REVIEW ARTICLE

Special Section on Transition Metal Catalyzed Synthesis of Medicinally Relevant Molecules

A review on transition-metal mediated synthesis of quinolines

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Abstract. Quinoline is one of the important class of heterocyclic compounds which have gained considerable importance because of its high pharmaceutical efficacy and broad range of biological activities such as anti-cancer, anti-malarial, anti-microbial and anti-asthmatic. As a consequence, the desire for new versatile and efficient route for the synthesis of quinoline scaffolds remains an active and growing area of interest both in academia and industry. However, developments of transition-metal catalyzed synthetic methods have witnessed a dominant position over the past few years for the synthesis of diverse range of complex heterocyclics containing quinoline scaffolds. This review specifically provides an overview of the literature available on the transition-metal catalyzed synthetic methodologies for the synthesis of polysubstituted quinoline derivatives.

Keywords. Heterocycles; quinolines; transition-metal catalyst; synthetic protocols; biological activities.

1. Introduction

Over the past few decades, heterocyclic compounds received remarkable attention for variety of reasons and notable amongst them are their bio-activity and their utility as drug molecule. Further, these are also known to occur in numerous functional molecules, natural products, organic materials and pharmaceuticals. Among heterocycles, quinoline scaffolds exhibit wide range of medicinal applications in the treatment of various types of diseases. Quinoline is an N-based six membered fused heterocyclic compound which also received significant attention in recent times¹ due to its wide range of applications particularly in industrial² and medicinal chemistry. Further, quinoline scaffolds play a significant role in drug discovery as their derivatives have been extensively applied as antimicrobial,³ anticancer,⁴ antimalarial,⁵ anti-inflammatory agents.⁶ Quinoline derivatives also find potential application as sensors,⁷ agrochemicals,⁸ luminescent materials⁹ and anti-foaming agents in refineries.¹⁰ Additionally, they are important constituents of several natural products with inherited medicinal properties.¹¹

2. Quinoline, a versatile biologically significant building block

2.1 Biologically active natural products containing quinoline scaffold

Quinoline heterocycles serve as main constituent of majority of natural products. For example, Transthorine (**1**) is a quinoline containing natural product extracted from the aerial parts of *Ephedra transitoria* and has been shown to inhibit bacterial growth of *Enterobacter cloacae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.¹² Cryptolepine (**2**) an indoloquinoline alkaloid has been applied to cure malaria.¹³ Quinine (**3**), a well-known anti-malarial drug is another significant molecule isolated from the bark of cinchona tree.¹⁴ On the other hand, Megistoquinone I (**6**) and Megistoquinone II (**7**) two potential antibacterial drugs are also belonging to alkaloids, an important class of natural product.¹⁵ Similarly, Skimmianine (**5**) is a very useful anti-inflammatory drug.¹⁶ Importantly, Streptonigrin (**8**) acting as scission between the DNA strands and lenvatinib (**4**) being a tyrosine-kinase inhibitor are also used as effective antitumour drugs as per literature records (Figure 1).¹⁷

2.2 Antimalarial activity

Most important application of quinoline based drugs is their efficiency in the treatment of malaria. Chloroquine (**9**), a 4-aminoquinoline derivative has been proved to be an effective medication for treatment of malaria.¹⁸ Subsequently; new

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Figure 1. Quinoline containing natural products.

Figure 2. Quinoline based antimalarial drugs.

drugs were developed with a hope to overcome the problem of drug resistance. In this context, Mefloquine (**10**) acting as blood schizonticide was introduced in 1970 and was considered as safe medicine by World Health Organization.¹⁹ Amodiaquine (**11**), quinidine (**12**), ablaquine (**13**), tafenoquine (**14**), primaquine (**15**) and sontaquine (**16**) are some other frequently used quinoline based antimalarial drugs (Figure 2).^{18,20}

2.3 Anticancer activity

Quinoline containing molecules have also been shown to possess potent anticancer properties. A few compounds with quinoline ring system displaying potential anti-cancer properties are shown in Figure 3. For example, Camptothecin (**17**) exhibits the property of topoisomerase inhibition. The

topoisomerase inhibition in this case is believed to be due to presence of planar pentacyclic ring structure. Irinotecan (**18**) is an another significant molecule useful for the treatment of colorectal cancer.^{21c} Topotecan (**19**) has known to apply for small lung cancer therapy by inhibiting the normal functioning of topoisomerase.^{21d} Cabozantinib (**20**) is known to treat medullary thyroid cancer^{21e} and renal cell carcinoma.^{21f} Exatecan (**21**) and TAS-103 (**22**) are some other quinoline based anticancer molecules (Figure 3).²²

2.4 Antimicrobial activity

Microbial infections pose a great danger in present day life and contribute a major factor for the increased mortality rate. Several drugs comprising quinoline moiety have been explored and developed as anti-microbial drugs during

Figure 3. Quinoline based anticancer drugs.

Figure 4. Quinoline containing antimicrobial drugs.

past decades. For example, Ciprofloxacin (**23**) and Norfloxacin (**29**), fluoroquinolone derivatives were developed as an effective antimicrobial drug and used for treatment of joint, respiratory and urinary tract infections.^{23a} It is often prescribed for polymicrobial infections involving clostridia. Sparfloxacin (**24**) is another commonly available drug used to treat community acquired acute sinusitis, chronic bronchitis and pneumonia.^{23b} However, other new drugs like levofloxacin (**25**), gatifloxacin (**26**) and moxifloxacin (**27**) also display excellent therapeutic activity for treatment of community acquired diseases.²⁴ Grepafloxacin (**28**), ofloxacin (**30**) and pefloxacin (**31**) are some other quinoline based antimicrobial drugs²⁵ (Figure 4).

3. Traditional routes for the synthesis of quinoline scaffolds

Due to widespread applications of quinoline, several classical approaches have been devised and well documented in the literature. The important amongst them are (i) Knorr (ii) Friedlander (iii) Skraup (iv) Combes (v) Doebner-von Miller (vi) Pfitzinger and (vii) Conrad-Limpach synthesis. These traditional methods have been utilized for long time to generate quinoline scaffolds through the reaction schemes as outlined in Figure 5. Although all these reported literature methods were

Figure 5. Traditional routes for the synthesis of quinolines.

highly appreciable as they provided infinite access to libraries of lead candidates but most approaches are plagued with disadvantages such as use of acid or hazardous catalysts, extreme reaction conditions and tedious work up procedures. Thus, over the years researchers tried to circumvent these problems and in this context, extensive efforts have been made by them by innovating new and efficient routes for organic transformations to access diversified quinoline scaffolds. As a consequence, development of new routes either through modification of the known methods or by employing transition-metal supported coupling reaction, or *via* multi-component approaches are amongst the prominent ones finding mention in the literature.

On the other hand, transition-metal catalyzed synthetic methods have witnessed a dominant position in the past decades in organic and medicinal chemistry especially for the synthesis of complex quinoline based heterocycles. Transition metal and their complexes are very attractive due to their appealing catalytic ability to generate lead drug candidates. They have created an edge over the traditional synthetic route as they aid in construction of complex compound libraries from readily available starting materials. These metals and their complexes can act as an alternative to more costly and hazardous catalysts for the preparation of quinoline based therapeutic molecules from the easily available materials.²⁶

Based on above mentioned therapeutic potential of quinoline scaffolds, many reviews on synthesis²⁷ and biological activities^{20,22,23,25,28} of quinoline based molecules have been documented in the literature during the past few years. Further, considerable efforts have been devoted for the preparation of these scaffolds during past few years using readily available transition metal salts and their complexes. However, till date there is no review reported which exclusively deals with transition metal catalyzed routes for the synthesis of substituted quinoline derivatives. In view of our interest in quinoline heterocycles²⁹ herein we aim to focus particularly on the comprehensive literature compilation of transition-metal based synthetic strategies devoted for the synthesis of quinoline scaffolds.

4. Various approaches for the synthesis of quinolines and their derivatives using transition-metal catalysis

A convenient and efficient protocol was developed by Zhong *et al.*, for the synthesis of series of 2,4-disubstituted quinolines (**34**) in moderate to good yields *via* iron-catalyzed reaction of arylhydrazones (**32**) with geminal-substituted vinyl acetates (**33**) (Scheme 1). Based on the initial investigation it was proposed that the

Scheme 1. Iron-catalyzed synthesis of 2,4-disubstituted quinolines. **Scheme 2.** Cu catalyzed synthesis of polysubstituted quinolines under aerobic condition. **Scheme 3.** Tandem oxidative cyclization route to substituted quinolines. **Scheme 5.** Palladium catalyzed synthesis of 3-phenylquinolines.

reaction proceeds through intermolecular [4+2] cyclization reaction directed by C-H activation. Further the developed protocol showed good functional group tolerance.³⁰

Yan *et al.*, has demonstrated copper-catalyzed one pot, simple, and efficient strategy for the synthesis of substituted quinolines (**34**) (Scheme 2).³¹ The method involves the reaction of anilines (**35**) and aldehydes (**36**) and proceeded initially *via* C-H functionalization followed by the construction of C-N/C-C bond, and cleavage of C-C bond. In this study, molecular oxygen was employed as an oxidant which makes this process a convenient and economical approach.

A modified one-pot Cu-catalyzed tandem aerobic oxidative cyclization procedure has been disclosed by Pang *et al.*, which allows the preparation of polysubstituted quinolines (**39**) from 2-vinylanilines/2-arylanilines (**37**) and 2-methylquinolines *via* C(sp³)-H/C(sp²)-H (**38**) bond functionalization by using dioxygen as oxidant (Scheme 3). Further, the protocol was successfully extended with 2-methyl-1,2,3,4-tetrahydroquinoline to deliver desired products in moderate yields.³²

Mondal *et al.*, has disclosed an unprecedented solvent free, CuBr-ZnI₂ combo-catalyzed Cu^I – Cu^{III} switching

strategy to generate substituted quinolines through sp² C-H activation of highly electron-rich arenes. In this protocol, substituted aniline (**35**), aldehydes (**41**), and terminal alkynes (**40**) were rapidly coupled to generate the desired quinoline (**42**) framework through cyclization of the c≡c bond (Scheme 4). Further, the developed methodology was efficiently utilized for the synthesis of valuable 4-substituted, 2, 4-disubstituted, and sugar-based chiral quinolines in good yields.³³

A novel, one-pot aerobic strategy with a broad substrate scope was introduced by Luo *et al.*, to deliver 3-phenylquinolines (**34**) from azides (**43**) and aldehydes (**36**) using 10% PdCl₂ in DMSO *via* C-H functionalisation and C-C bond cleavage followed by formation of one C-N and two C-C bonds (Scheme 5).³⁴

One-pot synthesis of quinolines was established by Nikolaev *et al.*, *via* cross-coupling of unprotected *ortho*-bromoanilines (**44**) with a wide range of cyclopropanols (**45**) (Scheme 6). They further demonstrated that the reaction proceeded in a single operation *via* intramolecular condensation and palladium-catalyzed oxidation sequence to afford the desired product (**46**).³⁵

A Palladium-catalyzed one-pot, controlled and efficient protocol leading to the construction of quinoline

Scheme 4. CuBr-ZnI₂ combo-catalyzed synthesis of quinolines *via* C-H activation.

Scheme 6. Construction of quinolines *via* cross coupling of *o*-bromoanilines and cyclopropanols.

derivatives (50) was reported by Selvakumar *et al.* The method proceeded *via* Heck reaction followed by cyclization of (het) aryl-substituted Morita–Baylis–Hillman (MBH) adducts (47) (Scheme 7) with 2-iodoaniline (48). In this reaction, the MBH adducts initially convert into α -benzyl β -keto ester derivatives (49) which finally undergoes cyclization to deliver desired quinolines in good yield.³⁶

A domino approach has been developed by Gao *et al.* (Scheme 8).³⁷ In this protocol benzimidoyl chlorides (51) undergoes reaction with 1,6-enynes (52) to form alkynyl amidine (53) which subsequently afford the desired quinolines motifs (54). The reaction proceeded through palladium catalyzed Sonogashira coupling to give good yield under mild reaction conditions utilizing easily accessible raw material.

Liu *et al.* has developed an effective, regioselective and robust route to afford series of 4-halo-2-aminoquinolines in moderate to excellent yields (47–94%) (57) through oxidative cyclization of easily accessible 2-ethynylanilines (55) with isocyanides (56) by Palladium (Scheme 9). Further, this strategy have been successfully used to generate diverse 6*H*-Indolo [2, 3-*b*] quinolines.³⁸

Straightforward benzylation approach has been developed by Tan *et al.*, to access β -benzylated quinoline (59)

Scheme 9. Regioselective synthesis of aminoquinolines through oxidative cyclization.

from 1,2,3,4-tetrahydroquinolines (58) and aryl aldehydes (41). This cross-coupling strategy employed the use of readily available [RuCl₂ (p-cymene)]₂ as a catalyst and O₂ as a green oxidant (Scheme 10). In this protocol it was proposed that reaction proceeded in a mono-dehydrogenation-triggered benzylation mode.³⁹

An improved, economical and highly-efficient palladium-catalyzed strategy for the construction of 3-aryl-2-aminoquinolines (62) from *gem*-dibromovinylanilines (60), tert-butyl isocyanide and arylboronic acids (61) was reported by Huet *et al.* (Scheme 11). This strategy initially involves insertion of isocyanide and then *gem*-dibromovinylanilines which finally undergoes reaction with arylboronic acids *via* Suzuki coupling to produce the suitably substituted quinoline.⁴⁰

Fe(acac)₃/TBAOH catalyzed multi-component approach was introduced by Patil *et al.*, for the synthesis of aminoindolizines and quinoline derivatives (64) *via* coupling-cycloisomerization reaction of amines (35), aldehydes (63) and terminal alkynes (40) (Scheme 12). The advantage of the methodology is its applicability to generate a diverse range of heterocyclic compounds.⁴¹

A solvent-free, one-pot, and environment-friendly synthesis of 2,4-disubstituted quinolines (67) was achieved by Baltork *et al.*, by the reaction of differently substituted 2-aminoaryl ketones (65) with range of arylacetylenes (66) utilizing K₃CoW₁₂O₄₀·3H₂O as catalyst

Scheme 7. Pd (OAc)₂-catalyzed synthesis of 2, 3-disubstituted quinolines from Morita–Baylis–Hillman (MBH) adducts.

Scheme 8. Domino approach to quinoline derivatives through Sonogashira coupling.

Scheme 10. Ruthenium catalyzed synthesis of β -benzylated quinolines. **Scheme 11.** Cascade synthesis of 3-aryl-2-aminoquinolines using Palladium catalyst. **Scheme 12.** Multi-component coupling-cycloisomerization route to quinoline derivatives. **Scheme 13.** Microwave promoted synthesis of 2,4-disubstituted quinolines. **Scheme 15.** Tandem approach for the synthesis of quinoline-2-carboxylates. **Scheme 16.** Copper catalyzed synthesis of quinolines *via* C-N and C-C bonds formation. **Scheme 17.** Iron mediated oxidative coupling route for the generation of quinoline derivatives.

under microwave irradiation. The important features of this protocol are the use of microwave technology, environmentally benign catalytic system, reusability of catalysts, and no use of solvent (Scheme 13).⁴²

Huma *et al.*, has developed a CuCl catalyzed one-pot approach by the reaction of substituted aryl aldehyde (41), aryl amine (35) and a terminal alkyne (40) to generate 2,4-disubstituted quinolines (42) in good yield (Scheme 14).⁴³

A copper-catalyzed, cost effective, efficient and convenient route has been established by Huang *et al.* for the preparation of varied quinoline-2-carboxylates (69) under ambient condition. It was proposed that the reaction occurred through intermolecular addition of alkynes (40) into imines (68) followed by intramolecular ring closure to give the desired products. (Scheme

15). Further, the method is compatible with range of functional groups to give the products in good yield.⁴⁴

Zeing and co-workers demonstrated a novel route for generating quinolines (71) in good yields under aerobic conditions. In this copper-catalyzed cascade synthetic route, anilines (35) and terminal acetylene esters (70) undergo transformation *via* formation of C-N and C-C bonds. (Scheme 16).⁴⁵

Liu *et al.*, has demonstrated a simple and efficient Fe-catalyzed oxidative coupling route for the synthesis of substituted quinoline (42). In this protocol N-alkyl anilines (72) undergoes reaction with alkynes (40) or alkenes (73). The cheap, easily available and environmentally benign iron was effectively used in presence of oxidant under mild conditions (Scheme 17).⁴⁶

Scheme 14. CuCl catalyzed one-pot preparation of 2,4-disubstituted quinolines.

Scheme 18. AgOTf-catalyzed synthesis of 2-substituted quinolines.

AgOTf-catalyzed, simple, cost-effective and atom-efficient pathway has been established by Xu *et al.* (Scheme 18). In this protocol construction of 2-substituted quinolines (**76**) was successfully done by the reaction of 2-aminobenzyl alcohol (**74**) and alkyne (**75**)/ketone. Similarly 2-aminophenethyl alcohol and aldehyde can also undergo reaction under this protocol to generate the desired products in moderate to excellent yield. Further the method is efficient with both electron-withdrawing and electron-releasing groups on aldehydes, ketones and alkynes.⁴⁷

An improved methodology for the preparation of quinolines derivatives (**79**) and quinolones (**80**) was reported by Maizuru *et al.*, in which readily available benzoxazinones (**77**) react with alkynes (**78**) to afford substituted quinolines or quinolones *via* nickel-catalyzed cycloaddition (Scheme 19).⁴⁸

Nickel-catalyzed simple, convenient and efficient method leading to the formation of disubstituted quinolines (**42**) was demonstrated by Korivi *et al.* (Scheme 20). In this study, 2-iodoanilines (**81**) undergoes cyclization with alkynyl aryl ketones (**82**) to deliver desired products in good yields. The protocol tolerates a broad range of functional group by utilizing inexpensive catalyst.⁴⁹

A Zinc(II) triflate catalyzed solvent-free, atom-economic, multi-component approach was demonstrated by Sarode *et al.*, for the preparation of substituted quinolines (**42**) (Scheme 21) by the reaction of amines (**35**), alkynes (**40**) and aldehydes (**41**) in an ambient atmosphere. Further, the protocol works under mild reaction conditions and avoids the use of toxic solvents and expensive metals.⁵⁰

Zheng *et al.*, has developed a new regioselective approach to construct 2, 3-disubstituted quinolines (**85**)

Scheme 20. Nickel-catalyzed preparation of substituted quinolines.

Scheme 21. Zn (OTf)₂ catalyzed preparation of 2,4-disubstituted quinolines.

via Pd-catalyzed intermolecular oxidative cyclization of *o*-vinylanilines (**83**) and alkynes (**84**) assisted with Cu and O₂ (Scheme 22). This transformation was supposed to proceed through sequential intermolecular amination of alkyne, olefin insertion, followed by aerobic cleavage of C-C bond.⁵¹

A Rh (III) catalyzed simple, regioselective and atom-economic approach has been developed by Song *et al.* for the synthesis of quinolines (**87**) using Cu (OAc)₂ as oxidant (Scheme 23). The reaction involves oxidative annulation of pyridine (**86**) with two alkyne molecules to give excellent yield. The reaction worked well with variety of pyridines to generate diverse quinolines.⁵²

A ruthenium-catalyzed one-pot domino protocol based on [3 + 3] annulation of anilines (**35**) with varied allyl alcohols (**88**) was introduced by Kumar *et al.*, for the synthesis of quinolines (**89**) (Scheme 24). In this reaction, a transient directing group strategy utilizing ruthenium-catalyzed C-H bond activation was used to deliver the required product.⁵³

A range of substituted quinolines (**46**) were synthesized using the palladium-catalyzed oxidative cyclization of aryl allyl alcohols (**90**) and anilines (**35**) by Xu and colleagues (Scheme 25). This process works well without the use of acid, base or any additive to deliver satisfactorily yield of products. Additionally, the demonstrated method offers broad substrate scope and

Scheme 19. Nickel-catalyzed formation of quinolines and quinolones.

Scheme 22. Aerobic annulation of *o*-vinylanilines and alkynes to synthesize 2,3-disubstituted quinolines.

Scheme 23. Cascade synthesis of quinolines using Rh (III) catalyst and Cu (OAc)₂ oxidant.

Scheme 24. Ruthenium-catalyzed domino synthesis of quinolines.

Scheme 25. Palladium-catalyzed synthesis of quinoline derivatives.

high tolerance of electron-withdrawing group such as fluorine, trifluoromethyl and nitril.⁵⁴

Mastalir and his colleagues presented a new approach for the regioselective synthesis of quinoline derivatives (93) using combinations of 2-aminobenzyl alcohols (91)

and secondary alcohols (92) in presence of hydride Mn (I) PNP pincer complex as catalyst (Scheme 26). It was observed that the reaction proceeded through sequence of dehydrogenation and condensation steps in excellent yields. Further, the disclosed methodology was eco-friendly, atom-efficient, sustainable and showed wide range of functional group tolerance.⁵⁵

Wang and co-workers introduced a novel approach to generate range of substituted quinolines based on acceptor less dehydrogenative cyclization in water. In this strategy, a water soluble [Cp*Ir (6,6'-(OH)₂bpy)(H₂O)] [OTf]₂ was utilized for the cyclization of *o*-aminobenzyl alcohols (94) with ketones (95) yielding quinolines (46) *via* acceptor less dehydrogenative cyclization (Scheme 27). Further, no side-product was observed by the self-condensation of *o*-aminobenzaldehyde akin to that of traditional Friedlander protocol.⁵⁶

Chen *et al.*, has introduced a [Ir Cp*Cl₂]₂/KOH catalyzed synthesis of quinolines (98) (Scheme 28) in moderate to good yields. This tandem approach involves the isomerisation/cyclization reaction of allylic alcohols (97) with 2-aminobenzyl alcohol (96). The reaction was successful with both the primary and secondary allylic alcohols to afford differently substituted quinolines.⁵⁷

A one-pot, simple, facile synthesis of quinolines (99) using bifunctional Ru-grafted hydrotalcite catalyst *via* aerobic oxidation condition and aldol reaction was

Scheme 26. Synthesis of quinoline derivatives using Mn (I) PNP pincer complex catalyst.

Scheme 27. Iridium-bifunctional catalyzed synthesis of quinolines *via* acceptorless dehydrogenative cyclization.

Scheme 28. [Ir Cp*Cl₂]₂/KOH catalyzed formation of quinoline derivatives.

Scheme 29. Ru-grafted hydrotalcite catalyzed synthesis of quinolines.

Scheme 30. Modified Friedlander protocol for the synthesis of quinoline derivatives.

Scheme 31. Ruthenium catalyzed cascade synthesis of quinolines.

developed by Motukura and co-workers. In this reaction, 2-aminobenzyl alcohol (**75**) was made to react with range of carbonyl compounds (**95**) to deliver varied quinoline (Scheme 29). Further, the method was successfully extended with α , β -unsaturated nitriles, ketones and aldehydes to generate diverse quinoline derivatives.⁵⁸

A ruthenium-catalyzed modified Friedlander synthesis of quinoline *via* oxidative cyclization of 2-aminobenzyl alcohol (**75**) with different ketones (**100**) was introduced by Cho *et al.* (Scheme 30). Under this protocol the reaction was carried out in dioxane at 80 °C using catalytic amount of ruthenium and KOH to afford high yield of the desired quinolines (**101**).⁵⁹

A [Ru (PPh₃)₃Cl₂]-catalyzed new and an efficient strategy for the synthesis of quinoline (**103**) based on modified Friedlander annulations of 2-nitrobenzaldehydes (**102**) with alcohols (**92**) was developed by Li *et*

Scheme 33. Cu(OTf)₂ modified Friedlander approach to quinolines.

al. (Scheme 31). Both these substrates which are hitherto un-reactive were initially converted to the reactive moieties *via* a hydrogen transfer reaction. The catalyst serves the dual role of catalyzing both the transfer hydrogen reaction and Friedlander annulation.⁶⁰

An inexpensive, sustainable and air-stable, combo CuSO₄-D-glucose catalyst system was developed by Anand and colleagues for the synthesis of functionalized quinoline *via* modified Friedlander approach (Scheme 32). The developed route was based on the domino multi-component approach which directly leads to the construction of substituted quinolines (**105**) from 2-bromoaromatic aldehydes/ketones (**104**) using H₂O-EtOH as green solvent. Further, the reaction was successfully extended for gram scale synthesis of quinoline derivatives.⁶¹

A solvent-free approach for the preparation of quinolines (**93**) was disclosed by Soleimani *et al.* (Scheme 33). In this approach, 2-aminoaryl ketones (**106**) undergoes Friedlander annulations with α -methylene ketones (**95**) using catalytic amount of Cu (OTf)₂ at room temperature to afford wide range of quinolines and poly-substituted quinolines. Further the developed methodology avoided the use of both harsh conditions and hazardous acids or bases.⁶²

Modified Friedlander synthesis of quinolines (**108**) was achieved by Cho and co-workers by using copper and KOH with either PEG 2000 or MS 4A *via* oxidation of 2-aminobenzyl alcohol (**75**) followed by coupling and cyclization with a wide range of ketones/secondary alcohols (**107**) under O₂ atmosphere (Scheme 34). The advantage of this protocol is reusability of catalyst as it can be reused for 10 times without appreciable loss in its activity.⁶³

A ruthenium based catalyzed new and improved pathway for the synthesis of quinolines was established by Mierde *et al.*, through modified Friedlander condensation. In this method, 2-aminobenzyl alcohol (**75**)

Scheme 32. Domino synthesis of quinoline derivatives using CuSO₄-D-glucose catalyst.

Scheme 34. Copper catalyzed preparation of quinoline derivatives.

Scheme 35. Ruthenium catalyzed synthesis of quinolines from ketones and 2-aminobenzyl alcohol.

Scheme 36. Palladium-KOH catalyzed synthesis of quinoline derivatives under aerobic conditions.

Scheme 37. CuCl₂ and KOH catalyzed synthesis of quinoline derivatives.

undergoes oxidative cyclization with ketone (**95**) in presence of second generation Grubb's catalyst and its analogues at 80 °C to afford desired quinolines (**99**) in good yields (Scheme 35).⁶⁴

A modified Friedlander synthesis catalyzed by Palladium-KOH was disclosed by Cho and colleagues to afford the desired quinolines (**101**) from 2-aminobenzyl alcohol (**75**) and ketones (**100**) at 100 °C under aerobic conditions (Scheme 36). The advantage of this process is use of recyclable catalyst which can be used up to five times without any loss of activity.⁶⁵

A simple and cost-effective protocol was demonstrated for the synthesis of quinolines derivatives (**101**) by the reaction of 2-aminobenzyl alcohol (**75**) and aldehydes (**100**)/ketones in dioxane at 100 °C under oxygen atmosphere in presence of CuCl₂ and KOH as efficient catalytic system. The reaction proceeded through oxidative coupling and cyclization with range of aldehydes and ketones under oxygen atmosphere (Scheme 37).⁶⁶

A recyclable yttrium triflate catalyzed mild and highly efficient, one-pot methodology was introduced by De *et al.* (Scheme 38). In this method, 2-aminoaryl ketones (**110**) undergoes reaction with α -methylene ketones (**95**) via Friedlander annulations at ambient temperature to form the desired quinolines (**111**) in excellent yields.⁶⁷

Scheme 38. One-pot approach to quinolines using Y(OTf)₃ catalyst.

Scheme 39. Oxidative coupling of 2-aminobenzyl alcohol and ketones for synthesis of quinolines.

Scheme 40. RhCl(PPh₃)₃ and KOH catalyzed synthesis of quinolines.

Scheme 41. [IrCl(cod)₂]/IrCl₃ catalyzed synthesis of quinolines under neat condition.

To the various modification introduced in the Friedlander synthesis for the generation of quinolines (Scheme 39), another Pd/C together with KOH catalyzed modification leading to the desired quinolines (**101**) from 2-aminobenzyl alcohol (**75**) and ketones (**100**) in dioxane at 100 °C was introduced.⁶⁸

Another modification in the Friedlander synthesis using RhCl(PPh₃)₃ and KOH as catalyst was reported by Cho and colleagues. In this process 2-aminobenzyl alcohol (**75**) initially undergoes oxidation to give *o*-aminobenzaldehyde which subsequently undergoes cross aldol reaction with a wide variety of ketones (**100**) followed by dehydration to afford the corresponding quinolines (**101**) in moderate to good yields (Scheme 40).⁶⁹

Another modification of the Friedlander synthesis was reported by Taguchi *et al.*, producing suitably substituted quinolines (**101**). In this protocol 2-aminobenzyl alcohol (**75**) undergoes reaction with 2-equivalent of ketones (**100**) utilizing catalytic amount of [IrCl(cod)₂] or IrCl₃ and KOH without using any solvent (Scheme 41). Further, the catalyst was effectively utilized for the synthesis of pyrrole.⁷⁰

An improved variant of Friedlander pathway was demonstrated by McNaughton *et al.*, for the synthesis of quinolines (**46**) directly from *o*-nitrobenzaldehyde

Scheme 42. SnCl_2 and ZnCl_2 catalyzed Friedlander synthesis of quinolines from *o*-nitrobenzaldehyde.

Scheme 43. Ruthenium catalyzed synthesis of 2- and 3-substituted quinolines.

Scheme 44. Niobium phosphate catalyzed Skraup synthesis of quinoline derivatives.

(112) and carbonyl compound (113) thus obviating the requirement of isolation and purification of *o*-aminobenzaldehyde (Scheme 42). This high-yielding process utilizes SnCl_2 and ZnCl_2 as a mild and efficient catalytic system.⁷¹

Ruthenium catalyzed straightforward approach was explored *via* single step cyclocondensation of anilines (35) with 1,3-diols (114) for the generation of substituted quinolines (115) as shown in (Scheme 43). The reaction was performed by employing catalytic amounts of $\text{RuCl}_3 \cdot x\text{H}_2\text{O}$, PBU_3 and $\text{MgBr}_2 \cdot \text{OEt}_2$ to generate variety of 2- and 3-substituted quinolines and only water and dihydrogen was obtained as by-products under this protocol. Further, it was believed that 1,3-diol initially undergoes dehydrogenation to form 3-hydroxyaldehyde which subsequently loses water molecule to form α , β -unsaturated aldehyde which finally undergoes reaction with aniline to give the desired product.⁷²

Niobium phosphate catalyzed modified Skraup synthesis was introduced by Jing *et al.*, resulting in synthesis of quinolines (117) *via* continuous reaction of solketal (116) with varied aromatic amines (35) (Scheme 44). Further, the method which worked at 250 °C and 10 MPa

Scheme 46. Cu-catalyzed regioselective synthesis of 2-arylthio quinolines.

Scheme 47. Cu catalyzed one-pot synthesis of 3-keto quinolines.

pressure was successfully applied to get both mono- and bis-quinoline.⁷³

An improved Rhodium catalyzed two-component synthesis of quinolines (120) in basic medium was devised (Scheme 45). This modified reaction was complementary in regioselectivity to the conventional Skraup-Doebner-Von Miller synthetic mode and exhibit the reaction between α , β -unsaturated ketones (119) and *o*-aminophenylboronic acid derivatives (118).⁷⁴

A regioselective Cu-catalyzed multi-component cascade cyclization reaction for the synthesis of pharmaceutically important 2-arylthio quinolines (123) was demonstrated by Khan *et al.* (Scheme 46). The reaction proceeded *via* intermolecular annulation of aryl isothiocyanates (121), alkynes (79) and iodonium salts (122) to give diversely functionalized quinolones in good to excellent yield. Further, the developed protocol showed great tolerance towards varied functional group.⁷⁵

Tiwari *et al.*, have demonstrated an efficient, one-pot approach to synthesize substituted quinolines (126) from easily accessible saturated ketones (124) with anthranils (125) (Scheme 47). In this one-pot, atom-economic cascade reaction, copper catalyzed dehydrogenation of saturated ketones lead to the in situ generation of α , β -unsaturated ketones which is then made to react with the anthranils producing quinolines through aza-Michael addition *via* amination followed by annulation.⁷⁶

A copper or palladium catalyzed, oxidative cyclization of aromatic enamines (127) with alkynes or alkenes

Scheme 45. Rh-catalyzed synthesis of quinolines in basic medium.

Scheme 48. Dual transition metal-visible light photo-redox catalyzed synthesis of multisubstituted quinolines.

Scheme 49. CuOTf catalyzed cascade synthesis of quinolines.

Scheme 52. Copper catalyzed synthesis of 4-carboxyl quinolines.

Scheme 50. Palladium catalyzed synthesis of quinoline derivatives.

under mild conditions was described by Xia and co-workers. This transformation was preceded by dual transition metal-visible light photo-redox catalyzed process in presence of dioxygen as an oxygen source to furnish multisubstituted quinoline derivatives (**128,131**) (Scheme 48). Following this approach, quinolines have been accessed in good to moderate yields through sequential formation of C-C and C-O bonds. This approach was further extended to the amino alkynes (**129**) for intermolecular oxidative cyclization with alkynes (**130**).⁷⁷

Chi *et al.*, investigated cascade synthesis of quinolines by [2+2+2] and [4+2] annulation reactions of heterocumulenes (**133**), alkynes (**79**), and diaryliodonium salts (**132**). The overall process is accomplished by using CuOTf as catalyst for generating final products in good yield with excellent selectivity (Scheme 49). This protocol also provides a new route to activate heterocumulenes by a unique highly reactive cationic intermediate.⁷⁸

Menoyo *et al.*, introduced palladium catalyzed intramolecular C-H alkenylation strategy for the preparation of quinolines (**137**) and 1, 2-dihydroquinolines (**136**) (Scheme 50). The proposed atom-economic dehydrogenative coupling leads to selective synthesis of quinolines in moderate to good yields.⁷⁹

A series of polysubstituted quinolines (**141,142**) were easily prepared from anilines (**138**), aldehydes (**41**) and alcohols (**139,140**) under mild conditions *via* sequential formation of two C-C bonds (Scheme 51). The utility of

Scheme 51. Silver catalyzed synthesis of polysubstituted quinolines.

Scheme 53. Copper catalyzed synthesis of 2-trifluoromethylquinolines.

Scheme 54. Silver catalyzed one-pot synthesis of quinolines.

Scheme 56. Rh-catalyzed construction of quinolines.

this reaction lies in the broad range of substrates including aliphatic alcohols, aryl alkanols, cycloalkanols, and ethylene glycol thereby generating a wide variety of products.⁸⁰

A much improved spectacular example of multisubstituted 4-carboxyl quinoline's (**145**) preparation using copper catalyst was presented (Scheme 52). In this alkyne metathesis cascade reaction, alkyne serves as a di-functional unit forming one C=N and one C=C bond on each carbon with azide (**143**) and diazo (**143**) groups respectively and giving the requisite product in excellent yields.⁸¹

Intramolecular oxidative cyclization of N-(2-alkenylaryl) enamines (**146**), in presence of copper leads to the generation of 2-trifluoromethylquinolines (**147(a)** and **147(b)**) via domino intramolecular oxidative cyclization (Scheme 53).⁸²

Another interesting atom-economic silver catalyzed approach was described. This process involved construction of polysubstituted quinolines (**150**) from arylamines (**148**), aldehydes (**149**), and ketones (**100**) or arylamines and 1, 3-diketones (Scheme 54). This strategy provides a straightforward eco-friendly route to synthesize complex quinoline moieties from readily available starting materials.⁸³

A range of differently substituted quinolines (**153**) were prepared from glycine esters (**151**) and simple alkenes (**152**) via aerobic oxidative dehydrogenative coupling/aromatization using visible-light (Scheme 55).

Scheme 57. Synthesis of 1,2,3,4-tetrahydroquinolines using cobalt oxide catalyst.

This simple and convenient reaction proceeds with the capability of wide substrate tolerance.⁸⁴

An elegant Rh-catalyzed hydroacylative addition of aldehydes (**41**) and *o*-alkynyl anilines (**154**) leading to 2-aminophenyl enones and finally to substituted quinolines (**155**) was described by Neuhaus and co-workers (Scheme 56). This methodology has the advantage of high functional group tolerance thus allowing rapid synthesis of libraries of diversely substituted quinoline architectures.⁸⁵

Aerobic dehydrogenation of 1,2,3,4-tetrahydroquinolines (**156**), using heterogeneous cobalt oxide catalyst enabled an efficient route for the generation of corresponding quinolines (**157**) under mild conditions (Scheme 57). Application of Co₃O₄ catalyst further aids in aerobic dehydrogenation process.⁸⁶

Kong *et al.*, devised a copper-catalyzed methodology generating a wide array of functionalised quinolines (**159**) through intermolecular Ullmann-type electrocyclization reaction. For this purpose, *o*-acylanilines (**65**)

Scheme 55. Visible light induced photocatalytic synthesis of quinolines under aerobic conditions.

Scheme 58. Copper-catalyzed Ullmann-type reaction for the generation of quinolines.

Scheme 59. Palladium catalyzed synthesis of 2-amino-3-bromoquinolines.

Scheme 60. Preparation of 3, 4-disubstituted quinolines using a palladium catalyst.

and alkenyl iodides (158), were employed. The desired transformation took place by following oxidative addition, reductive elimination, intramolecular cyclization and aromatization steps (Scheme 58). The reaction has the advantage of increased efficiency, mild reaction conditions, easy operation, and broad functional-group tolerance.⁸⁷

In the presence of palladium, a tandem isocyanide insertion followed by intramolecular cyclization of *gem*-dibromovinylanilines (160) in 1,4-dioxane provided new and efficient methodology for the generation of 2-amino-3-bromoquinolines (161) (Scheme 59).⁸⁸

A novel catalytic route leading regioselective generation of 3,4-disubstituted quinolines (164) from readily available simple alkenes (162) and *o*-acyl anilines (163) under palladium catalysis *via anti*-Markovnikov selectivity was reported (Scheme 60).⁸⁹

Zhang *et al.*, explored FeCl₃ catalyst for the synthesis of diverse 3-arylquinolines (166). In this approach, anilines (35) undergoes domino reaction with styrene oxides (165) followed by the cleavage of C-C bond and C-H activation from easily available raw material (Scheme 61). The summarized protocol was simple to obtain 3-arylquinolines in good yield.⁹⁰

Copper catalyzed aerobic synthetic methodology of multi-substituted quinolines (168) from N-(2-alkynylaryl) enamine carboxylates (167) (Scheme 62) was achieved. The transformation took place through intramolecular carbo-oxygenation of alkynes. Imidazole and

Scheme 61. Fe catalyzed synthesis of 3-arylquinolines from anilines and styrene oxides.

Scheme 62. Copper catalyzed synthesis of highly substituted quinolines.

Scheme 63. Gold(I) catalyzed synthesis of 3-aminoquinolines.

Scheme 64. Synthesis of quinolines from NO-acetal and 2-ethnylanilines.

quinazoline derivatives were also synthesized by applying this strategy.⁹¹

A series of 3-aminoquinolines (171) was synthesized *via* one-pot approach of easily accessible 2-aminobenzaldehyde (169) and propargyl amine (170) using Ph₃AuOTf catalyst (Scheme 63). Importantly, 3-aminoquinolines is not an easily accessible class of materials and can be utilized as building blocks to synthesize functionalized quinoline.⁹²

Sakai *et al.*, has disclosed a new approach which involves copper-catalyzed [5+1] annulations of 2-ethnylanilines (172) with N,O-acetal (173) to generate substituted quinoline (174). The method was further extended for [5+1] annulations with 2-ethnylanilines and ethyl glyoxylates utilizing combo CuBr₂-TFA catalytic system to afford quinoline skeleton (Scheme 64).⁹³

A facile and effective approach was developed to synthesize differently substituted quinoline (42). In this protocol, 2-aminophenyl-1-en-3-ols (175) undergoes intramolecular allylic amination to get the target product. This conversion was completed using 2 mol% FeCl₃ to afford excellent yields of quinolines (Scheme 65).⁹⁴

Scheme 65. FeCl₃ catalyzed synthesis of quinolines.

Scheme 66. Chemo-selective approach for the synthesis of substituted quinolines.

Scheme 67. Iron (III) chloride catalyzed synthesis of quinolines.

A facile, effective and chemo-selective approach was developed by Xing and colleagues for the synthesis of substituted quinoline (**99**). The synthesis of target quinolines were achieved by the reduction of nitroarenes using Hantzsch ester as reducing agent (**176**) in presence of Pd/C catalyst (Scheme 66). The HEH acts both as the reductant and the modifier of the palladium surface. The high yield obtained in this protocol makes this protocol a remarkable approach for the synthesis of substituted quinolines.⁹⁵

A convenient and inexpensive approach catalyzed by iron(III) chloride and TEMPO oxoammonium salt as an innocuous oxidant for the preparation of wide range of substituted quinolines was reported (Scheme 67). This Povarov-type reaction allows dehydrogenation of N-alkyl anilines (**177**) with mono- and 1, 2-disubstituted aryl and alkyl olefins (**152**). In this conversion, TEMPO oxoammonium salt plays a major role in dehydrogenation of tetrahydroquinolines to final quinoline derivatives (**178**).⁹⁶

An operationally simple cycloisomerization tandem methodology was discovered by employing CuI and pyrrolidine cooperative catalysts to furnish 2-substituted quinolines (**181**) from 2-aminobenzaldehydes (**179**) and alkynes (**180**) (Scheme 68). In this reaction, application of either of the catalysts alone couldn't afford the product and thus both the catalysts proved vital in the final conversion process.⁹⁷

Scheme 68. Synthesis of 2-substituted quinolines by CuI and pyrrolidine catalysts.

Scheme 69. Synthesis of substituted quinolines via electrophilic cyclization of 1-azido-2-(2-propynyl)benzene.

Scheme 70. Ionic liquid catalyzed synthesis of 2, 4-disubstituted quinolines.

An unprecedented synthesis of substituted quinolines (**183**) from suitable substrates *via* intramolecular electrophilic cyclization was devised. In presence of electrophilic reagents (I₂, Br₂, ICl, NBS, NIS and HNTf₂), 1-azido-2-(2-propynyl)benzene (**182**) undergoes intramolecular electrophilic cyclization under mild conditions in CH₃NO₂ or through catalysis with AuCl₃/AgNTf₂ in THF at 100 °C forming the desired quinolines (Scheme 69).⁹⁸

A facile, environmentally benign route was developed for generating a series of substituted quinolines. Here 2-aminoaryl ketones (**184**) and phenylacetylenes (**185**) interacted *via* Meyer-Schuster rearrangement in presence of zinc trifluoromethanesulfonate (Scheme 70). In this protocol, ionic liquid [hmim] PF₆ was applied as a promoter to accomplish the synthesis of final desired product (**186**).⁹⁹

Zhang and co-workers described Aza-Wacker oxidative cyclization approach for the development of 2-methylquinolines (**188**) using aniline derivative (**187**)

Scheme 71. Synthesis of 2-methylquinolines via Aza-Wacker oxidative cyclization.

in presence of palladium as catalyst (Scheme 71). This work was executed in the presence of air under mild conditions.¹⁰⁰

6-endo-dig cyclization-dehydration was carried for regioselective synthesis of substituted quinolines (190) from 1-(2-aminoaryl)-2-yn-1-ols (189) (Scheme 72). This reaction was mediated by copper or palladium catalyst affording product in good to excellent yields. The crude substrates required for the synthesis of quinolines were generated by reacting alkynylmagnesium bromide and 2-aminoaryl ketones.¹⁰¹

Au (I)-catalyzed tandem hydroamination-hydroarylation reaction synthesized suitably substituted 1,2-dihydroquinolines (192) from primary aryl amines (35) and alkynes (191) and quinolines (194) from 2-aminoaryl ketones (193) and alkynes (191) efficiently under microwave conditions (Scheme 73). The reaction showed compatibility with large number of substrates giving efficient output and required a short reaction time (10–70 min).¹⁰²

A simple, efficient silver-catalyzed route with a broad substrate scope to synthesize quinolines was reported (Scheme 74).¹⁰³ In this method, 2-aminobenzophenone (103) is made to react with ethyl acetoacetate (195) in

Scheme 74. Synthesis of quinolines employing silver phosphotungstate.

Scheme 75. Synthesis of tricyclic quinolines.

presence of catalytic amount of silver salt of heteropoly acid ($\text{Ag}_3\text{PW}_{12}\text{O}_{40}$) forming ethyl 2-methyl-4-phenyl-3-quinoline carboxylate (196) in excellent yields. This methodology was further extended for the generation of suitable tricyclic quinolines (198) using cyclic ketones (197) such as cyclopentanone and cyclohexanone (Scheme 75).¹⁰³

A simple, improved and efficient iron-catalyzed route generating 3-substituted quinolines (200) in presence of catalytic amount of $[\text{Cp}^*\text{Fe}(\text{CO})_2]_2$ was devised through reductive cyclization of *o*-nitro-substituted Baylis-Hillman acetates (199) in presence of carbon dioxide (Scheme 76).¹⁰⁴

Hatano *et al.*, devised a novel and efficient cationic BINAP Pd(II) catalyzed methodology generating asymmetric quinoline derivative (202) containing one quaternary carbon atom from 1,7-enynes (201) through

Scheme 72. Copper/palladium catalyzed synthesis of substituted quinolines.

Scheme 73. Au (I)-catalyzed tandem synthesis of substituted 1,2-dihydroquinolines and quinolines.

Scheme 76. Synthesis of 3-substituted quinolines using [Cp*Fe(CO)₂]₂ catalyst.

Scheme 77. Synthesis of quinoline derivatives by ene-type cyclization of 1,7-enynes.

ene-type cyclization (Scheme 77). The transformation proceeded in presence of Pd(II) catalyst such as [(MeCN)₄Pd](BF₄)₂ together with S-BINAP as chiral bidentate PP-ligand and DMSO.¹⁰⁵

Giorgio Abbiati *et al.*, devised an eco-friendly multi-component stereo-selective strategy for the synthesis of 2-aryl-4-amino quinolines (**206**) using 2-ethynyl-arylamines (**172**), aryl iodides (**203**), primary amines (**204**) and carbon-monoxide (**205**) in presence of palladium as a catalyst (Scheme 78).¹⁰⁶ The reaction occurred through carbonylative coupling between aryl iodides and 2-ethynyl-arylamines (**172**) to form an intermediate which subsequently undergoes intra- and intermolecular addition reactions on carbon-carbon triple bond and carbon-oxygen double bonds to afford desired products in good yield.

Another significant and efficient mode for the generation of this quinoline scaffold was introduced by Anguille and co-workers as shown in Scheme 79.¹⁰⁷ This synthetic route involves aniline (**148**) and *n*-Bu₃N (**207**) for the generation of *N*-butylaniline (**208**) and 2-propyl-3-ethylquinoline (**209**) in presence of platinum bromide *via ortho*-C-H activation of aromatic anilines.

Scheme 79. Platinum-catalyzed synthesis of quinolines *via* C-H activation.

Scheme 80. Regioselective synthesis of quinoline.

Lee and Yi devised an efficient and green methodology forming the coveted product (**211**) using ruthenium complex as catalyst *via* C-H coupling. This regioselective synthesis was done using arylamines (**148**) and 1,3-diols (**210**) as shown (Scheme 80) without the formation of any by-products.¹⁰⁸

Silver metal served as an efficient catalyst for the generation of quinolines (**215,216,217**) from *N*-arylimines (**212**) and alkynes (**78,213,214**) through C-H activation *via* oxidative coupling and cyclization processes (Scheme 81).¹⁰⁹ This protocol worked well with both internal and terminal alkynes and also tolerated both electron withdrawing and electron releasing group on *N*-arylimines to afford the diverse range of desired heterocyclic scaffolds.

Mohsenimehr and his co-workers introduced a new, efficient, less time-consuming and green methodology synthesizing pyrimido[4,5-*b*]quinolines (**220**) derivatives using aryl aldehyde (**149**), dimedone (**219**) and a suitable enamine (**218**) (Scheme 82).¹¹⁰ This multi-component approach was carried out in presence of recyclable [γ-Fe₂O₃@HAp-SO₃H] nanocatalyst. The recyclability of catalyst, mild reaction conditions, and excellent yield are the promising feature of this protocol.

Nickel-assisted sequential dehydrogenation and condensation approach for the synthesis of highly substituted quinolines (**224**) is reported. This protocol involves the reaction of both primary/secondary α-2-aminoaryl alcohols (**221**) either with ketones (**222**)/secondary alcohols (**223**) and occurred through C-N and C-C bonds formations using low catalytic loading

Scheme 78. Stereo-selective synthesis of 2-aryl-4-amino quinolines.

Scheme 81. Quinolines synthesis using N-arylimines and alkynes.

Scheme 82. Synthesis of pyrimido[4,5-b]quinolines.

Scheme 83. Dehydrogenative strategy for the generation of quinolines.

Scheme 84. One-pot Co(III)-catalyzed synthesis of quinolines involving DMSO.

(Scheme 83).¹¹¹ This pathway is cost-effective, efficient and has good substrate scope to afford excellent yield of products. Further, the method is utilized to synthesize series of wide range of substituted quinolines.

Xu *et al.*, demonstrated a Co(III)-catalyzed new approach for the synthesis quinolines (**226**) in which DMSO is involved *via* C-H activation/coupling of easily accessible anilines (**35**) with alkynes (**225**) (Scheme 84).¹¹² In this reaction, DMSO not only acts as a solvent but also as C₁ building block of the products. The added advantages of this procedure are the enhanced regioselectivity, use of non-toxic solvents and good to excellent yields.

Tan and colleagues reported a one-pot approach for the synthesis of quinolines (**229**) using the cross-coupling between the secondary alcohol (**227**) and

Scheme 85. One-pot Cu(I)-catalyzed cross-coupling pathway forming quinolines.

Scheme 86. Synthesis of quinolines and pyrimidines using oxidative annulation.

2-aminobenzyl alcohol (**228**) in presence of hexanuclear Cu(I) cluster of 4,6-dimethylpyrimidine-2-thiolate as bifunctional catalyst (Scheme 85).¹¹³ This methodology was also reported to produce α -alkylated ketone and pyridines through the annulations reaction of secondary alcohol with primary alcohol and γ -amino alcohols respectively.

Scheme 87. One-pot nickel-catalyzed acceptorless dehydrogenative strategy.

Scheme 88. Regioselective one-pot synthesis employing anilines and ketones.

Scheme 90. Combo-catalytic strategy for the synthesis of 4-hydroxyalkyl-quinoline.

Recently, Jadhav and co-workers disclosed a procedure for the synthesis of quinolines (**231**) and pyrimidines (**232**) *via* oxidative annulations using anilines (**148**), aryl ketones (**230**) and DMSO as a methine equivalent (Scheme 86).¹¹⁴ The reaction was accelerated by $K_2S_2O_8$ and catalytic amount of $FeCl_3$ was reported to produce the desired product in excellent yields. This cascade reaction occurred through the initial formation of the sulfenium ion followed by C-C and C-N bond generation and cyclization. The protocol was extended for the synthesis of 4-arylpyrimidines *via* activation of acetophenone-formamide conjugates.¹¹⁴

A series of substituted quinolines (**46**) was synthesized from *o*-aminobenzylalcohols (**94**) and ketones (**95**)/secondary alcohols (**233**) using nickel complex as catalyst (Scheme 87).¹¹⁵ This one-pot acceptorless dehydrogenative coupling strategy was established by Parua and co-workers in which nickel-catalyst $[Ni(MeTAA)]$, initially catalyzed the dehydrogenation of alcohol succeeded by the cross-aldol condensation in basic medium which is followed by intramolecular cyclodehydration. The advantages of this method is that the catalyst is inexpensive, easy to synthesize and avoidance of hazardous oxidants.

A one-pot, Co(III) catalyzed operationally simple, eco-friendly and regioselective synthesis of diversely

substituted quinolines (**234**) was described by Xu and co-workers (Scheme 88) by the reaction of anilines (**148**) and ketones (**100**).¹¹⁶ The reaction occurred *via* C-H activation/carbonylation/cyclization in which paraformaldehyde was serving as the source of carbonyl for C_1 framework of required product. Furthermore, this protocol is atom-economical, produces no harmful by-products and has the excellent functional group tolerance.

A novel and simple methodology for the synthesis of 2-substituted quinolines (**237**) was described by Jixiang and co-workers by the reaction 2-vinylanilines (**235**) and alkynoates (**236**) in presence of catalytic amount of Palladium (Scheme 89).¹¹⁷ The reaction proceeded *via* Michael addition followed by cyclization. Mechanistic studies revealed the interaction of enamine with the Pd catalyst, forming an intermediate which upon nucleophilic addition generates another intermediate which finally undergoes $C\equiv C$ cleavage to afford the desired quinoline.

Jiang *et al.*, disclosed a combo-coupling strategy in which anilines (**35**) are made to react with aldehyde (**41**) and aliphatic alkynes (**238**) *via* sequential catalysis by Cu(I) and Au(I) resulted in the isolation of the 4-hydroxyalkyl-quinoline (**42**) in good to excellent yields (Scheme 90).¹¹⁸

Scheme 89. One-pot Pd-catalyzed synthesis of 2-substituted quinolines.

5. Conclusions

The biological applicability of this quinoline scaffold has raised the consciousness of the chemists towards the synthesis of this pharmacophore. Because of this, search for the development of efficient methodologies remains an active and emergent area of research. We herein compiled important transition-metal catalyzed strategies for the generation of quinoline in a comprehensive style after carrying out extensive survey of the literature. We believe that this review will definitely be helpful for the academicians and researchers to search for new and more efficient routes for the synthesis of quinoline based potential lead molecules which may further be exploited for discovery of drug molecules.

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