-catalysts as additives, or inert atmospheric conditions. Then, the synthesis of 2,4-diarylquinolines **90** was reported *via* a three-component reaction of arylamine **1**, aryl aldehyde **5** and aryl acetylene **12** under solvent-free conditions at a temperature of 110 °C, employing 30 mol% *p*-toluenesulfonic acid as catalyst.[73] Next, we developed a new eco-friendly method for producing 2,3-diarylquinolines **91** in a one-step process that combines arylamines **1**, benzaldehyde **5** and styrene oxide **23**.[74] The reaction takes place at 120 °C in the presence of 20 mol% *p*-TSA, eliminating the need for additional metal catalysts, additives, or oxidizing agents. Detailed investigations into the mechanism of the reaction established the vital function of *p*-TSA and demonstrated



Scheme 35 Microwave-promoted synthesis of 2-aryl quinoline.



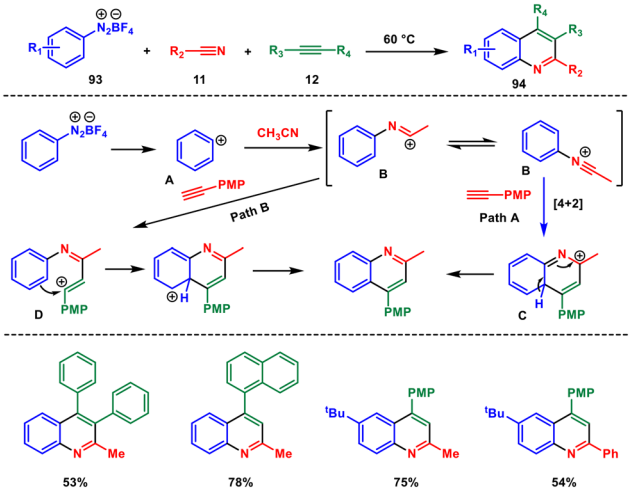
Scheme 37 *p*-TSA-catalysed multicomponent synthesis of various substituted quinolines.

that air serves as the exclusive oxidizing agent. Then, we documented a highly efficient method for creating 2-benzyl-3-arylquinoline **92** compounds. This synthesis involves using aryl amines **1** and styrene oxides **23** with the assistance of 20 mol% *p*-toluenesulfonic acid, all without the need for metals or solvents.[75] This process is achieved through a pseudo-three-component reaction. This is the first metal-free synthesis of 2-benzyl-3-phenylquinoline using aniline and styrene oxide derivative (Scheme 37).

4. Catalyst-free reactions

In traditional chemical reactions, catalysts are often used to speed up reactions or facilitate specific chemical transformations. However, catalyst-free organic transformations have gained significance as they are more environmentally friendly and cost efficient, and eliminate the need for potentially toxic or expensive catalysts, reducing waste and minimizing environmental impact. However, there are very few reactions that can occur without a catalyst. These reactions often rely on appropriate reaction conditions, such as temperature, concentration, and choice of solvent, to drive the desired chemical changes.

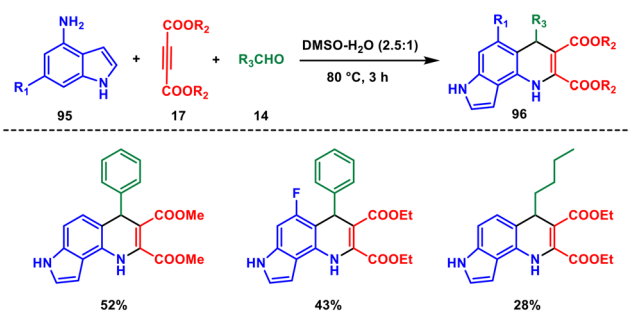
For instance, in 2017, Shen and Yu *et al.* published a study on a fast and effective method for synthesising multiple substituted quinolines.[76] This technique utilises a three-component cascade annulation process involving commonly available aryl diazonium salts **93**, nitriles **11**, and alkynes **12**. The reaction does not require any catalysts or additives (Scheme 38). A wide range of aryl diazonium salts, nitriles, and alkynes can be used in this process, resulting in yields of up to 83%. This environmentally friendly and cost-effective procedure holds great promise for the advancement of potential industrial applications.



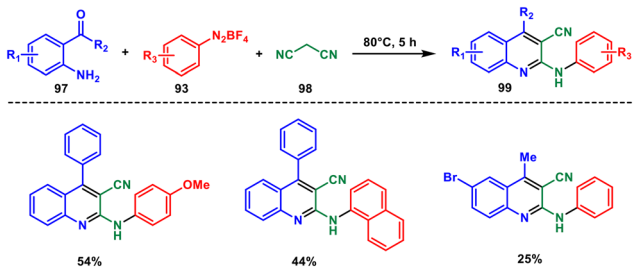
Scheme 38 Catalyst-free synthesis of quinoline using aryl diazonium salt as nitrogen source.

Mechanistically, upon heating the aryl diazonium salt undergoes decomposition, yielding the aryl cation **A** with concominant release of N_2 gas. Acetonitrile functions as a nucleophile, engaging with the aryl cation **A** to produce the nitrilium cation **B**. There are two potential routes for product formation. In pathway A, the nitrilium cation reacts with an alkyne through a concerted Diels–Alder reaction, leading to the formation of intermediate **C**. Subsequent deprotonation of the intermediate results in the corresponding product. Conversely, the same product can be formed through a stepwise process in pathway B. In this case, intermediate **B** is attacked by the alkyne, generating the vinyl cation **D**, followed by a Friedel–Crafts-type cyclization that ultimately yields the desired quinoline **94**.

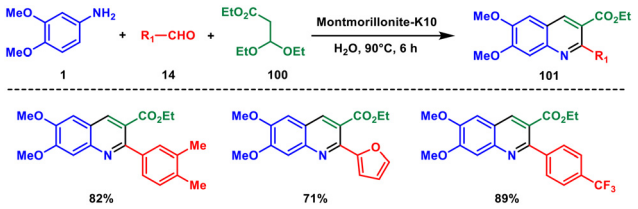
In 2020, Zhu and Liao introduced an effective and gentle catalyst-free three-component reaction for synthesising two novel series of dihydropyrrolo[2,3-*h*]quinolines with moderate to good yields.[77] The reaction employed readily available 4-aminoindoles **95**, but-2-ynedioates **17** and aldehydes **14** as starting materials, with water–DMSO mixtures serving as the solvent (Scheme 39). They showed that the ratio of water–DMSO mixtures played a crucial role and observed a synergistic



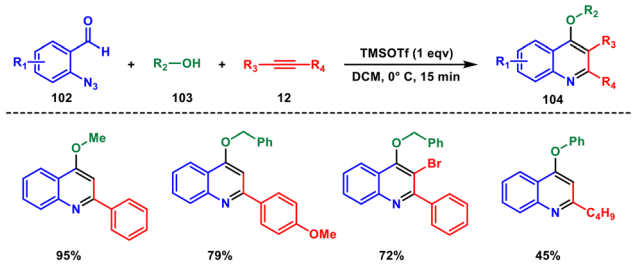
Scheme 39 Synthesis of dihydropyrrolo quinoline under catalyst-free conditions.



Scheme 40 Catalyst-free synthesis of 2-amino-3-cyano quinoline.



Scheme 41 Green synthesis of substituted quinoline using montmorillonite in water.



Scheme 42 Three-component synthesis of diversely substituted quinolines with TMSOTf.

effect of water and DMSO, as they formed hydrogen bonds and acted as proton donors and acceptors, respectively. This synergistic behaviour facilitated the smooth progress of the reaction, leading to fewer byproducts. This study represents the first investigation into the catalyst-free one-pot synthesis of pyrrolo[2,3-*h*]quinolines **96**. Furthermore, the dihydropyrrolo [2,3-*h*]quinoline ring could be nearly completely oxidized to the pyrrolo[2,3-*h*]quinoline ring at room temperature using Cu $(NO_3)_2$ as an oxidizing agent. Most organic reactions are conducted using different solvents, the intriguing synergistic promotion effect of water–DMSO observed in this study encourages the exploration of new solvent mixtures with similar effects, which attracts further theoretical research on solvent mixture synergistic promotion.

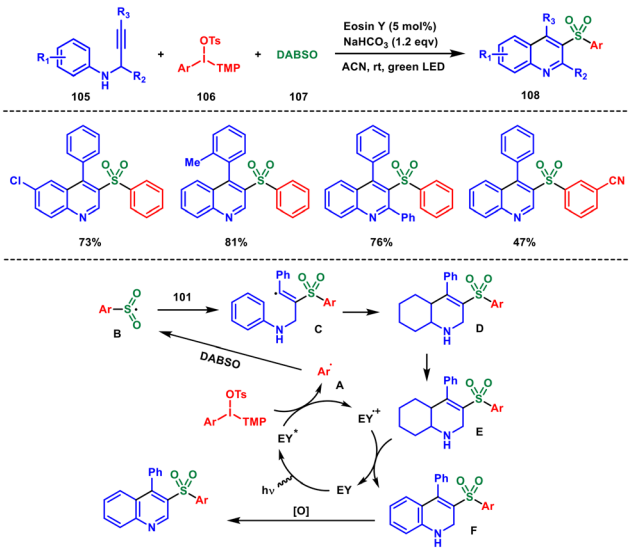
In 2020 Liu and coworkers developed a new method for the preparation of 2-amino-3-cyanoquinolines from readily available 2-aminoarylketones **97**, aryldiazonium salts **93** and malononitrile **98** *via* a cascade reaction.[78] The one-pot method described involves the formation of an *N*-arylnitrilium intermediate through the direct reaction of aryldiazonium salts and malononitrile (Scheme 40). This intermediate undergoes intermolecular amination, Knoevenagel condensation, and subsequent aromatization, resulting in the formation of the desired compound in moderate to good yields. This approach enables the rapid synthesis of quinolines with functional groups at positions C2 and C3.

5. Miscellaneous reactions

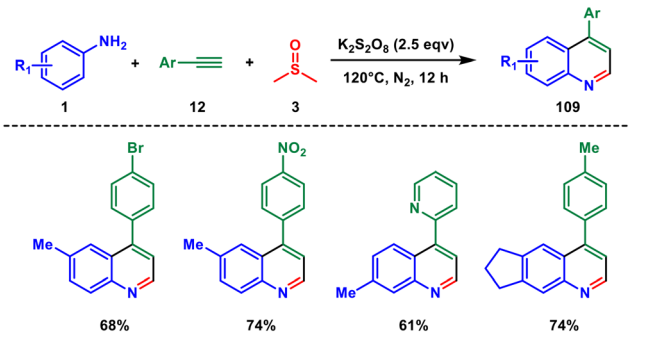
In 2012, Pal *et al.* achieved a direct one-pot synthesis of 2-substituted quinolines employing a 3-component reaction of aniline **1**, aldehydes **14** and ethyl 3,3-diethoxypropionate **100** in aqueous medium with oxygen from air.[79] Montmorillonite K-10 was identified as a green and reusable catalyst (Scheme 41). The reaction likely involves a Mannich reaction between an imine and 3-hydroxy acrylate, followed by intramolecular cyclization to produce a 1,2-dihydroquinoline intermediate. Subsequent oxidation using atmospheric oxygen yielded the desired product. This green approach holds promise for creating a diverse collection of 2-substituted quinoline-related molecules in an eco-friendly pathway.

In 2017, Gharpure and coworkers developed a metal-free, Lewis acid-mediated multisegment cascade coupling approach for the synthesis of diversely substituted quinolines using 2-azido benzaldehyde **102**, alcohol **103** and alkyne **12**.[80] The reaction proceeds *via* an oxonium ion-triggered alkyne carboamination sequence involving C–C and C–N bond formations to produce densely substituted 4-alkoxy quinolines **104** (Scheme 42). The versatility and practicality of this methodology were showcased through the post-functionalization of the obtained products, as well as its application in the synthesis of potent drug molecules. Furthermore, this high-yielding and straightforward technique exhibited excellent selectivity towards different functional groups, allowing for the synthesis of cyclic ether-fused quinolines and sugar-fused quinoline derivatives. They have also shown that the protocol gave a rapid access to biologically active natural products and drug molecules. Overall, this approach not only demonstrated efficient performance within a short timeframe but also allowed for sequential execution of multiple cascade reactions.

Considering the benefits of organophotocatalysed reactions compared with metal-based photocatalysts, Zhang and coworkers in 2018 reported a novel method for synthesising 3-arylsulfonylquinoline derivatives **108** using visible light with Eosin Y acting as the photocatalyst (Scheme 43). They used *N*-propargyl aromatic amines **105**, diaryliodonium salts **106** and sulfur dioxide **107** in this three-component synthesis allowing the formation of C–S bonds and quinolines in a single step.[81] The approach not only demonstrates high efficiency but also boasts excellent substrate scope and tolerance towards different functional groups. This protocol is particularly appealing for the utilization of easily manageable diaryliodonium salts, sulfur dioxide sources, and the cost-effective photocatalyst Eosin Y.



Scheme 43 Green LED-mediated synthesis of 3-arylsulfonyl quinoline using Eosin Y as photocatalyst.



Scheme 44 Synthesis of 2-aryl quinoline using DMSO as methine source.

To begin, the photocatalyst Eosin Y was activated by visible light, leading to the creation of Eosin Y*. Then it underwent oxidative quenching in conjunction with diaryliodonium salts, resulting in the formation of aryl radical **A** and Eosin Y^{+}. Following this, radical **A** engaged in a reaction with DABSO to produce another radical **B** which reacted with the *N*-propergyl amine, forming an alkenyl radical **C**. Subsequently, the alkenyl radical underwent an intramolecular cyclization process, giving rise to an aryl radical **D**. The deprotonation of radical **D** resulted in the formation of a radical anion **E**. This radical anion was then oxidized by Eosin Y^{+}, resulting in the production of the sulfonated compound 1,2-dihydroquinoline, labelled as **F**. Finally, compound **F** underwent a dehydro-aromatization reaction to yield the corresponding final product.

In 2018, Tiwari and coworkers introduced a transition-metal-free three-component cascade reaction using anilines **1** and alkynes **12**, along with potassium persulfate ($K_2S_2O_8$) in dimethyl sulfoxide (DMSO) for an environmentally friendly approach to synthesize 4-arylquinolines **109**.[82] They demonstrated that a wide range of alkynes and anilines with various substitution patterns could be successfully employed in this one-pot cascade process (Scheme 44). The use of DMSO as a carbon source in this methodology significantly improved atom efficiency and minimized environmental impact. Moreover, the authors expanded the synthetic applicability of this approach to the preparation of biologically significant compounds such as 4-aryl-2-morpholinoquinoline and 4-aryl-2-tosylquinoline.

In the future, the development of novel multicomponent reactions for quinoline synthesis could lead to more efficient and diverse routes to access quinoline derivatives. This could enable the rapid generation of structurally diverse compound libraries for drug discovery and materials science applications. Further optimization of MCRs for quinoline synthesis with an emphasis on sustainability and atom economy can contribute to the principles of green chemistry. Designing MCRs with minimal waste generation and environmentally benign reagents would be beneficial for large-scale production. Computational modelling and virtual screening approaches can help identify promising reaction pathways, predict reactivity, and optimize reaction conditions, thereby accelerating the development of efficient synthetic routes. Continued research efforts in these areas are essential to unlock the full potential of MCRs for the synthesis of quinoline derivatives with diverse properties and applications.

6. Conclusion

This review article describes various strategies for quinoline synthesis *via* multicomponent reaction. Different synthetic techniques based on catalyst, *viz.* (i) iron-catalysed, (ii) copper-catalysed, (iii) other metal-catalysed, (iv) iodine-catalysed, (v) acid-catalysed, and (vi) catalyst-free syntheses, are illustrated. The broad scope of multicomponent reactions allows for the incorporation of various starting materials, making them adaptable to the synthesis of diverse quinoline derivatives. As research in this field continues to advance, we can anticipate the development of new, more efficient, and selective multicomponent reactions for quinoline synthesis, further expanding the possibilities for their incorporation into complex molecule construction. Despite the promise offered by existing techniques, there exists an opportunity to explore new pathways in the field. This includes the pursuit of diversity-oriented synthesis and the creation of enriched quinoline structures using affordable starting materials and catalysts. Such endeavours lay the groundwork for the development of even more captivating methodologies within this field.

Conflicts of interest

The authors have no conflict of interest to declare.

Acknowledgements

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