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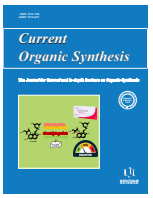
REVIEW ARTICLE



Recent Progress in the Synthesis of Quinolines

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ARTICLE HISTORY

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Abstract: ***Background*:** Quinoline-containing compounds present in both natural and synthetic products are an important class of heterocyclic compounds. Many of the substituted quinolines have been used in various areas including medicine as drugs. Compounds with quinoline skeleton possess a wide range of bioactivities such as antimalarial, anti-bacterial, anthelmintic, anticonvulsant, antiviral, anti-inflammatory, and analgesic activity.

Due to such a wide range of applicability, the synthesis of quinoline derivatives has attracted a lot of attention of chemists to develop effective methods. Many known methods have been expanded and improved. Furthermore, various new methods for quinoline synthesis have been established. This review will focus on considerable studies on the synthesis of quinolines date which back to 2014.

***Objective*:** In this review, we discussed recent achievements on the synthesis of quinoline compounds. Some classical methods have been modified and improved, while other new methods have been developed. A vast variety of catalysts were used for these transformations. In some studies, quinoline synthesis reaction mechanisms were also displayed.

***Conclusion*:** Many methods for the synthesis of substituted quinoline rings have been developed recently. Over the past five years, the majority of those reported have been based on cycloisomerization and cyclization processes. Undoubtedly, more imaginative approaches to quinoline synthesis will appear in the literature in the near future. The application of known methods to natural product synthesis is probably the next challenge in the field.

Keywords: Quinolines, Friedländer synthesis, bioactivity, microwave, yield, Povarov reaction, one-pot reaction.

1. INTRODUCTION

Quinoline-containing compounds present in both natural and synthetic products are an important class of heterocyclic compounds. Many of the substituted quinolines have been used in various areas including medicine as drugs. Compounds with quinoline skeleton possess a wide range of bioactivities such as antimalarial, anti-bacterial, anthelmintic, anticonvulsant, antiviral, anti-inflammatory, and analgesic activity.

Antimalarial: Quinolines are well-known for their antimalarial potential. This bioactive compound isolated from the bark of Cinchona trees has been used for the treatment of malaria. Based on this structure, many other antimalarial drugs have been synthesized such as chloroquine, primaquine, santoquine, pentaquine, isopentaquine, amodiaquine and mefloquine (Fig. **1**) [1].

Analgesic: The synthetic 4-Substituted-7-trifluoromethyl quinolines (Fig. **2A**) showed good analgesic activity [2]. This property has also been found in some quinoline derivatives synthesized by Manera *et al.* (Fig. **2B**) [3].

Antiprotozoal: Fournet *et al.* isolated some 2-substituted quinolines from the bark of *Galipea longiflora* and tested their bioactivity. Two of them (Fig. **3A**) were effective against the parasites (*Leishmania* sp.), which are the agents of leishmaniasis [4]. Fakhfakh *et al.* synthesized alkenyl and alkynyl quinolines (Fig. **3B**), which are the potential agents for the treatment of cutaneous leishmaniasis, visceral leishmaniasis, African trypanosomiasis and Chagas' disease [5].

Anthelmintic: Four substituted 2,4-dimethoxy arylquinolines synthesized by Rossiter *et al.* (Fig. **4**) exhibited good activity against the nematode (*H. contortus*). Notably, these quinoline derivatives maintained their activity against some strains of *H. contortus*, which are resistant to levamisole, ivermectin and thiabendazole [6].

Antibacterial: Some 3-benzyl-6-bromo-2-methoxy quinoline derivatives (Fig. **5A**), which exhibited antibacterial activity against *M. tuberculosis* H37Rv strain, were synthesized by Upadhayaya *et al.* by molecular modelling techniques [7]. 7-chloro quinoline derivatives obtained by De Souza synthesis (Fig. **5B**) showed good activity against multi-drug resistant tuberculosis [8]. Some mefloquine-like quinolines (Fig. **5C**) developed by Eswaran *et al.* were found to be active against *E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumoniae* [9].

Antiinflammatory: 2-(Furan-2-yl)-4-phenoxy-quinoline derivatives synthesized by Chen *et al.* (Fig. **6A**) showed good inhibition of lysozyme and β-glucuronidase release [10]. Baba *et al*. prepared

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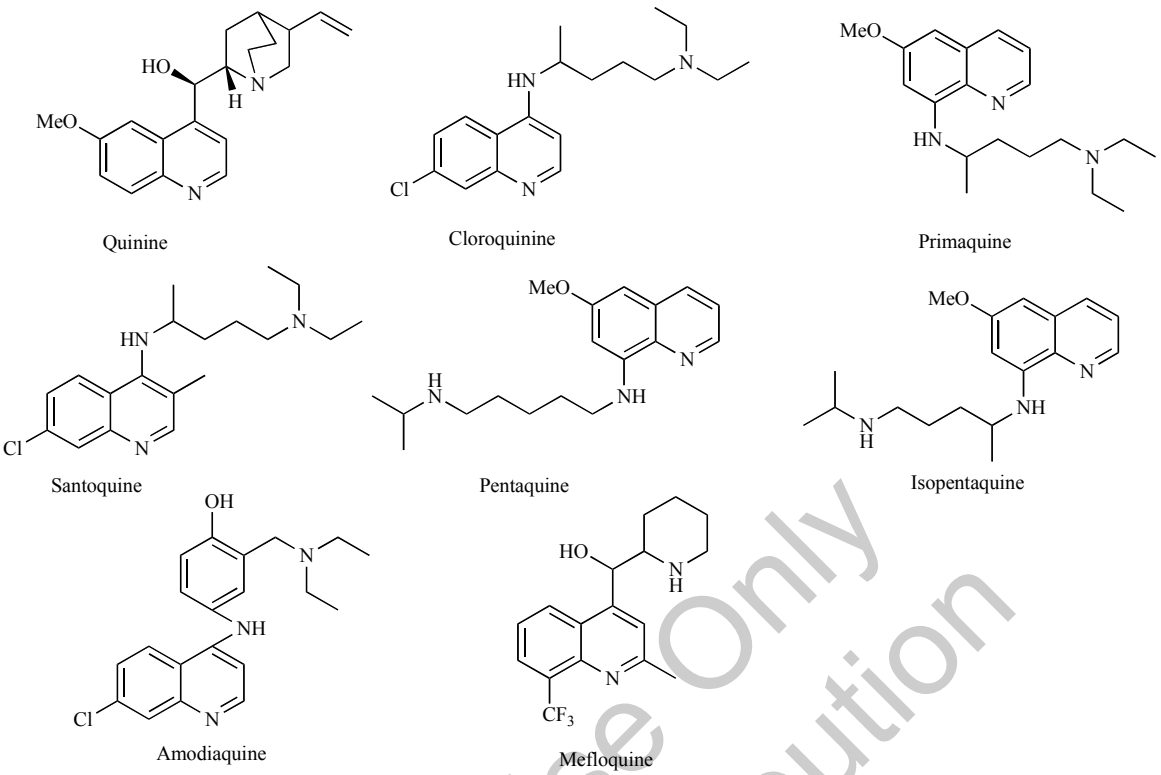

Fig. (1). Quinoline derivatives with antimalarial activity.

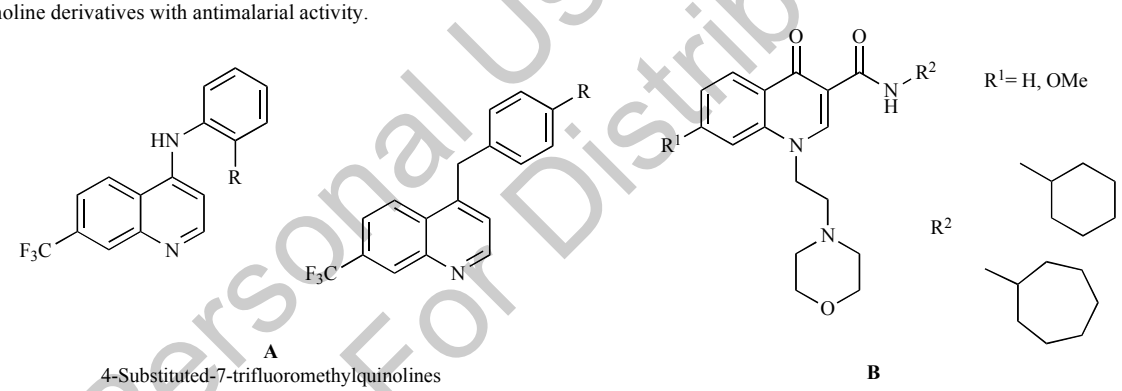

Fig. (2). Quinoline derivatives with anlgesic activity.

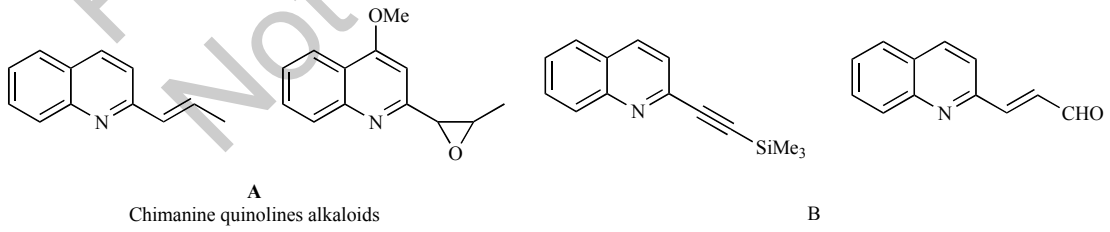

Fig. (3). Quinoline derivatives with antiprotozoal activity.

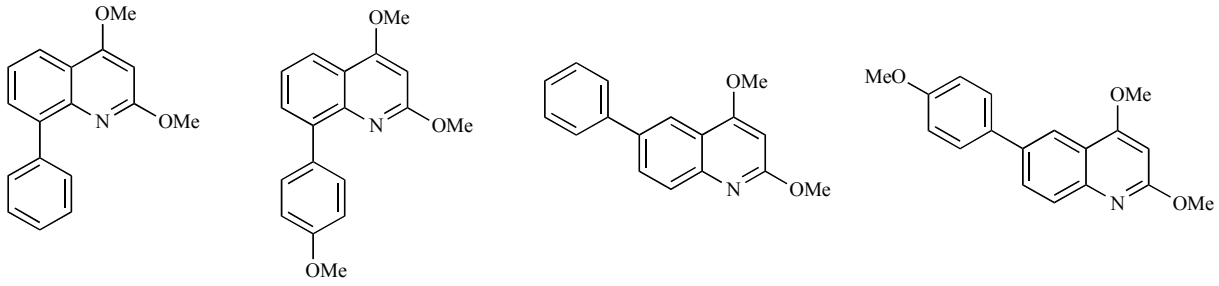

Fig. (4). Quinoline derivatives with anthelmintic activity.

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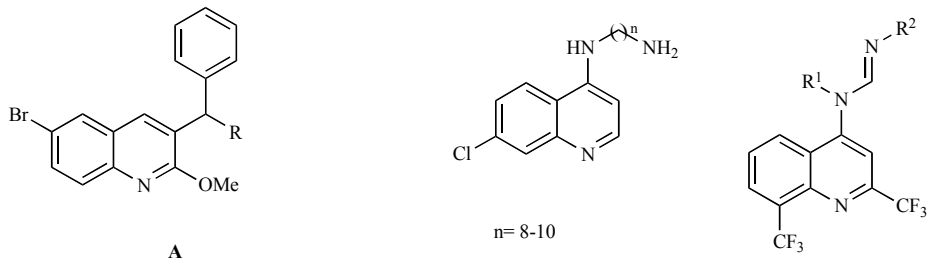
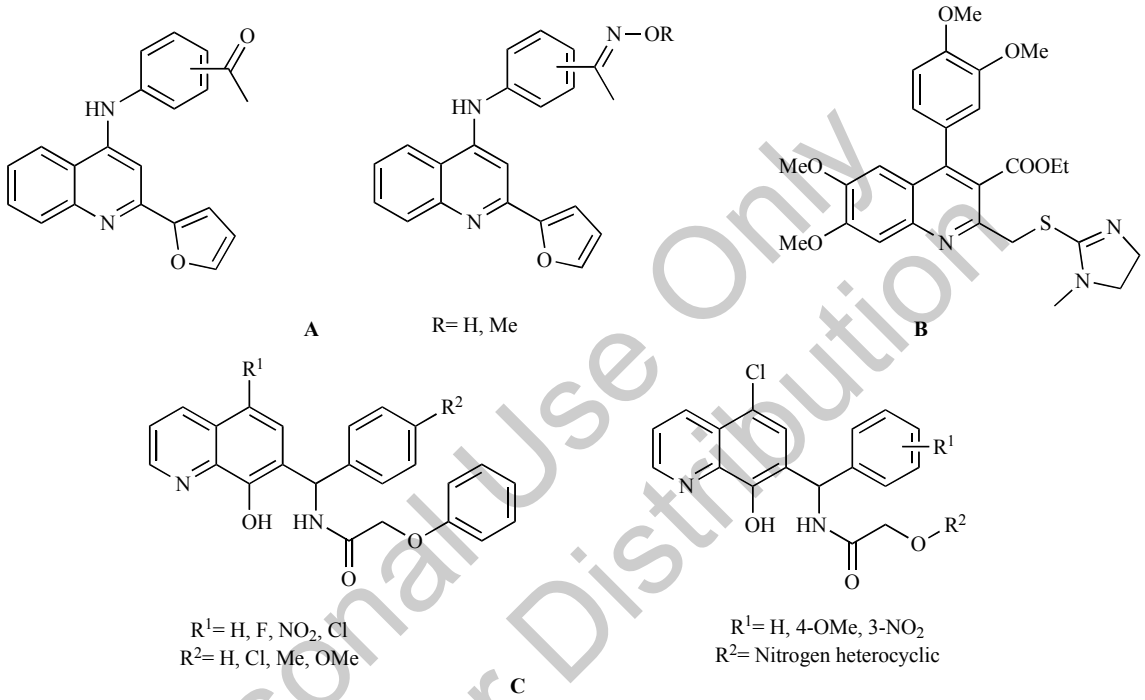


A
R = Imidazolyl, Pyrazolyl, 1-(3-Trifluoromethyl-phenyl)-piperazinyl, 6-Amino-chromen-2-one

n= 8-10

B **C**

Fig. (5). Quinoline derivatives with antibacterial activity.



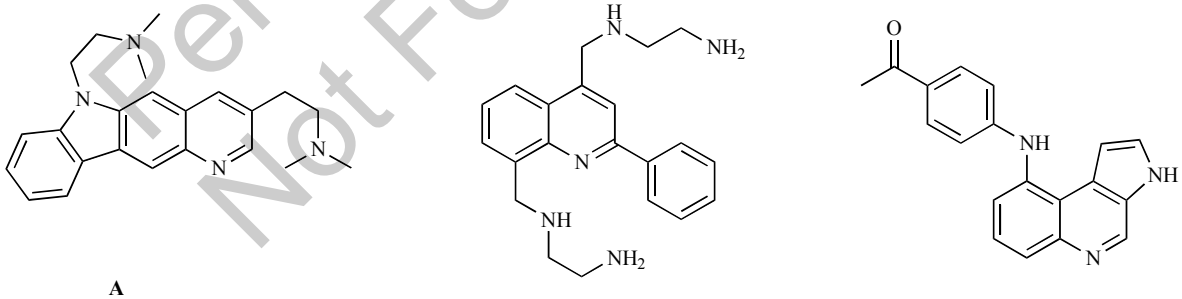
A R= H, Me **B**

R^1= H, F, NO_2, Cl
R^2= H, Cl, Me, OMe

R^1= H, 4-OMe, 3-NO_2
R^2= Nitrogen heterocyclic

C

Fig. (6). Quinoline derivatives with antiinflammatory activity.



A **B** **C**

Fig. (7). Quinoline derivatives with anticancer activity.

a substituted quinoline (Fig. **6B**), which exhibited potent anti-inflammatory activity in the adjuvant arthritis rat model [11]. Gilbert *et al.* developed some quinolines for the treatment of osteoarthritis (Fig. **6C**). These compounds are active against Aggrecanase-2 [12].

Anticancer: Vittorio Caprio *et al*. synthesized indole fused 10H-indolo[3,2-*b*]quinoline bearing bis-dimethylaminoethyl (Fig. **7A**) with anticancer activity acting on telomerase [13]. New derivatives of 2-phenyl quinoline having [(2- aminoethyl)amino-methyl] group (Fig. **7B**) were synthesized and evaluated for the ability to intercalate into double-stranded DNA by Yuzi Mikata *et al.* [14]. 1-[4-(3*H*-pyrrolo[3,2-*f*]quinolin-9-ylamino)-phenyl]-ethanone hydrochloride (Fig. **7C**) with high antiproliferative activity and inhibition of DNA topoisomerase II was synthesized by Dalla Via *et al*. [15].

Antimicrobial: The synthesis of 1-aryl/heteroaryl-5 methyl-1, 2, 4-triazolo[4,3-*a*]quinoline derivatives (Fig. **8A**) and evaluation *in vitro* for their antimicrobial activity were reported by Sanada *et al*. and one compound exhibited good activity against salmonella typhae. The moderate activity against *C. albicans, A. niger,* and

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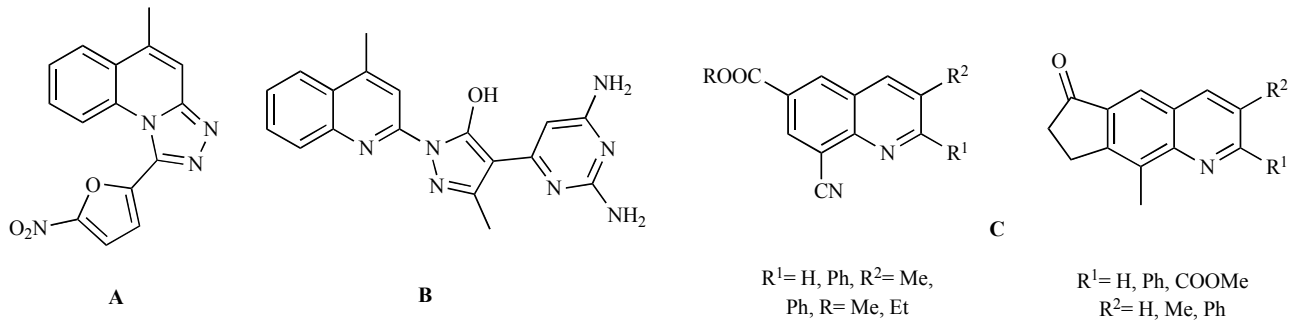

Fig. (8). Quinoline derivatives with antimicrobial activity.

Salmonella typhae of 4-(4-pyrozolyl)-2-aminopyrimidines (Fig. **8B**) was reported by Singh *et al.* [16]. Rao *et al.* [17] prepared some new multi quinolines derivatives (Fig. **8C**) by Baylis-Hillman reaction and evaluated their activity against some of the Gram-positive organisms, *viz*., *B. subtilis*, *B. sphaericus*, and *S. aureus*, and three Gram-negative organisms, *viz*., *C. violaceum*, *K. aerogenes*, and *P. aeruginosa.* Most of them exhibited broad-spectrum antibacterial activity [18].

Anticonvulsant: The synthesis and bioactive evaluation of 5-alkoxy-[1,2,4]triazolo[4,3-*a*]quinoline derivative were reported by Zhe-Shan Quan *et al.* [19]. Among these compounds, 5-hexyloxy-[1,2,4]triazolo[4,3-*a*] quinoline (Fig. **9**) showed the best anticonvulsant activity, with a median effective dose of 19.0 mg/kg.

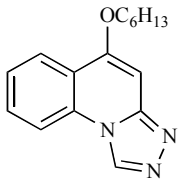

Fig. (9). Quinoline derivative with anticonvulsant activity.

Cardiovascular: Bekhit *et al.* synthesized some new 4-(diphenyl methyl)-α-[(4-quinolinyloxy]methyl]-1-piperazinethanol derivati-ves, which exhibited cardiovascular activity on rat and guinea pig models. Among them, compound DPI 201-106 (Fig. **10A**) was found to be inotropically effective in rat heart [20]. 3H pyrrolo[3,2- *f*]quinoline (Fig. **10B**) showed endothelium-independent relaxing action in the rat-tail arteries [21]. The hypotensive activity of centhaquin (Fig. **10C**) was studied by Srimal *et al*. and it helped to reduce the blood pressure as well as lowered the heart rate in cat in a dose-dependent manner [22].

Antiviral: Anilidoquinolines synthesized by Ghosh *et al*. (Fig. **11A**) demonstrated a good degree of *in vitro* activity against Japanese encephalitis virus [23]. Chen *et al*. prepared several quinolines (Fig. **11B**), which acted as HIV-1 Tat–TAR interaction inhibitors. [24] Several quinolines synthesized by Fakhfakh *et al*. (Fig. **11C**) showed activity against HIV-1 [5].

Due to such a wide range of applicability, the synthesis of quinoline derivatives has attracted a lot of attention of chemists to develop effective methods. Many known methods have been expanded and improved. Furthermore, various new methods for quinoline synthesis have been established. This review will focus on considerable studies on the synthesis of quinolines which date back to 2014.

2. ESTABLISHED METHODS FOR THE SYNTHESIS OF QUINOLINE

2.1. Friedländer Reaction

Among methods for the synthesis of quinolines derivatives, the Friedländer heteroannulation is still one of the simplest and most straightforward methods. The reaction usually starts with 2-aminoaryl aldehyde or ketone and an aldehyde or ketone containing α -methylene group. Many methods based on this reaction or its modifications have been reported recently.

An efficient and straightforward Friedländer synthesis of polysubstituted quinoline-3-thiocarboxamides from 3-oxo-N,3-diarylpropanethioamide and 2 aminoarylketone/2 aminoaryl-carboxylic acid ester was accomplished by Yadla *et al*. [25]. The

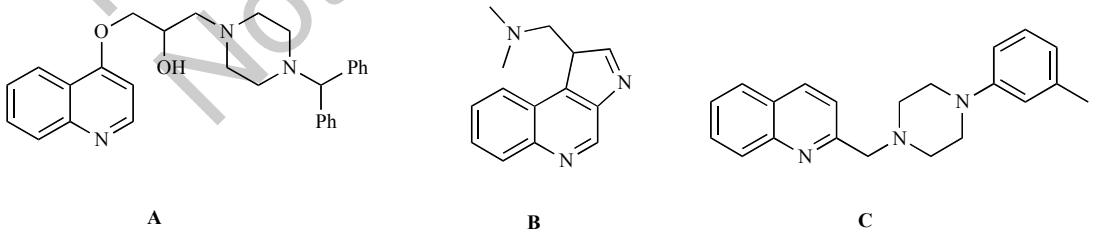

Fig. (10). Quinoline derivatives with cardiovascular activity.

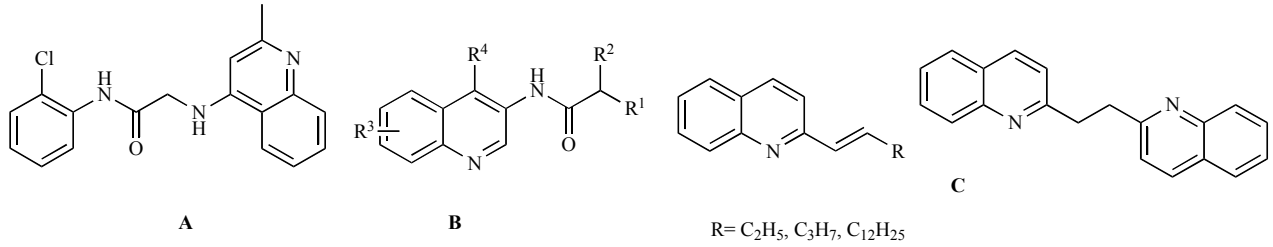

Fig. (11). Quinoline derivatives with antiviral activity.

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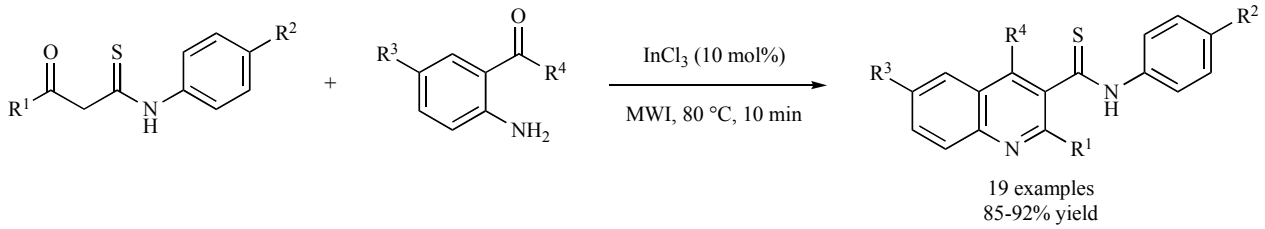
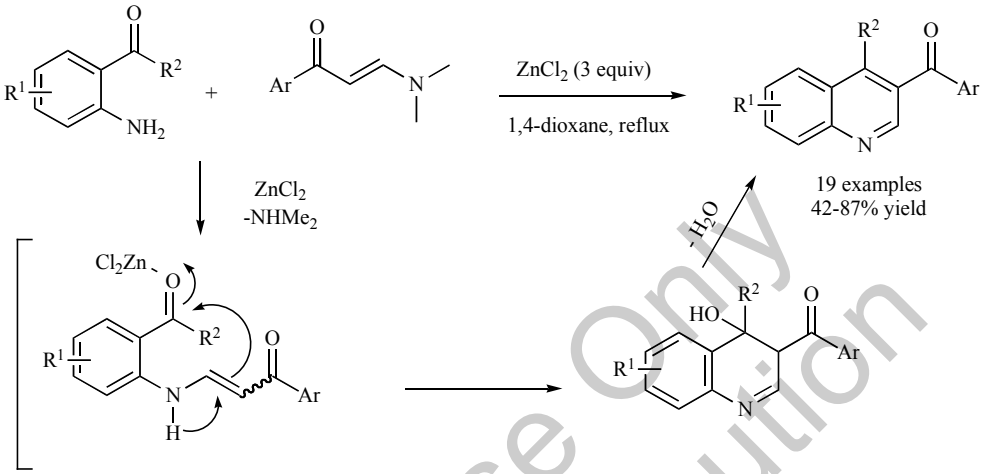
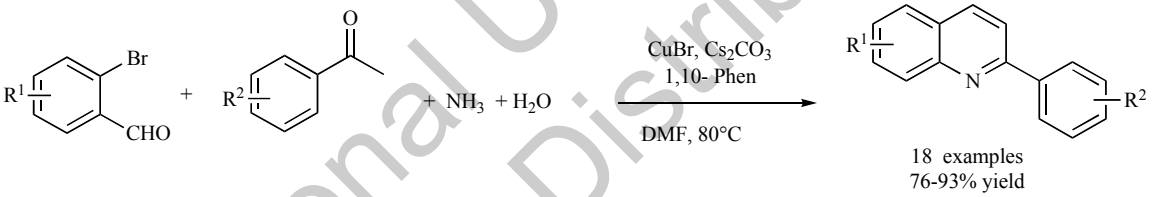


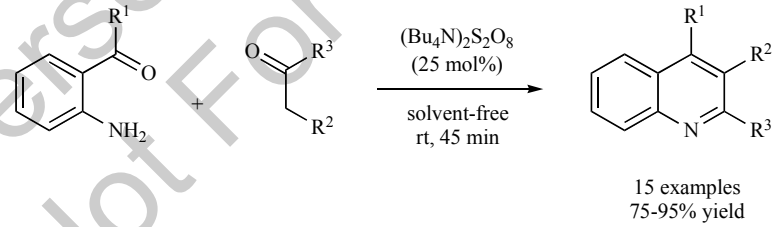
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

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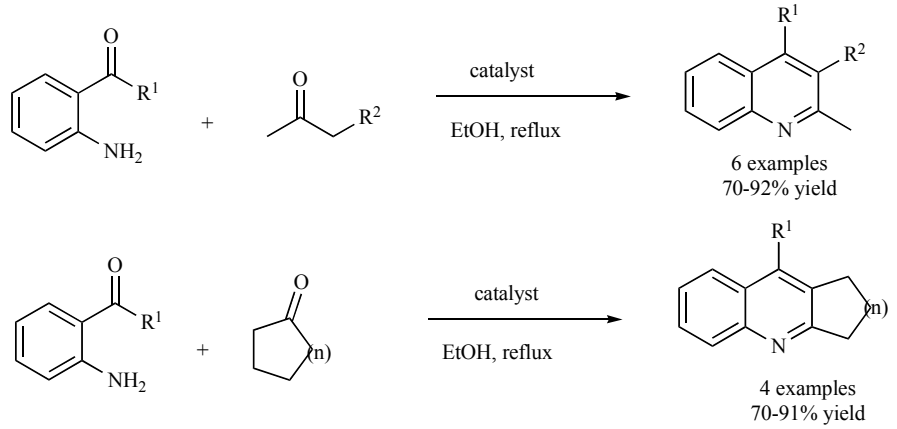
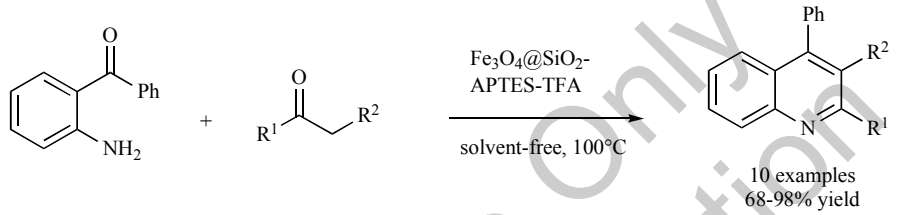
two-component solvent-free reaction protocol was performed under microwave irradiation and catalyzed by $InCl_3$ giving quinolines in excellent yields (Scheme **1**). For the synthesis of 4-substituted 3-aroyl quinolines from *o*-aminoaryl ketones with enaminones, Luo *et al.* employed $ZnCl_2$ as the catalyst (Scheme **2**) [26]. From 2-bromobenzaldehydes, aryl methyl ketones, and aqueous ammonia, quinolines were produced by a copper-catalyzed one-pot cascade reaction under mild conditions and simple operation in good to excellent yields (Scheme **3**) [27]. The inexpensive catalyst $(Bu_4N)_2S_2O_8$ was used by Vanajatha and Prabhakar Reddy as the catalyst for quinoline synthesis at ambient temperature under solvent-free conditions. Good to excellent yields were obtained for most products and the synthesis was suitable for many functional groups (Scheme **4**) [28].

Nanomaterials have also been used as catalysts for Friedländer quinoline synthesis. A one-pot, efficient, and environmentally friendly procedure was designed by Chermahini and Teimouri for the preparation of quinolines with the employment of Montmorrilonite K-10 or zeolite or nano-crystalline SZ as catalysts [29]. The reaction between 2-aminoarylketones and carbonyl compounds or β-keto esters was proceeded in mild conditions and provided easy work-up and simple product purification (Scheme **5**). In another report, quinolines were obtained in good to excellent yields from 2-aminoarylketones and carbonyl compounds under solvent-free conditions using easily prepared and recyclable Fe_3O_4@SiO_2 APTES-TFA nanoparticle as the catalyst (Scheme **6**) [30]. Baghbanian and Farhang described the use of $CuFe_2O_4$ nanoparticles as the catalyst for the synthesis of quinoline derivatives. Products were isolated in very good yields and the catalyst can be reused successively 5 times without any significant decrease in activity (Scheme **7**) [31].

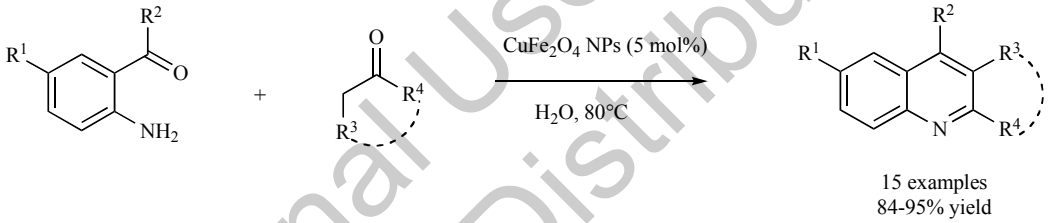
Borah *et al.* prepared two acidic ionic liquids [Hmim][$OOCCCl_3$] and [Msim][$OOCCCl_3$] and applied them as catalysts for the Friedlände quinoline synthesis [32]. The



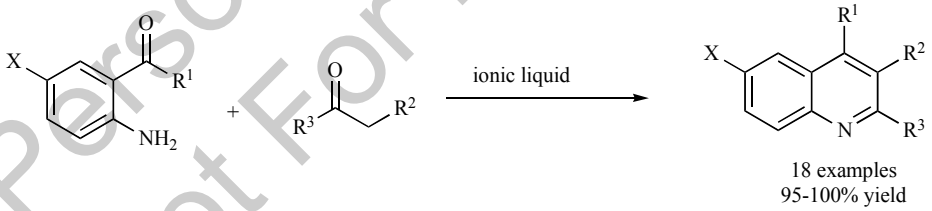
Scheme 5.



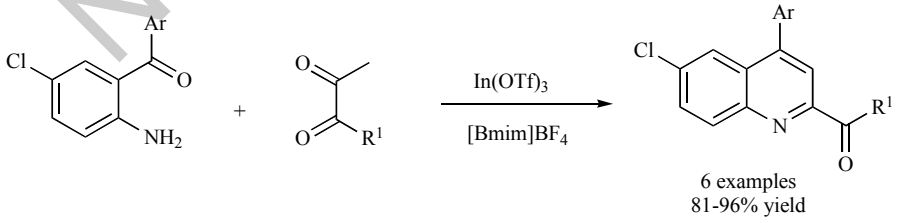
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

advantages of the synthesis include single product formation, easy work-up, short reaction time, catalysts recyclability and high yields of products (Scheme **8**). In the study by Prasad *et al.*, indium triflate $In(OTf)_3$ and the recyclable ionic liquid $[Bmim]BF_4$ were employed for the synthesis of 2-acetylquinolines from 1,2-diketones and 2-aminoarylketones [33]. The reaction of unsymmetrical 1,2-diketones with 2-aminoarylketones provided 2-propanoylquinolines over 2-acetyl-3-methylquinolines. Products were produced in excellent yields and the ionic liquid could be recovered and subsequently run four times more with insignificant loss of activity (Scheme **9**). 1,3-disulfonic acid imidazolium hydrogen sulfate was used by Shirini *et al.* for the preparation of quinoline derivatives [34]. The catalyst was also reused several times without any considerable loss of activity (Scheme **10**).

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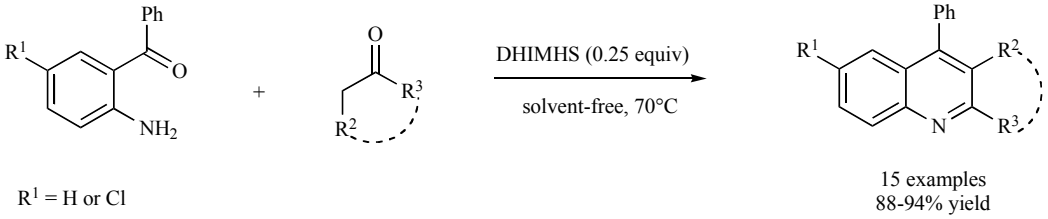
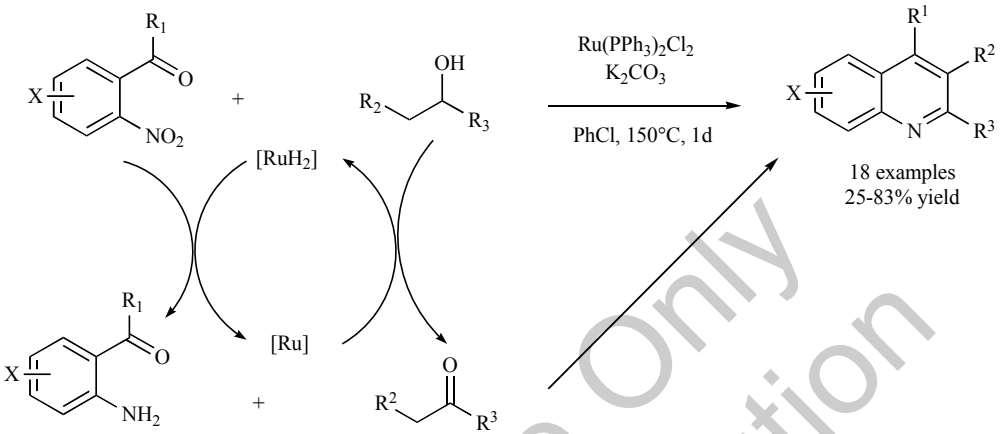
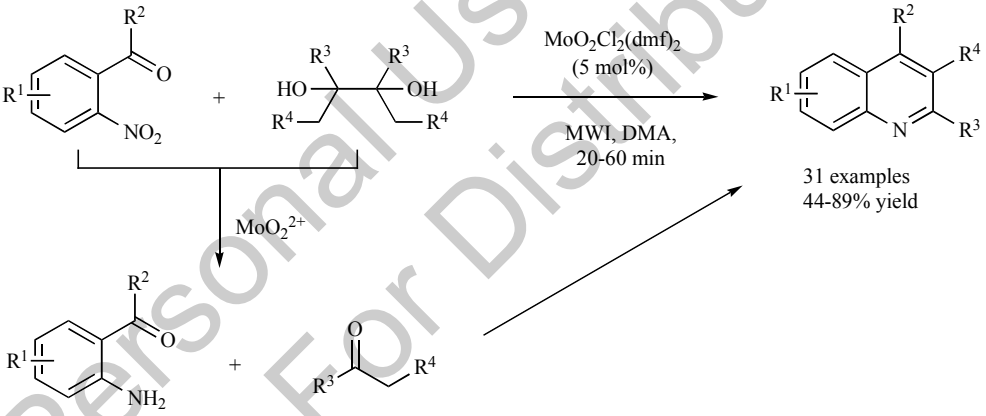


Scheme 10.



Scheme 11.



Scheme 12.

Many modifications of Friedländer quinoline synthesis have been developed by changing the starting materials. A synthesis from alcohols and 2-nitroaryketones by a Ru(II)-catalyzed annulation was described by Wu *et al*. At first, using tris(triphenylphosphine)ruthenium(II) dichloride [$Ru(PPh_3)_2Cl_2$] catalyst, 2-nitroaryketones and alcohols were concurrently transformed to 2-aminoaryl ketone the Friedlander reactive reactants through hydrogen transfer (Scheme **11**) [35]. Similarly, Sanz *et al*. disclosed the synthesis of polysubstituted quinolines catalyzed by dioxomolybdenum(VI)-catalysis from 2-nitroaryketones and glycols (Scheme **12**). All quinolines were produced in good to high yields in short reaction times by the microwave irradiation technique [36]. Xiao *et al.* prepared quinolines from 2-nitrobenzyl alcohol and ketones in water without using transition-metal catalyst (Scheme **13**). The reaction was initially proceeded by an intramolecular hydrogen transfer process catalyzed by *t*- BuOK to form 2 amino-benzaldehyde, which could be isolated from a reaction without ketone [37]. An iron-catalyzed redox condensation of alcohols, formic acid and 2-nitrobenzyl methylether/2-nitrobenzyl alcohols, which resulted in the formation of quinolines was described by Liu *et al*. Carbon dioxide and water are the only side products of the synthesis, (Scheme **14**). Among the products, 2-phenyl quinoline was prepared in good yield at gram- scale (10 mmol) [38].

Substrates for Friedländer modification quinoline synthesis can be ketones and 2-aminobenzyl alcohol. Cai *et al.* obtained 2, 3-substituted quinolines from a metal-free NHC-catalyzed indirect Friedländer annulation of ketones with 2-aminobenzyl alcohol (Scheme **15**). Quinoline derivatives were furnished in good to excellent yields through a one-pot, two-step tandem reaction [39]. Rangappa *et al.* reported the synthesis of 2-phenylquinolines through a simple, solution-phase T3P®-DMSO mediated method with microwave irradiation (Scheme **16**). In only five minutes, quinolines were obtained in excellent yields [40]. From enones and 2-aminobenzyl alcohols, Ling *et al.* demonstrated the synthesis of quinolines through iridium-catalyzed transfer hydrogenative reactions (Scheme **17**). The synthesis employed $[IrCp^*Cl_2]_2$/t-BuOK as the efficient catalyst system allowing reactions to occur at mild conditions. The synthesis was supposed to initiate with transfer hydrogenation, followed by the Friedländer condensation to afford the final quinoline products [41].

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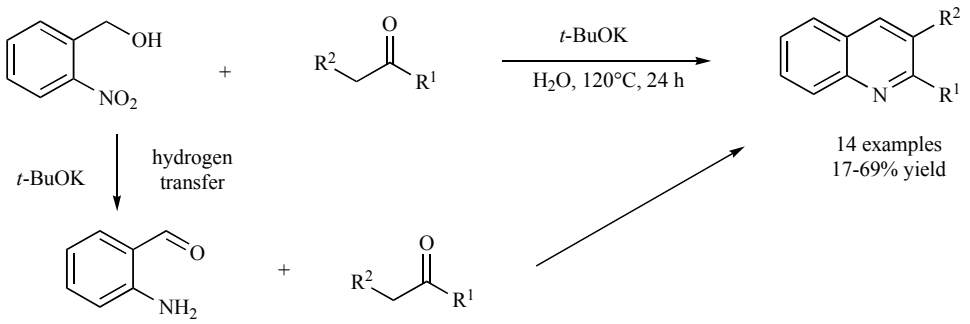
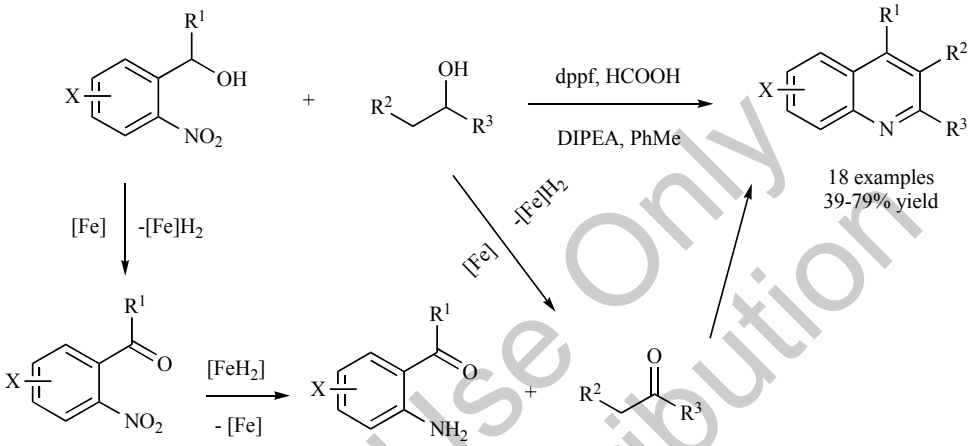
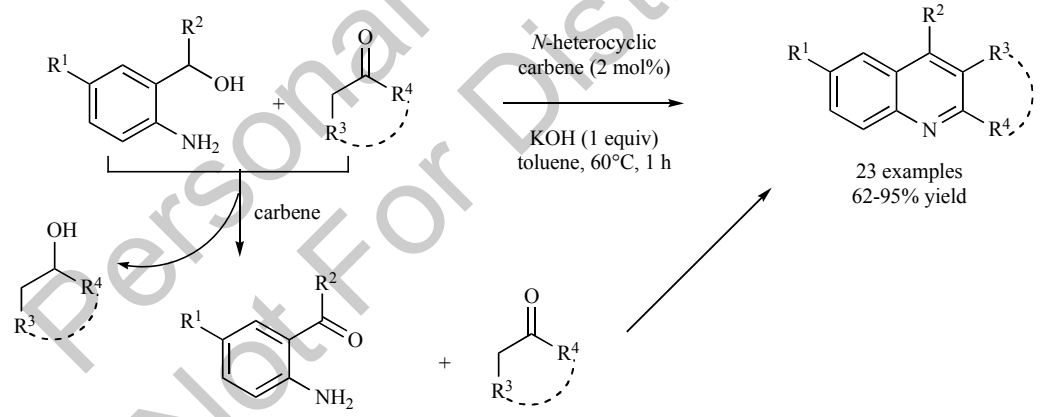


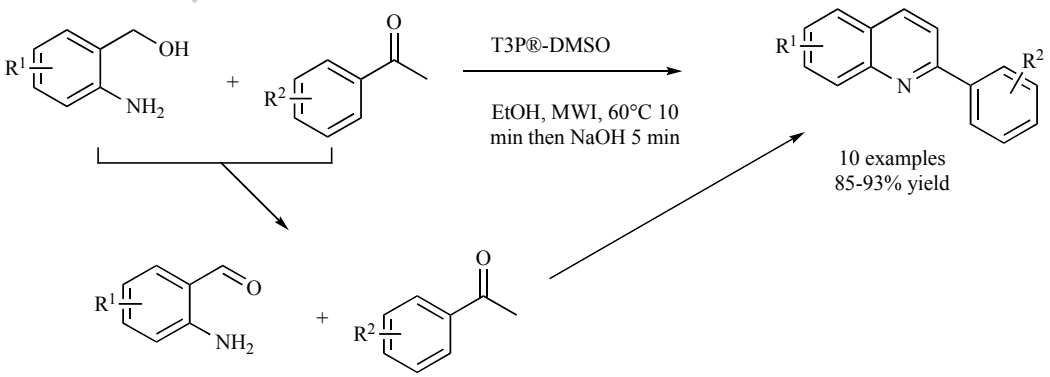
Scheme 13.



Scheme 14.



Scheme 15.



Scheme 16.

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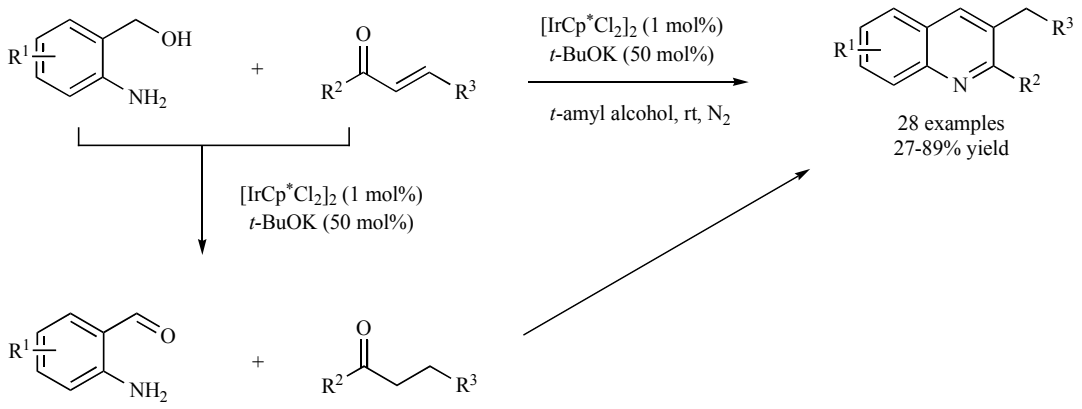
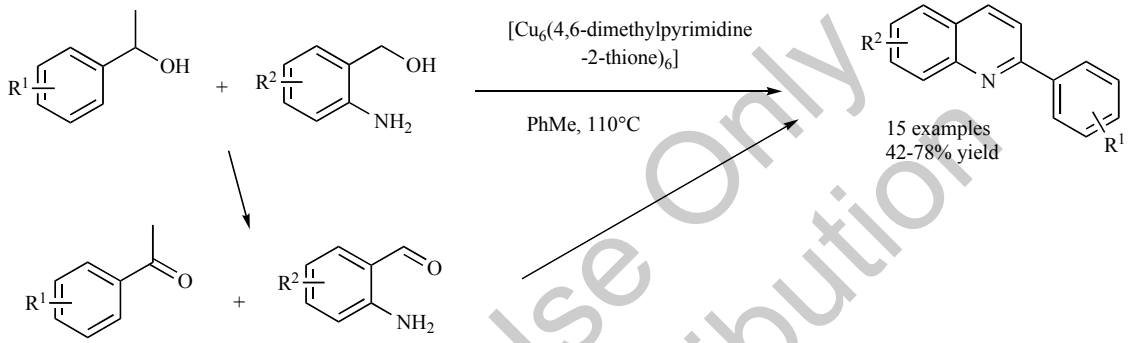
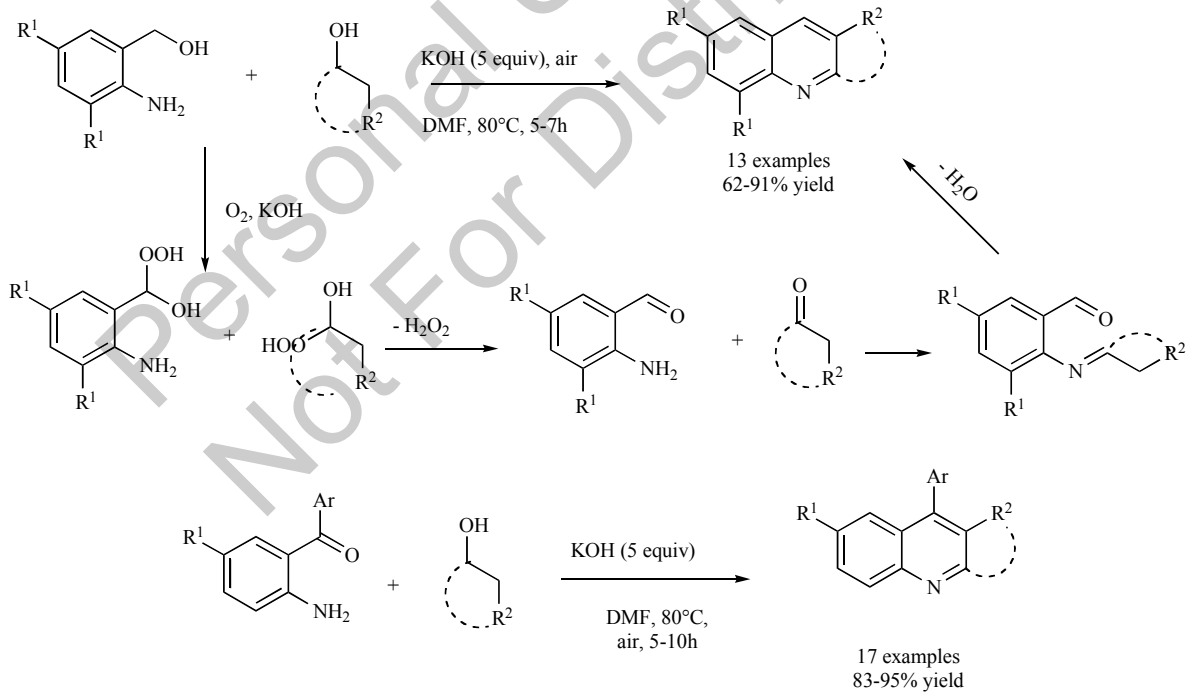


Scheme 17.



Scheme 18.



Scheme 19.

2-aminobenzyl alcohols and secondary alcohols have also been used as starting materials for Friedländer quinoline synthesis. A cross-coupling annulation of 2-aminobenzyl alcohols with secondary alcohols was investigated by Li *et al.* for the preparation of quinolines using well-defined copper(I) 4,6-dimethylpyrimidine-2-thiolate cluster catalyst (Scheme **18**). The reaction was supposed to undergo a one-pot sequence of dehydrogenation of alcohols, condensation of aldehydes and ketones resulting in α,β-unsaturated ketones, and intramolecular nucleophilic addition of amine groups to ketone group followed by dehydration [42]. Singh reported the one-pot synthesis of structurally diverse substituted/annulated quinoline derivatives by two-component coupling of 2-aminobenzyl alcohol/2-aminobenzophenones with alkyl/aryl alcohols in the presence of air (Scheme **19**). A metal-free *in situ* aerial oxidation of

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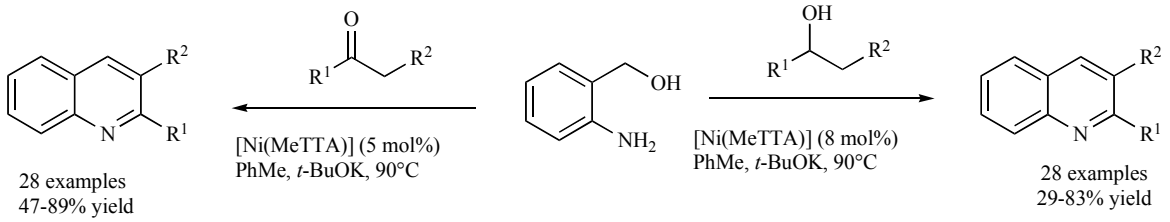
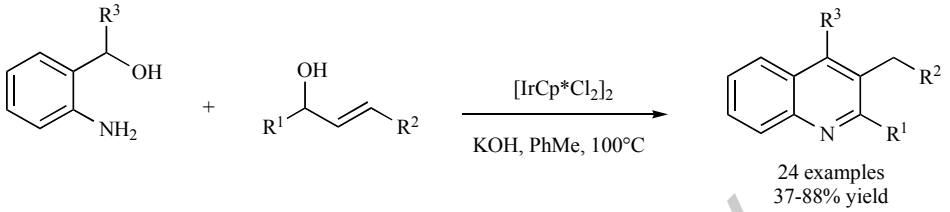
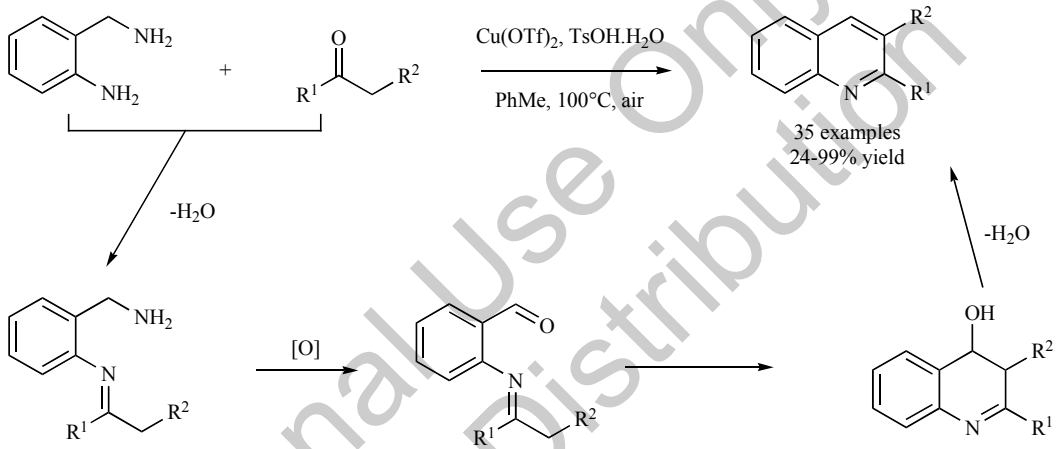


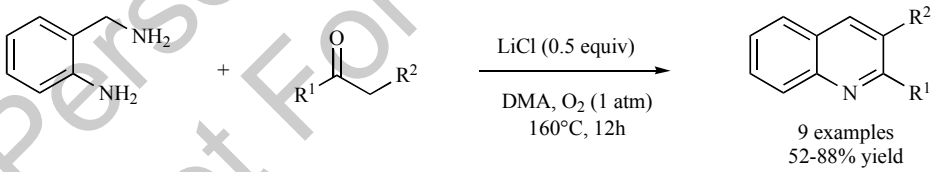
Scheme 20.



Scheme 21.



Scheme 22.



Scheme 23.

alcohols to aldehydes and ketones is supposed to occur at the first step. The synthesis has many advantages such as simple operations, high yields of the products, easy purification, and economic viability [43]. Acceptorless dehydrogenative coupling of *o*-aminobenzylalcohols with ketones or secondary alcohols catalyzed nickel catalyst [Ni(MeTAA)] was carried out to prepare 2,3 disubstituted quinolines (Scheme **20**) [44]. The preparation of quinolines derivatives from allylic alcohols and 2-aminobenzyl alcohols catalyzed by $[IrCp^*Cl_2]_2$/KOH was demonstrated by Cai *et al.* (Scheme **21**). The reaction possibly follows a tandem process integrating isomerization of allylic alcohols and oxidative cyclization of 2-aminobenzyl alcohol [45].

From ketones and *o*-amino benzylamine Yu *et al.* reported the synthesis of disubstituted quinolines. The Friedländer-type reaction proceeded *via* a C-N cleavage of amines followed by condensation with ketones under copper catalyst affording quinolines in moderate to excellent yields (Scheme **22**). The proposed reaction mechanism is presented below [46]. In an analogous study, the aerobic C-N bond activation reaction was catalyzed by LiCl using oxygen as the sole oxidant. The same mechanism was proposed for this transformation (Scheme **23**) [47].

From *o*-aminobenzaldehyde, 2-methylindole, and ketone, Gu *et al.* synthesized quinoline-fused 1-benzazepine derivatives through a Mannich-type reaction (Scheme **24)**. This is also a version of Friedländer reaction. The key intermediate of this synthesis is a hitherto-unreported C,N-1,6- bisnucleophile generated from *o*-aminobenzaldehyde and 2-methylindole by an indole-to-quinoline transformation. The proposed reaction mechanism is outlined below [48].

An efficient protocol for the preparation of disubstituted 2-quinolin-2-yl malonates and β -ketoesters from N-protected *o*-aminobenzaldehydes and α,γ-dialkylallenoates was demonstrated by Selig and Raven (Scheme **25**). The reactions underwent a sequence of Michael addition, aldol condensation, and 1,3-N → C rearrangement sequence forming products in high yields. Substrates with carbamate protection(N-Boc, N-Cbz, N-Alloc) gave 2-

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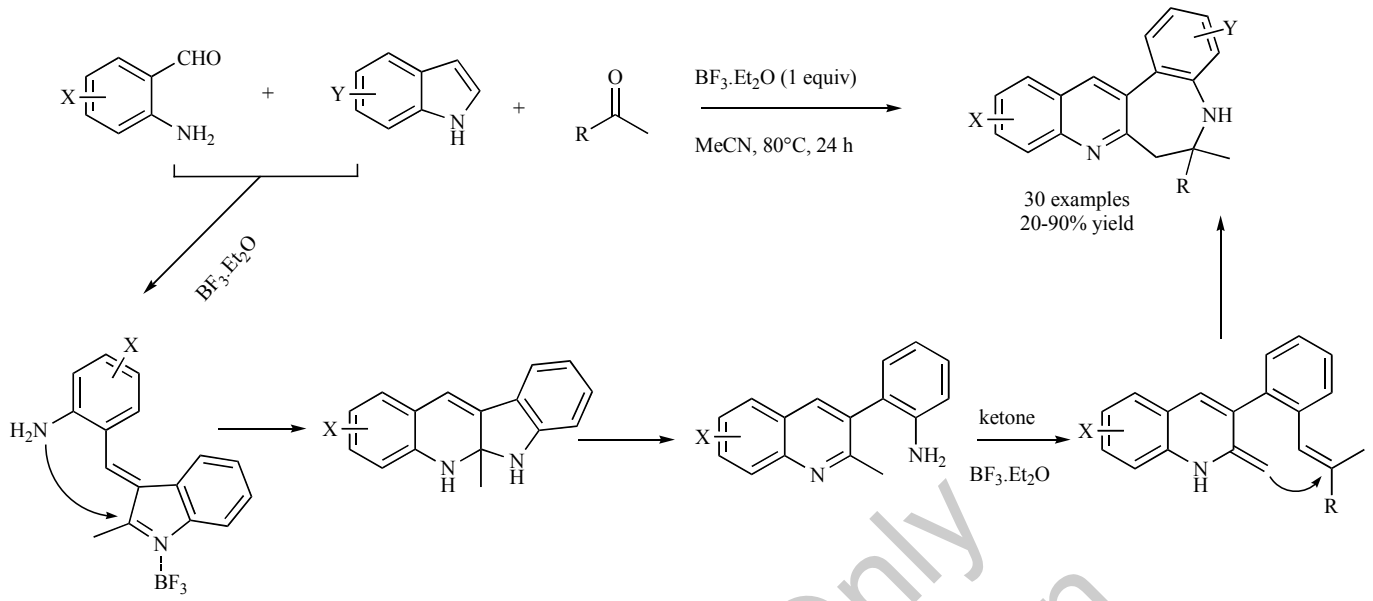
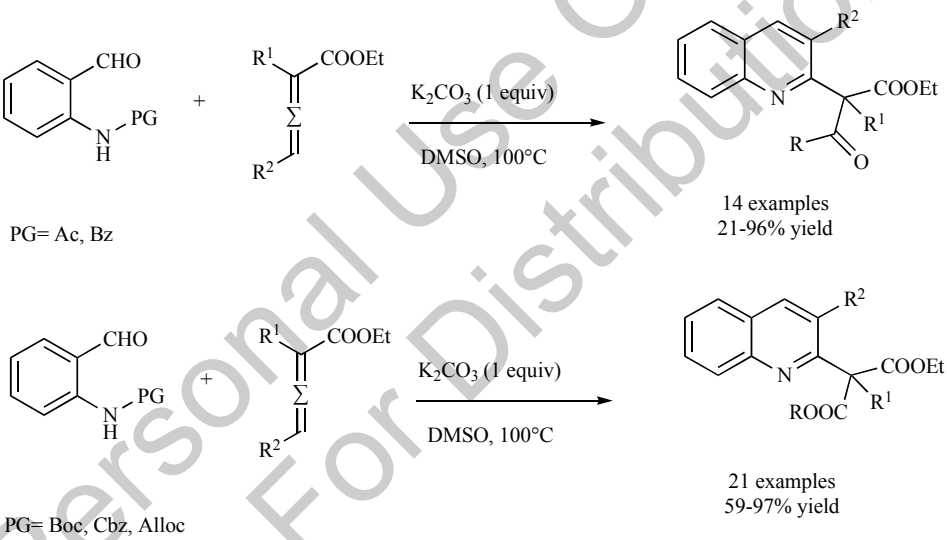
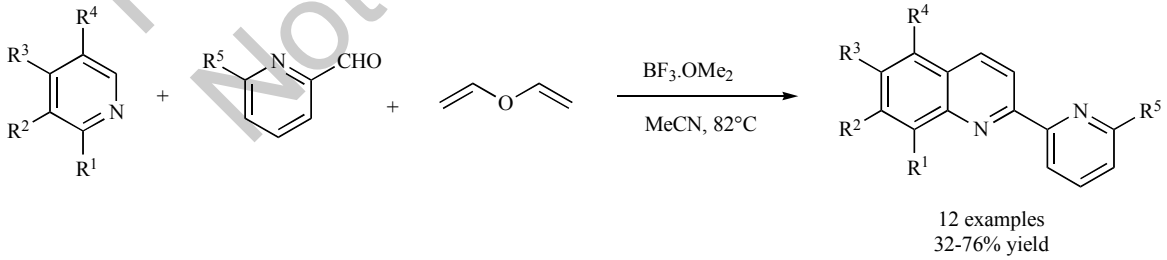


Scheme 24.



Scheme 25.



Scheme 26.

quinolin-2-yl-malonates, while amide protected substrates (N-Ac, N-Bz) furnished 2- quinolin-2-yl-β-ketoesters [49].

2.2. The Povarov Reaction

The Povarov reaction is also one of the most useful methods for quinolines synthesis. Besides the original reaction, many modifications have been developed and many reports involving the Povarov reaction have been found in the literature.

Barbosa *et al.* developed a procedure for the 2-(2-pyridyl) quinolines synthesis *via* three-component Povarov reaction of aromatic aldehydes, anilines, and ethyl vinyl ether employed BF_3OMe_2 as the catalyst (Scheme **26**). The synthesis has many advantages such as mild conditions, simple work-up, clean reaction profile, a broad range of substrate applicability, and high yields of the products [50].

Wu *et al*. described a highly efficient, I_2-catalyzed method for the synthesis of quinolines from methyl ketones, arylamines, and α-

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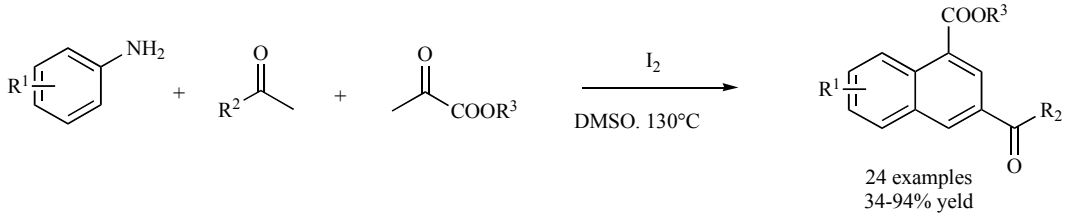
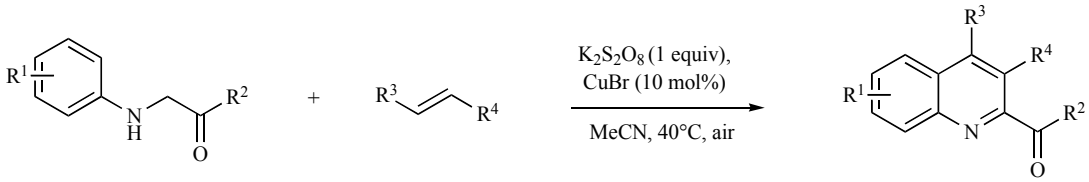
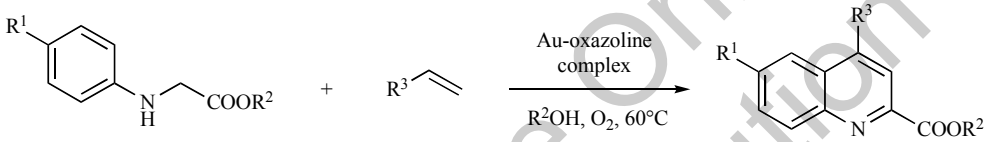


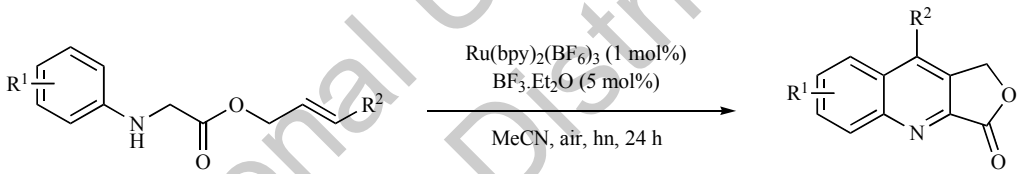
Scheme 27.



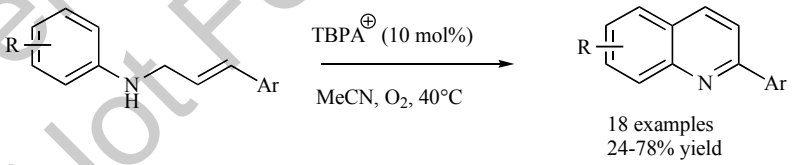
Scheme 28.



Scheme 29.



Scheme 30.



Scheme 31.

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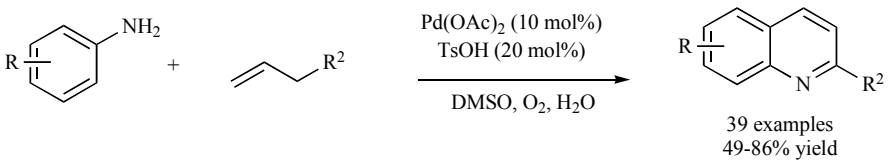
ketoesters (Scheme **27**). Their approach utilized a catalytic amount of HI co-product as a promoter and showed good functional group compatibility. In most cases, quinoline derivatives were formed in very good yields. Notably, the synthesis of ethyl 2-benzoyl-6-methylquinoline-4-carboxylate was accomplished on a large scale (10 mmol) with good yield (84%) [51].

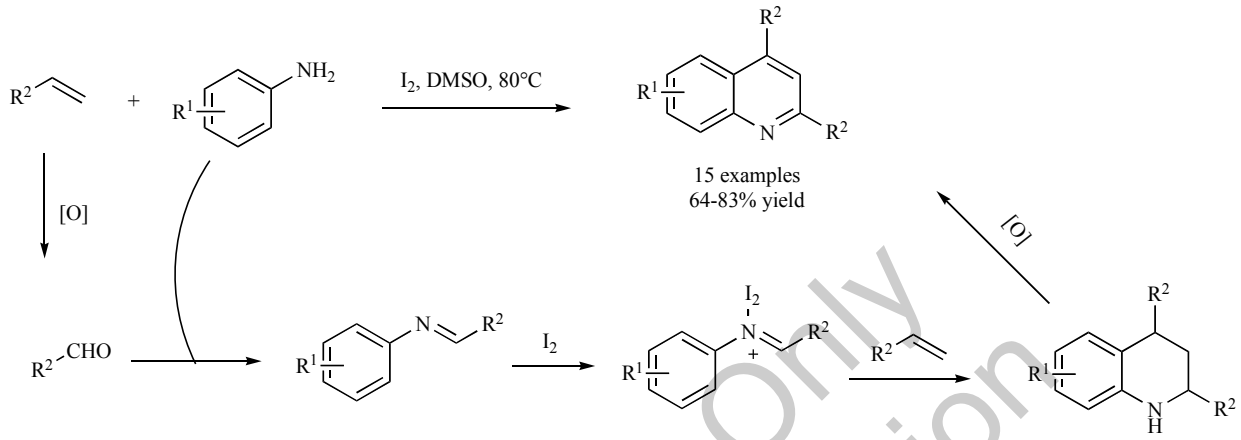
A practical and economical $K_2S_2O_8$-mediated oxidation cross-dehydrogenative coupling reaction of a variety of N-aryl glycine derivatives with olefins was performed by Liu *et al.* (Scheme **28**). The advantages of the reaction include low cost, insignificant toxicity, easy handling of $K_2S_2O_8$, no hazardous byproducts and the easy workup [52]. Feng *et al.* discovered a method for the preparation of substituted quinolines from analogous substrates by dehydrogenative Povarov/oxidation tandem reaction using gold-oxazoline complex catalyst (Scheme **29**). The reaction was performed under mild reaction conditions using O_2 as the oxidant and displayed a wide range of substrate scope and very good functional group tolerance [53].

An intramolecular Povarov cyclization reaction for the synthesis of quinoline-fused lactones was developed by Zhang *et al.* through visible-light-induced photocatalytic aerobic oxidation (Scheme **30**) [54]. The reaction was operated under mild reaction conditions providing products in moderate to good yield. In a study by Jia *et al.*, the cyclization of cinnamylaniline led to the formation of 2-arylquinolines *via* sp^3 C-H aerobic oxidation promoted by a radical cation salt (Scheme **31**) [55].

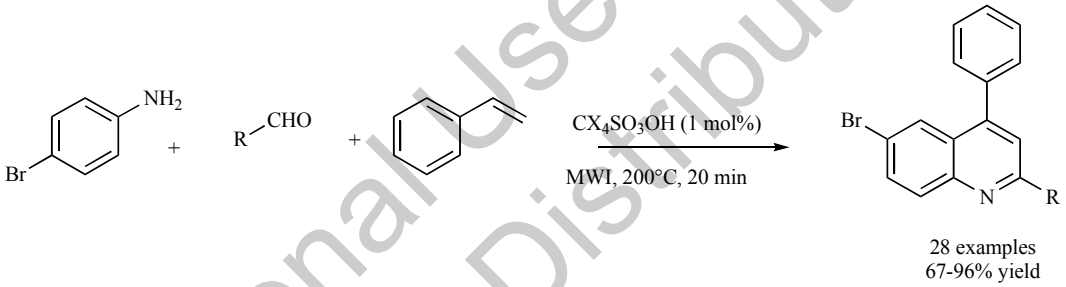
An efficient and practical palladium-catalyzed aerobic oxidative approach for the synthesis of quinoline from allylbenzenes and anilines was examined by Jiang *et al.* (Scheme **32**). The transformation was supposed to proceed through oxidation of allylic C–H functionalization to form C–C and C–N bonds in one pot [56]. In an investigation by Shah *et al.*, the reaction between



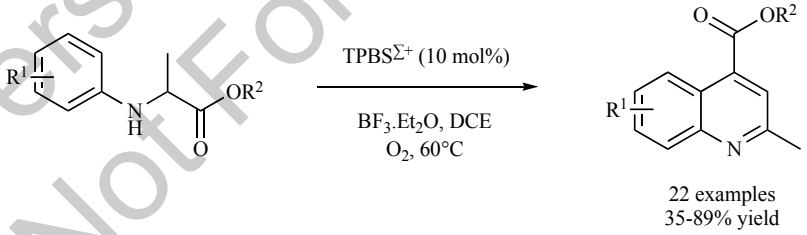
Scheme 32.



Scheme 33.



Scheme 34.



Scheme 35.

styrenes and anilines resulted in the formation of 2,4-disubstituted quinolines (Scheme **33**). The reaction proceeded efficiently over a wide range of substrate scope and showed broad functional group tolerance without using metal/oxidizing agent [57]. From 4-bromoanilin, styrene and aldehyde, Fernandes *et al.* disclosed a convenient method for the synthesis of quinolines catalyzed by *p*-sulfonic acid calix[4]arene. The merits of the synthesis include environmentally friendly operation, mild conditions and easy work-up (Scheme **34**). Twenty-eight quinolines were obtained in good to excellent yields under microwave irradiation [58].

Jia *et al.* introduced an efficient method for the synthesis of quinolin-4-carboxylate through the reaction between the 2-azadiene and dienophile enabled by the dual removable activating groups (Scheme **35**). The reaction showed good functional group tolerance and provided products in good yields in most cases [59].

The three components Povarov-type reaction between aniline, aldehyde and terminal alkyne has attracted a lot of attention recently and been reported a lot in the literature. An efficient and economical method for the synthesis of SF_5-bearing quinolines using $FeCl_3$ catalyst through a sequence of coupling, hydroarylation and dehydrogenation of *meta*/*para*-pentafluorosulfanyl anilines, aldehydes and alkynes was conducted by Xu *et al.* (Scheme **36**). The reaction was performed in the presence of air and SF_5- bearing quinolines were achieved in good yields [60]. In a study by Silva-Filho, $NbCl_5$ was used as the Lewis acid catalyst and quinolines derivatives were formed in 67 to 96% yields in MeCN at reflux (Scheme **37**) [61]. A mechanism was also suggested for the transformation. Chandak employed Zinc(II) triflate catalyst for this coupling reaction (Scheme **38**). The *pseudo* three-component Povarov reaction was performed with the absence of ligand, co-catalyst, solvent or inert atmosphere providing products in good

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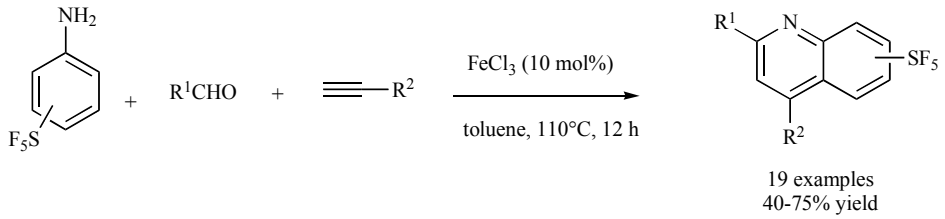
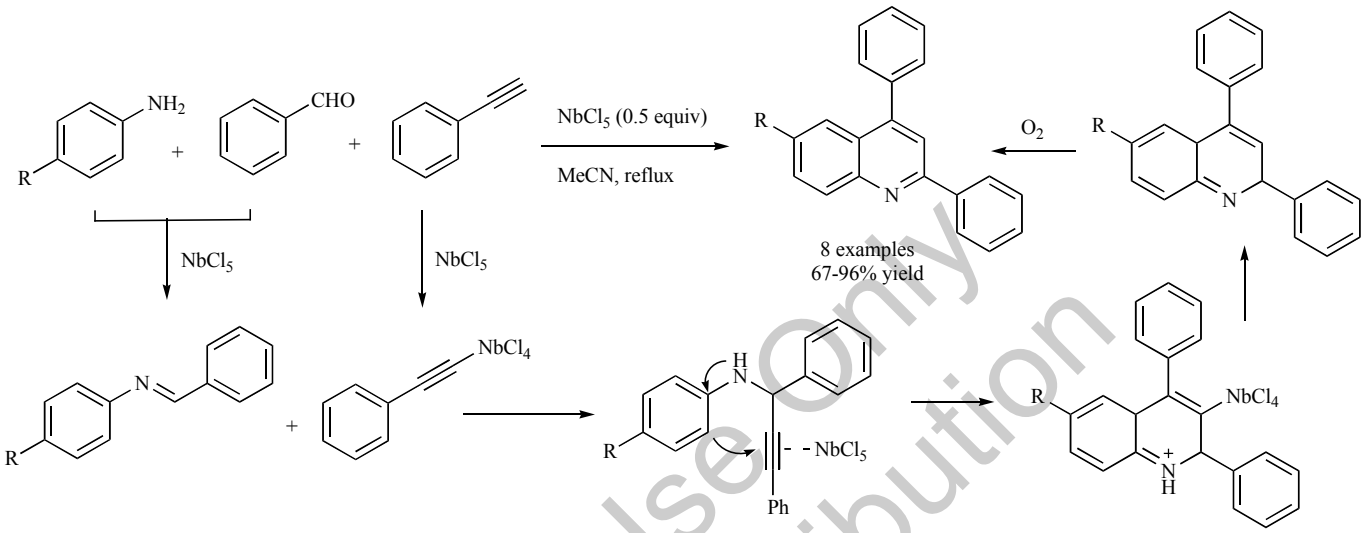
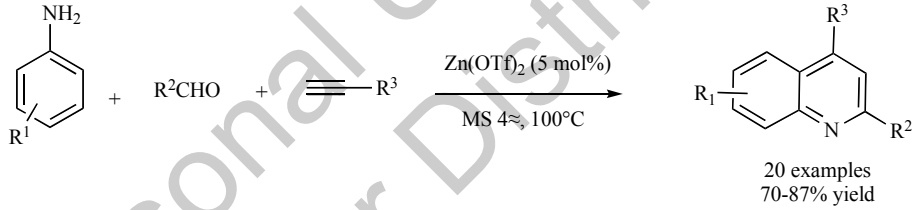


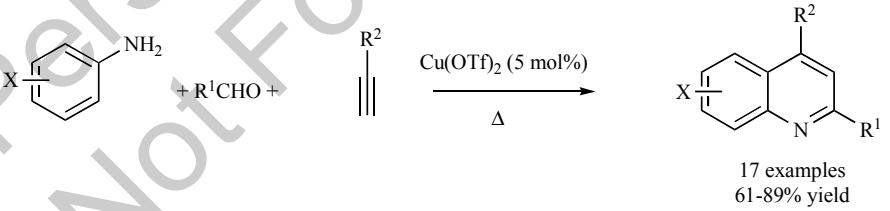
Scheme 36.



Scheme 37.



Scheme 38.



Scheme 39.

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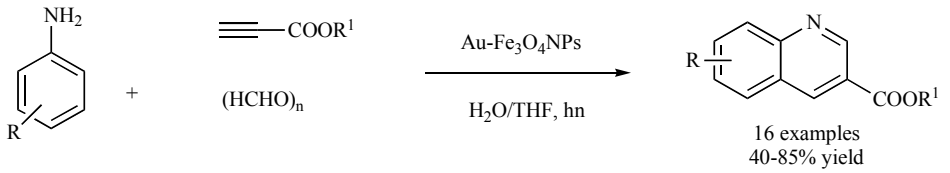
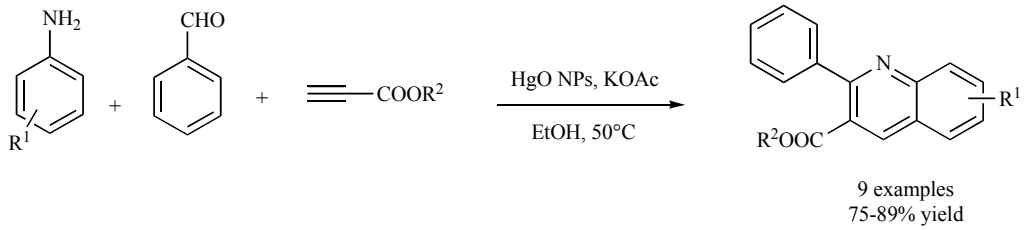
yields [62]. In another report, Larsen and Mayet performed this reaction with Copper(II) triflate catalyst to prepare quinoline derivatives (Scheme **39**). The Povarov reaction proceeded well without ligand, cocatalyst, solvent, or inert atmosphere forming products in good yields [63].

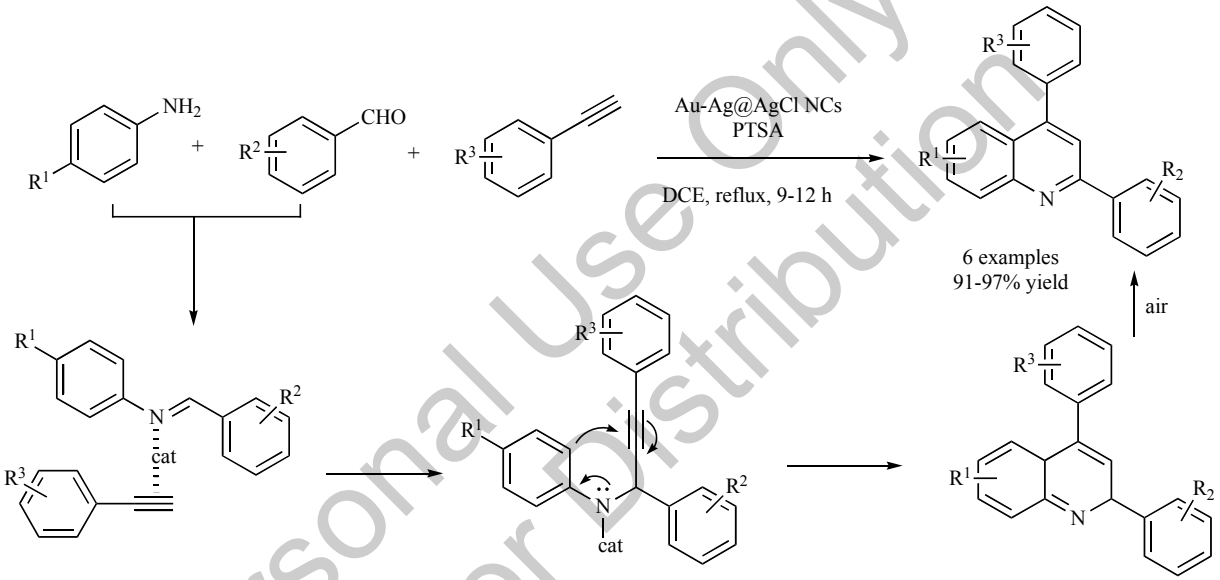
The use of nanomaterials as catalyst for this Povarov-type reaction has also been well- investigated. Bhalla *et al.* prepared polythiophene-encapsulated bimetallic $AuFe_3O_4$ nanohybrid materials having a fibrous morphology and used this complex as a catalyst for the synthesis of quinolines through C-H activation, carbonylation, and subsequent annulation (Scheme **40**). The synthesis featured many advantages such as aqueous media, room temperature, visible-light irradiation, and aerial conditions [64]. This group also prepared supramolecule ensemble of tetraphenylcyclopentadienone aggregates and HgO nanomaterial as the catalyst for Povarov synthesis of quinoline through ortho C-H functionalization of anilines. Diverse quinolines were furnished in very good yields (Scheme **41**). In addition, the nanocatalyst could be reused up to three times without a major decrease in the activity [65]. Han and Sapkota developed an environmentally friendly method for the efficient synthesis of Au-Ag@AgCl NCs and used this nanomaterial as the catalyst for the synthesis of pharmaceutically important quinoline derivatives in excellent yields. The synthesis was supposed to proceed through a three-component sequence of annulation and aromatization reaction of aldehydes, amines, and alkynes (Scheme **42**). The catalytic system was reused five times without any considerable loss of activity [66]. Baltork *et al.* investigated an efficient microwave-assisted synthesis of quinoline derivatives. The use of efficient and reusable catalyst Fe_3O_4-TDSN-Bi(III) produced quinolines in good to excellent yields in a regioselective manner (Scheme **43**) [67].



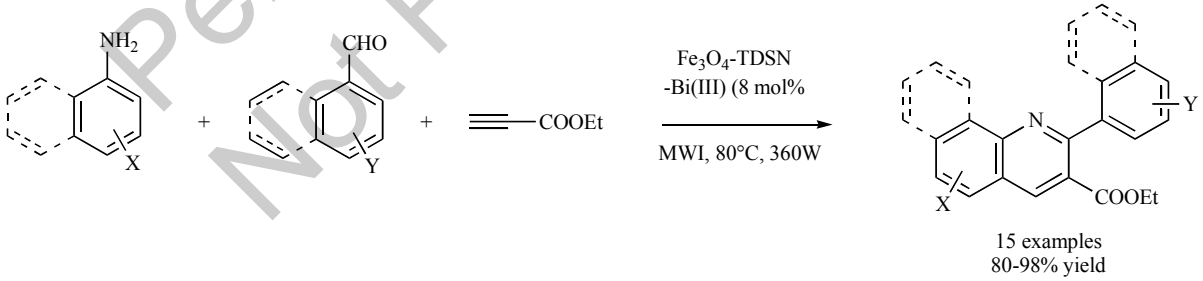
Scheme 40.



Scheme 41.



Scheme 42.



Scheme 43.

Jin reported that 4-hydroxalkyl-quinoline derivatives can be synthesized following the same Povarov-type reaction. The three-component cascade reaction was catalyzed by Cu(I)Cl and Au(I)Cl giving quinolines in high yields (Scheme **44**). The intermediate **A** could be isolated and converted into the final product by changing reaction conditions [68].

2.3. Pfitzinger Reaction

Lee *et al*. reported the Pfitzinger synthesis of pyrrolo[3,4-*c*]quinoline-1,3-dione derivatives by microwave-promoted cascade reaction between isatins and β-ketoamides in [Bmim]BF_4/toluene (Scheme **45**). The synthesis had many advantages such as short reaction time, mild reaction conditions, high yields, simple operations, easy product purification, and recyclability of the catalyst [69]. A simple three-step process for the Pfitzinger synthesis of substituted quinoline- 4-carboxylic acids from anilines was reported by Lindsay-Scott and Barlow (Scheme **46**). Mixtures of regioisomers were formed and separated without chromatographic purifications due to their solubility differences. The synthesis was completed at multigram-scale for all substrates (22-54.4 mmol of isatins was used in the second step) [70]. Elghamry and Al-Faiyz described a simple one-pot synthesis of quinoline-4-

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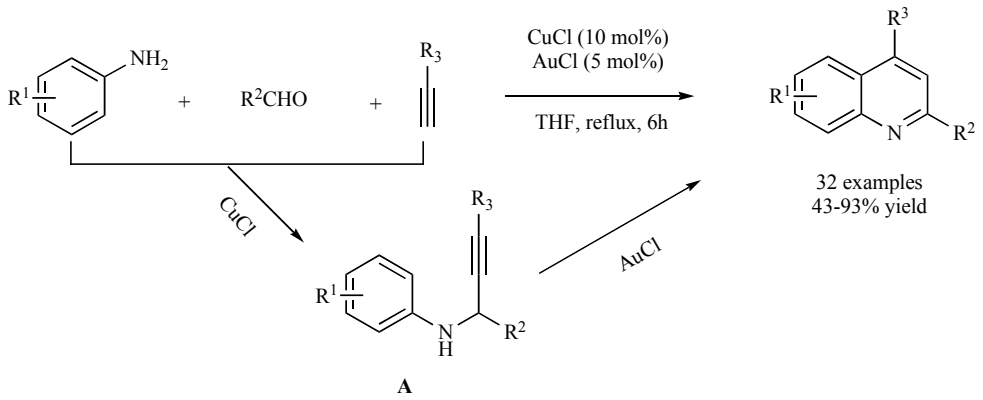
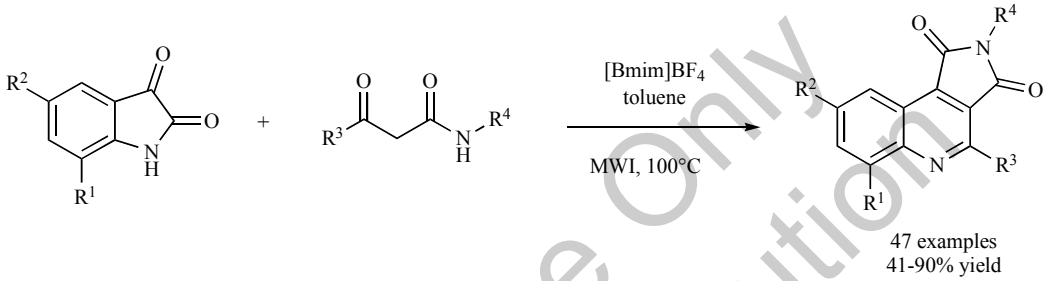
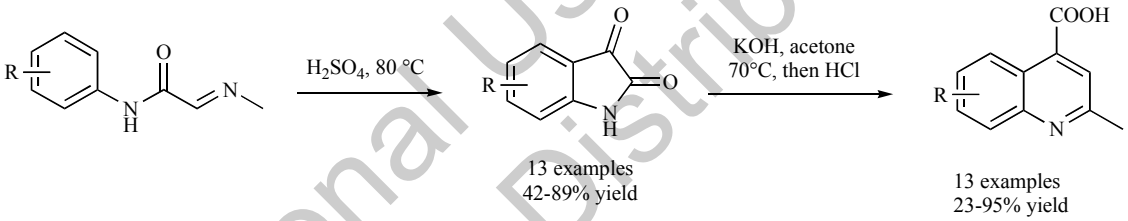


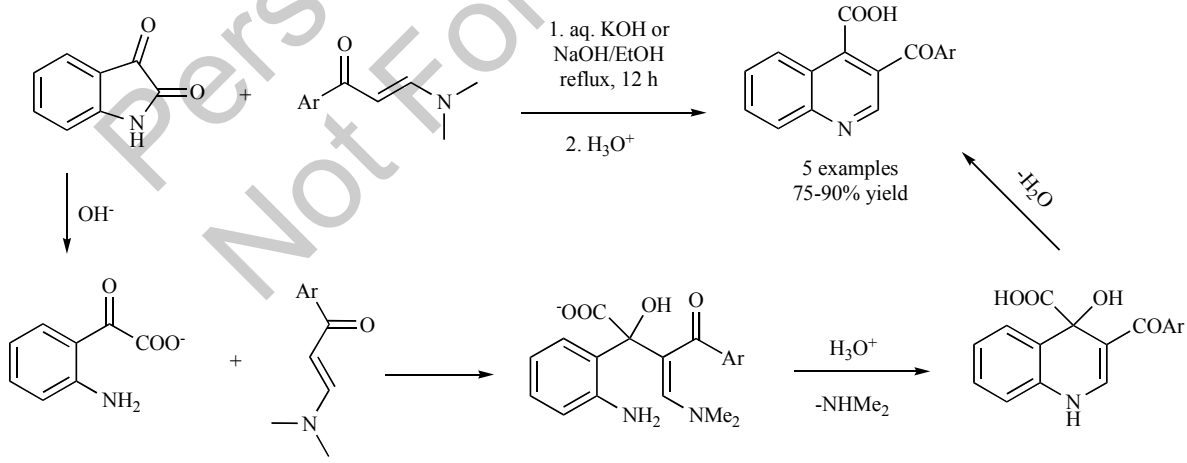
Scheme 44.



Scheme 45.



Scheme 46.



Scheme 47.

carboxylic acids between enaminones and isatin (Scheme **47**). High yield of quinoline derivatives was obtained. A plausible mechanism for the transformation was also presented [71].

Gao *et al.* reported an efficient Pfitzinger quinoline synthesis from ketoxime acetates and isatins. The reaction underwent N-O/C-N bond cleavages and new C-C/C-N bond formations, along with the activation of Csp^3-H bond (Scheme **48**). The synthesis did not employ metal catalysts or extra oxidants and a high yield of products was obtained in most cases [72]. Perumal *et al.* demonstrated a new and efficient one-pot, three-component procedure for the regioselective synthesis of isoxazolo[5,4-*b*]quinolin-4-yl)pyrimidine-2,4(1H,3H)-diones and isoxazolo[5,4-b]quinolin-4-yl)-1H-pyrazol-5-amines by the cleavage of the isatin *C-N* bond followed by ring expansion in one-pot reaction using

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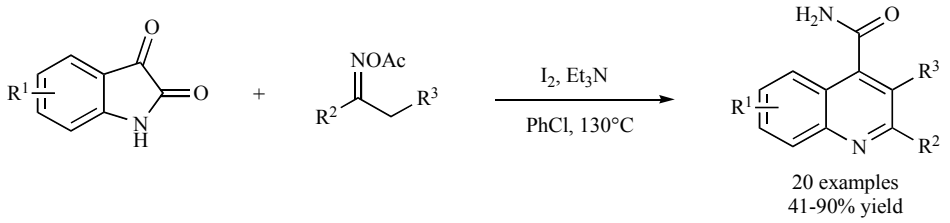
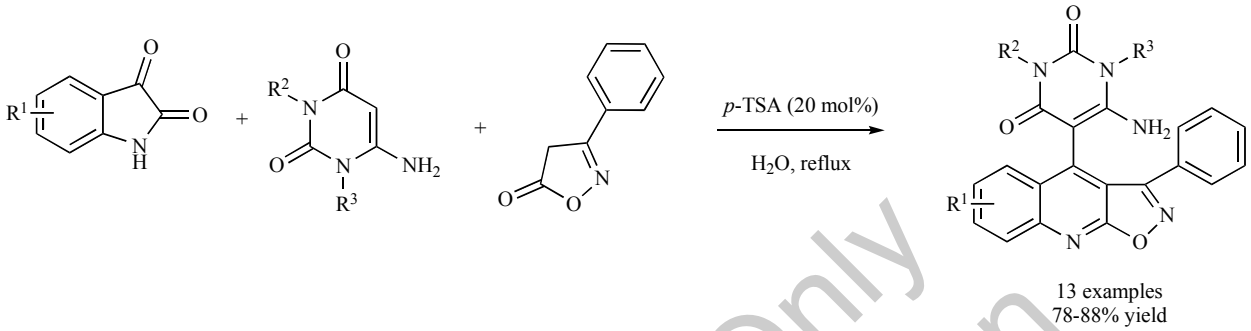
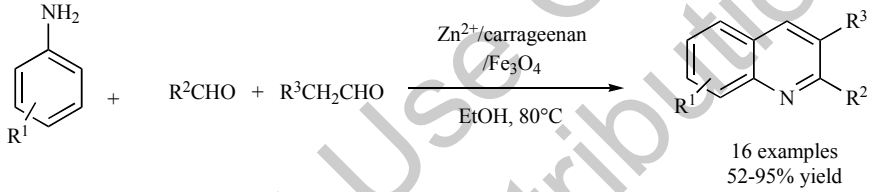


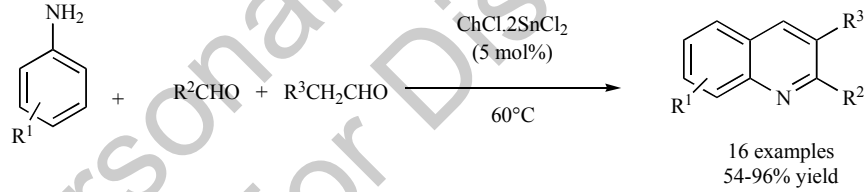
Scheme 48.



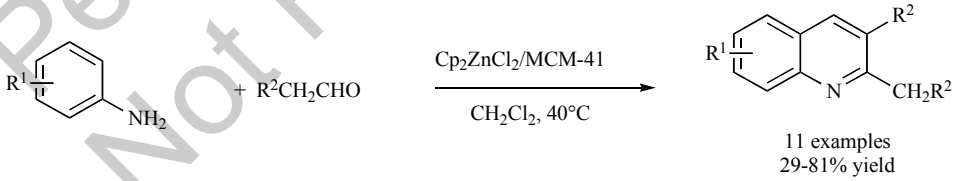
Scheme 49.



Scheme 50.



Scheme 51.



Scheme 52.

environmentally benevolent *p*-toluene sulphonic acid as a catalyst (Scheme **49**). The simple operation procedure, the use of inexpensive and environmentally friendly catalyst and high yields of products are the merits of the synthesis [73].

2.4. The Doebner Reaction

Tavakol and Keshavarzipour reported the synthesis of Zn^{2+}/ƛ-carrageenan/Fe_3O_4 magnetic nanoparticles and applied this material as a catalyst for the synthesis of multi-substituted quinolines (Scheme **50**). Sixteen quinolines were prepared in high yields through a one-pot reaction protocol between aromatic aldehydes, enolizable aldehydes and aniline derivatives in a nontoxic solvent [74]. Later, Tavakol group continued to develop a one-pot, multi-component quinoline synthesis protocol for the synthesis of quinolines. In this synthesis, the deep eutectic solvent Choline chloride/tin(II) chloride ($ChCl_2/SnCl_2$) was also employed as a green catalyst (Scheme **51**). The reaction between aniline derivatives, aryl aldehydes and enolizable aldehydes occurred at 60 °C for 2–3 h giving quinoline derivatives in high yields (54-96)% [75]. Meng *et al.* used Cp_2ZrCl_2 or Cp_2ZrCl_2 supported on MCM-41 (Cp_2ZrCl_2/MCM-41) as the catalyst for the synthesis of quinolines from anilines and aldehydes (Scheme **52**). When Cp_2ZrCl_2/MCM-41 was employed, the yields of the products were increased by 5-15% in comparison with Cp_2ZrCl_2 alone under the same reaction conditions [76]. A dehydrogenative cross-coupling process between primary alcohols and imines toward the synthesis of substituted quinolines catalyzed by ruthenium complex under microwave conditions was investigated by Porcheddu *et al.*

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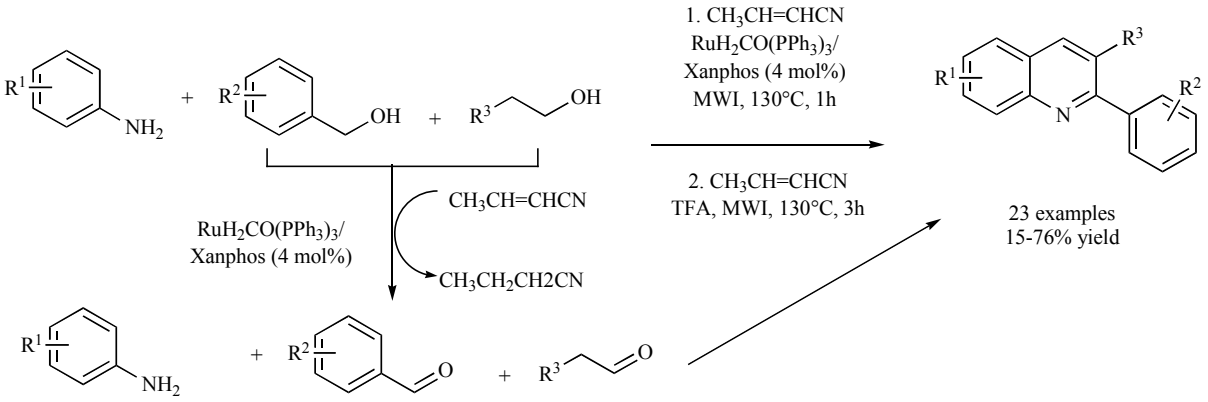
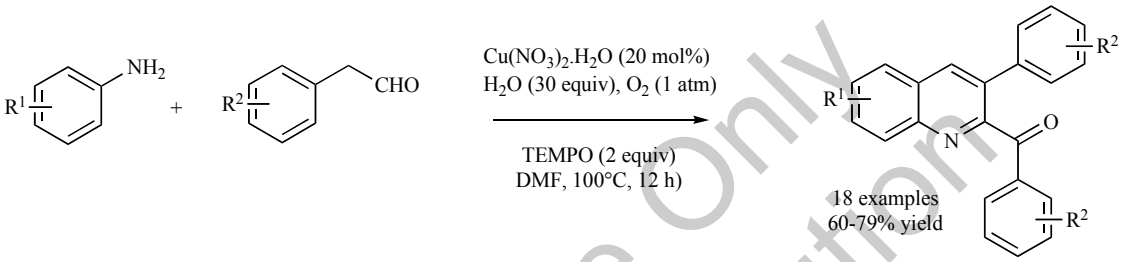
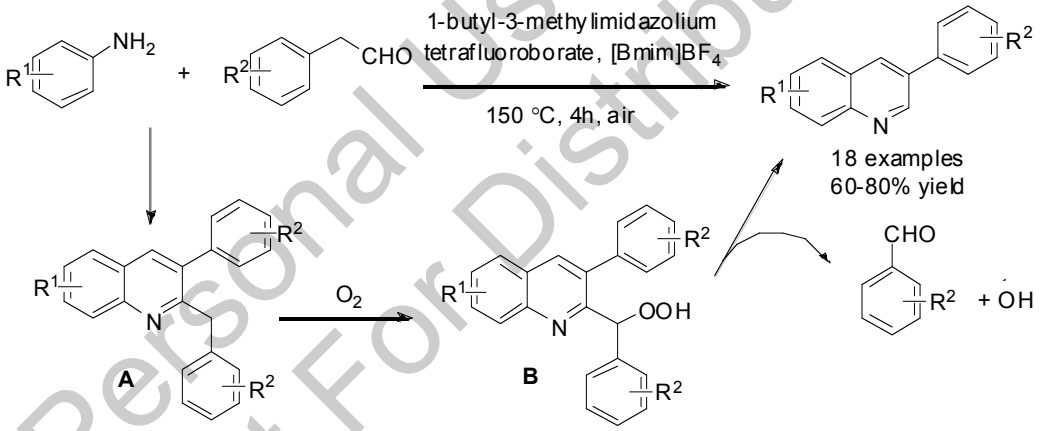


Scheme 53.



Scheme 54.



Scheme 55.

(Scheme **53**). Quinolines were produced in moderate to good yield in the presence of TFA (30 mol%) [77].

With modification, the Doebner reaction between aniline derivatives and aldehydes could also form other products. Liao *et al.* synthesized 2-aroylquinolines through a copper-catalyzed selective aerobic oxidation and oxygenation approach (Scheme **54**). Environment-benign O_2 was used to oxidize the keto moiety in the final products and this was proved by using O^{18}-labelling (O^{18} appeared in the keto moiety of the products) [78]. From anilines and phenylacetaldehydes, Vishwakarma *et al.* developed an expedient method for the synthesis of substituted quinolines using imidazolium cation-based ionic liquids as the catalyst and the reaction medium (Scheme **55**). Isolable 2,3-disubstituted quinoline intermediates were supposed to occur through C-C and C-N bond formation first, followed by C-C bond cleavage to produce 3-substituted quinolines. The synthesis has many advantages such as nonmetal catalyst, environmentally friendly conditions, recyclability of reaction media, higher yields of products and short reaction times. The use of $[Bmim]BF_4$ alone led to a mixture of the final product and the intermediate **A** with some substrates [79].

A simple and metal-free method was conducted by Nan *et al.* for the synthesis of quinolines through **a** three-component tandem reaction of arylamines, ethyl glyoxylate, and α-ketoesters catalyzed by inexpensive iodine (Scheme **56**). The mild conditions synthesis resulted in quinoline-2,4-carboxylates in moderate to good yields with excellent functional group tolerance [80].

2.5. Other Reactions

Cowen and Ramann performed an improved Doebner–Von Miller reaction to synthesize quinoline derivatives from acrolein diethyl acetal and aniline substrates without organic solvent (Scheme **57**). Diverse substituted aniline substrates were found to be compatible with the reaction conditions. The reaction showed a broad range of functional group tolerance such as alkyl groups, halogens, phenols, and heterocycles. The corresponding quinoline products were isolated in moderate to good yields [81].

Regioselective synthesis of alkyl 2-(3- arylbenzo[*f*]quinolin-1-yl)acetate catalyzed by camphorsulfonic acid was accomplished through δ-selective of *β*-ketoester (Scheme **58**). The formation of

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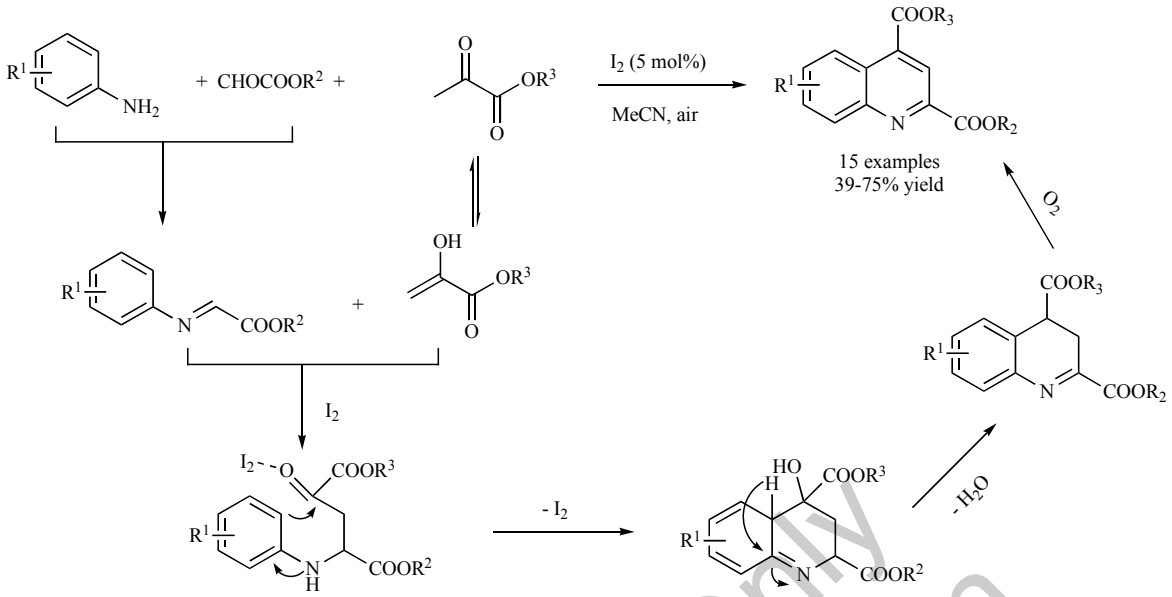
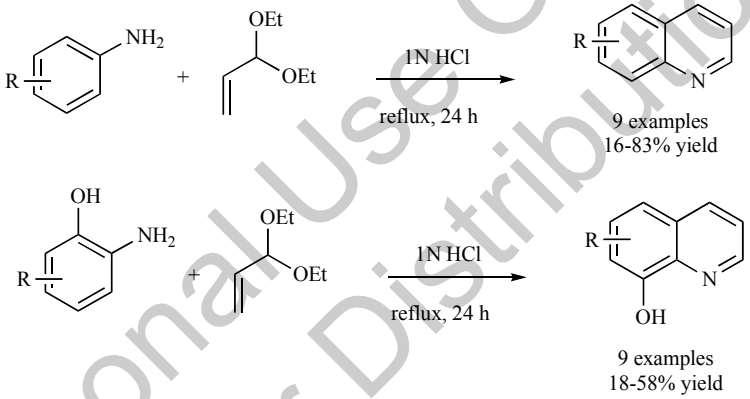
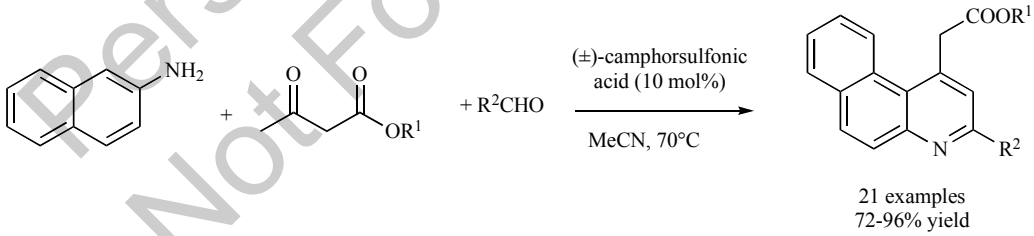


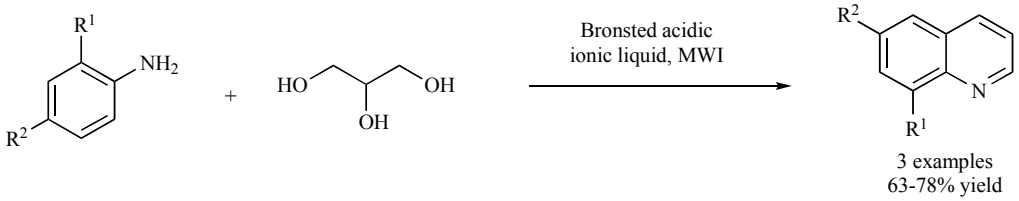
Scheme 56.



Scheme 57.



Scheme 58.



Scheme 59.

two new C-C bonds was performed in a one-pot fashion under mild Conrad-Limpac reaction conditions providing trisubstituted benzo[*f*]quinolines in good to excellent yields [82].

Amarasekara and Hasan reported Skraup synthesis of quinolines in which 1-(1-alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquids were employed as catalyst and reaction mediums (Scheme **59**) [83]. The synthesis was performed under microwave irradiation in the absence of nitrobenzene as an oxidant and metal catalysts. Microwave irradiation was also used by Len *et al.* for Skraup quinoline

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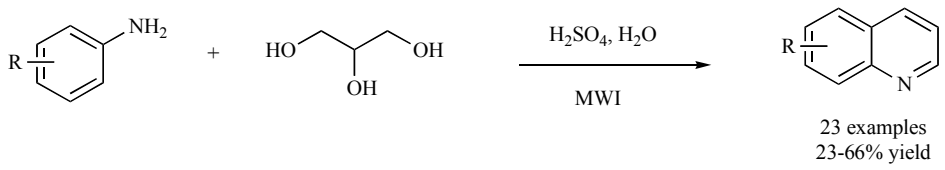
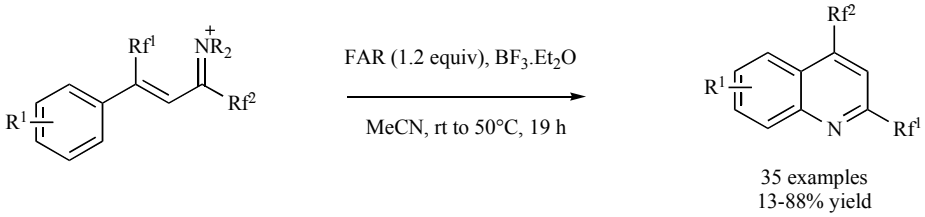
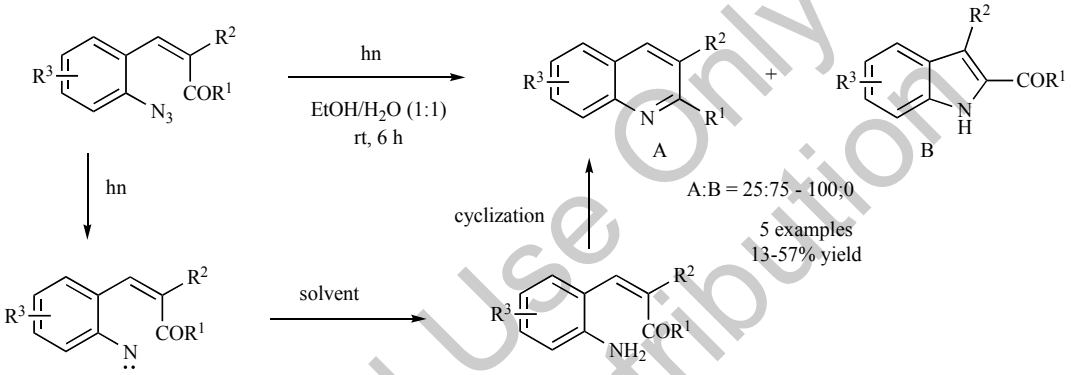


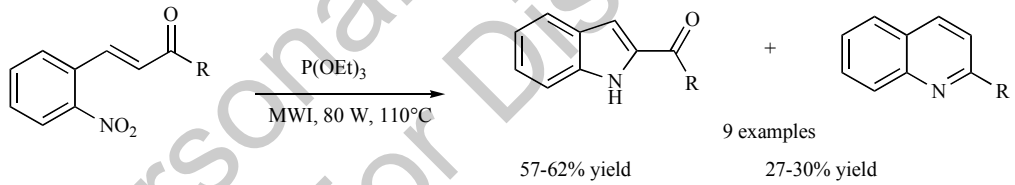
Scheme 60.



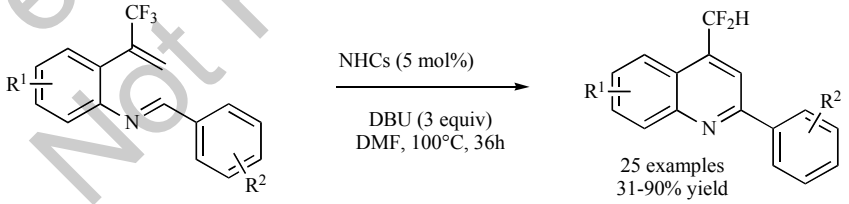
Scheme 61.



Scheme 62.



Scheme 63.



Scheme 64.

synthesis with a catalyst of sulfuric acid (Scheme **60**). All reactions were performed in gram-scale (10 mmol of aniline derivatives) [84].

3. QUINOLINE SYNTHESIS THROUGH NOVEL SYNTHETIC ROUTES

3.1. One-component Reaction

Leroux *et al.* described the synthesis of 2,4- bis(fluoroalkyl)-substituted quinoline derivatives using fluoroalkyl amino reagents (FARs) in two steps (Scheme **61**). Under mild reaction conditions , high yields and very good regioselectivity of the products were observed [85].

A photochemical procedure for the synthesis of quinolines and indoles was developed by Chassaing *et al.* (Scheme **62**). Quinolines products were formed only when the reaction was performed in EtOH/H_2O media. The proposed mechanism for quinolines formation is outlined below [86].

In the investigation by Kapoor *et al.*, 2-arylquinolines were formed as side products through one-pot synthesis by the reductive cyclization of 3-(2-nitrophenyl)- 1-arylprop-2-en-1-ones assisted by microwave irradiation using triethoxyphosphite [$P(OEt)_3$] catalyst (Scheme **63**) [87].

The preparation of 2-aryl-4-difluoromethylquinolines by NHC-catalyzed umpolung of aldimines was introduced by Biju *et al.* (Scheme **64**). The NHC generated from the bicyclic triazolium salt

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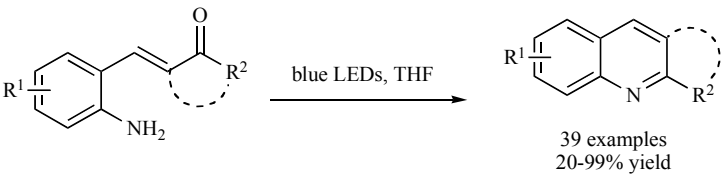
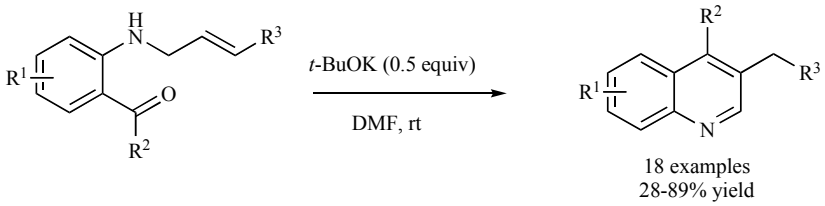
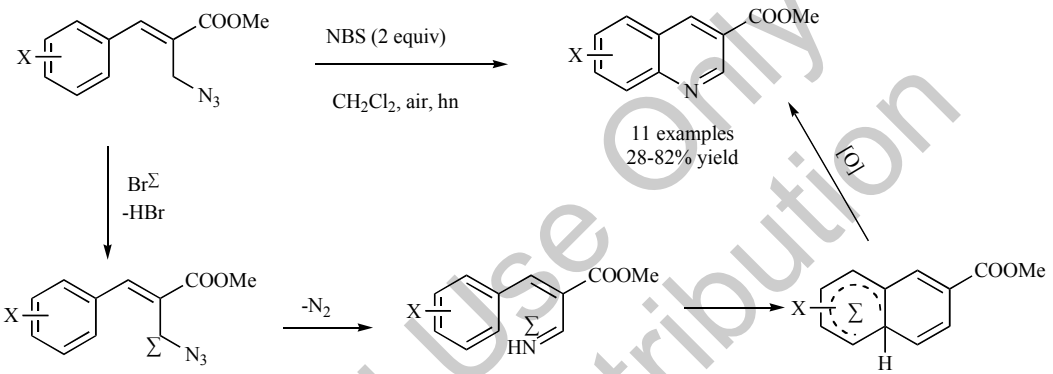


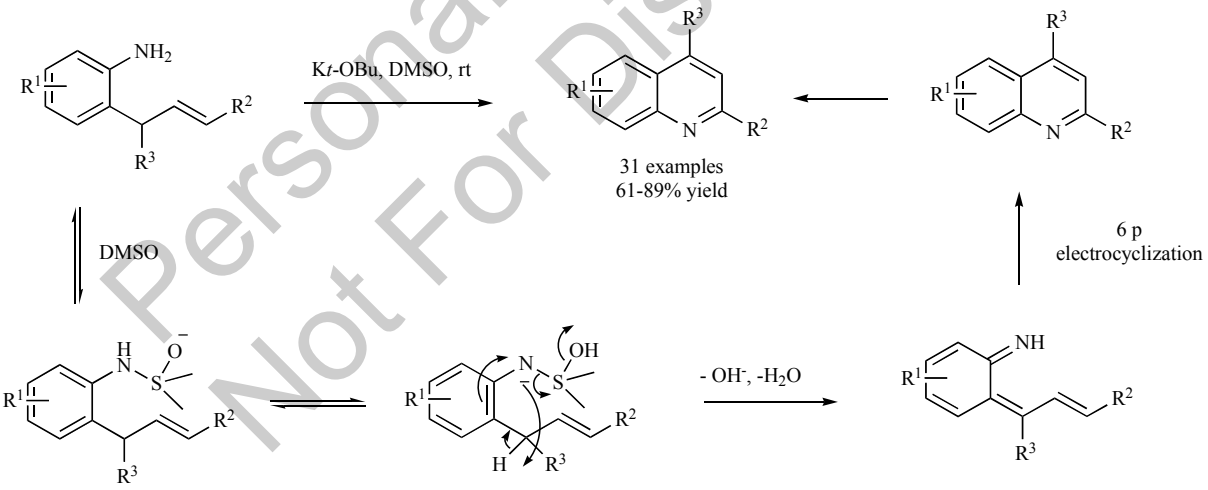
Scheme 65.



Scheme 66.



Scheme 67.



Scheme 68.

and DBU base played the key success to this aza-Stetter type transformation [88].

In a study by Wang *et al.*, quinolines were obtained through carbon–carbon double bond isomerization of α, β-unsaturated ketone derivatives under simple aerobic conditions (Scheme **65**). Attractive features of the synthesis include catalyst-free, convenient operation, good functional group tolerance, the use of invisible light and atom economy [89].

Yan *et al.* reported an intramolecular cyclization of allylamines and ketones catalyzed by KO-t-Bu for quinoline synthesis (Scheme **66**). The reaction might undergo a rearrangement of α-aminoallyl radicals and generate nucleophilic enamine intermediates [90].

A new procedure for the synthesis of quinoline-3-carboxylic acid derivatives from methyl 2-(azidomethyl)-3-arylpropenoates and 2-(azidomethyl)-3-arylacrylonitriles was established by Yu *et al.* (Scheme **67**). These substrates reacted with NBS with the assistance of visible light to generate iminyl radicals, which then underwent an intramolecular ortho attack on the aryl ring, yielding quinolone derivatives [91].

A novel and environmentally friendly approach for the synthesis of 2-arylquinoline and 2- styrylquinolines from *o*-cinnamylanilines catalyzed by *t*-BuOK/DMSO was investigated by Ghorai *et al.* (Scheme **68**). Regioselective *6-endo-trig* intramolecular oxidative cyclization mediated by *t*-BuOK using DMSO

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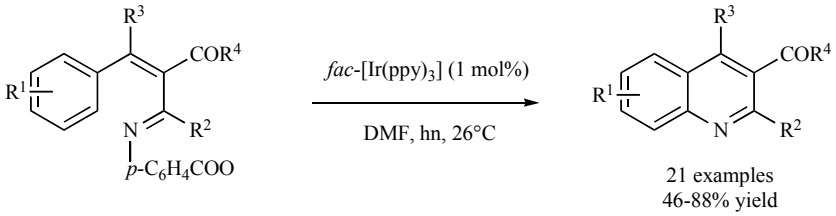
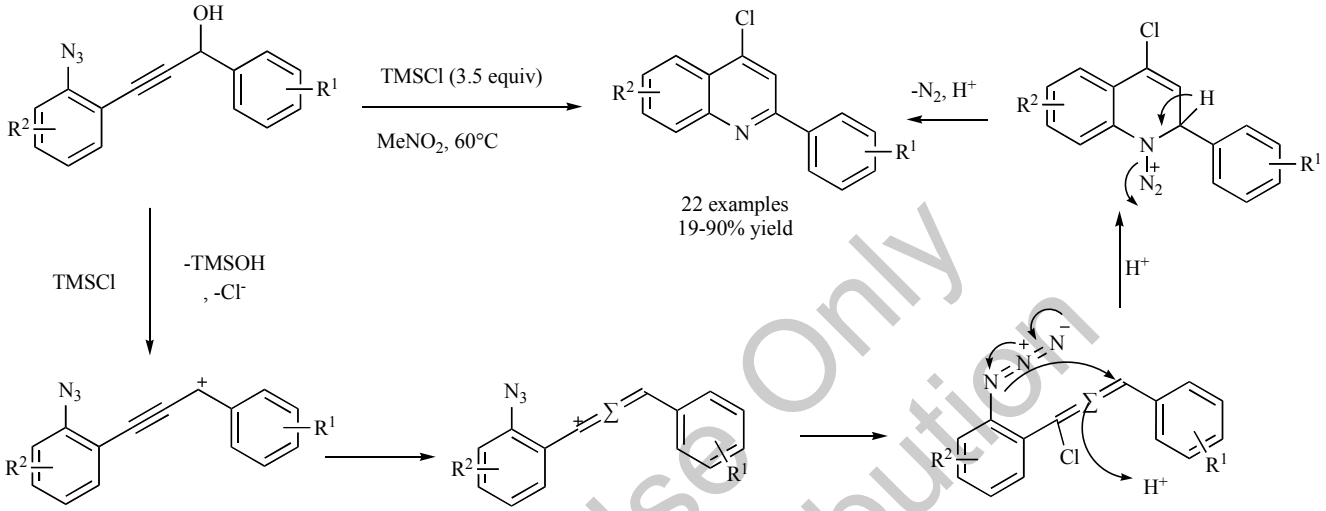
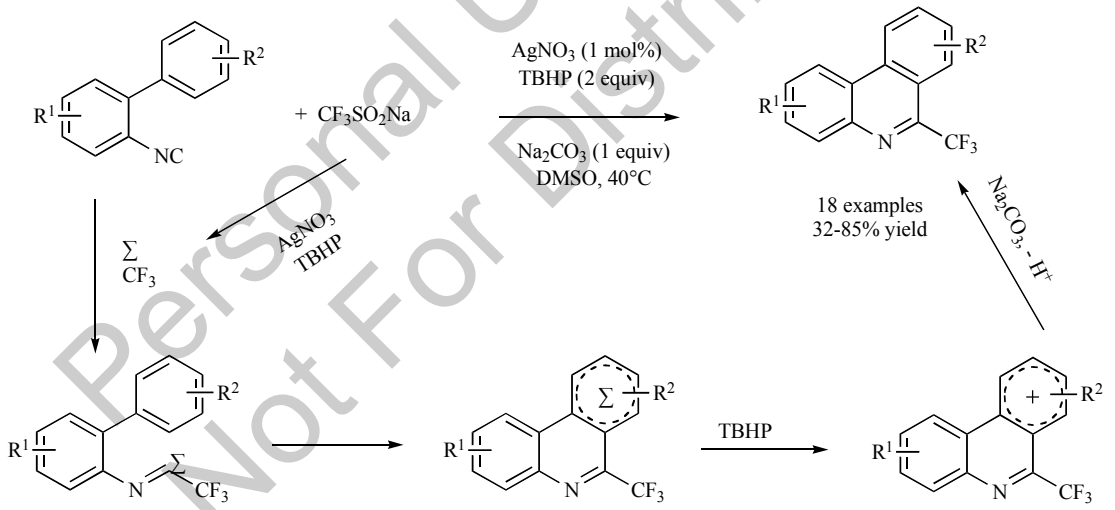


Scheme 69.



Scheme 70.



Scheme 71.

as an oxidant was supposed to occur at room temperature. The reaction has a wide substrate scope and good functional group tolerance, furnishing quinoline derivatives in moderate to good yields [92].

Yu *et al.* introduced a new method for the synthesis of quinolines from acyl oximes through visible-light induced iminyl-radical formation (Scheme **69**). In the presence of fac- [Ir(ppy)3] photoredox catalyst, the acyl oximes were transformed into iminyl radical intermediates, which then formed quinoline derivatives through intramolecular homolytic aromatic substitution. These reactions tolerate a wide range of substrates at room temperature giving products in high yields [93].

Xiao *et al.* presented a novel cascade cyclization of *ortho*-propynol phenyl azides for the synthesis of multi-substituted 4-chloro quinoline derivatives using TMSCl as the mediator (Scheme **70**). The C-N and C-Cl bonds were formed in one step through the cascade cyclization. Under mild conditions, quinoline products were afforded in moderate to excellent yields with a wide range of functional group tolerance [94].

In a study by Zhang *et al.*, Langlois reagent was utilized for the synthesis of 6-(trifluoromethyl) phenanthridines under mild oxidative cyclization (Scheme **71**). In the presence of silver nitrate, *tert*-butyl hydroperoxide, and sodium carbonate, a series of phenanthridines were yielded from corresponding aryl isonitriles in moderate to good yields, through a tandem trifluoromethylation–cyclization process [95].

Quinolines can be formed by the reduction of 1,2,3,4-tetrahydroquinoline derivatives. A dehydrogenative procedure for

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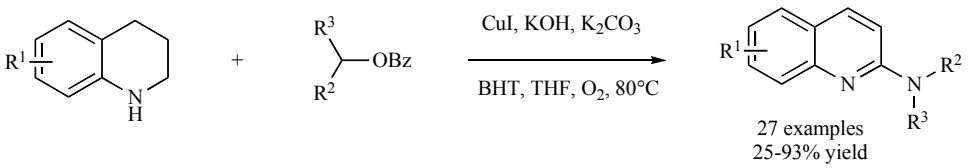
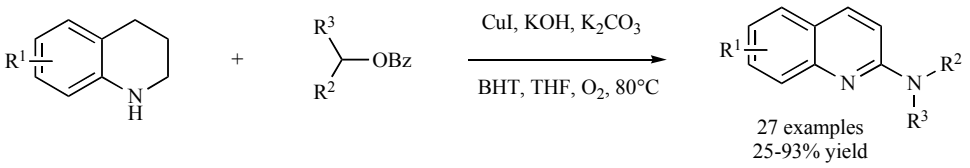
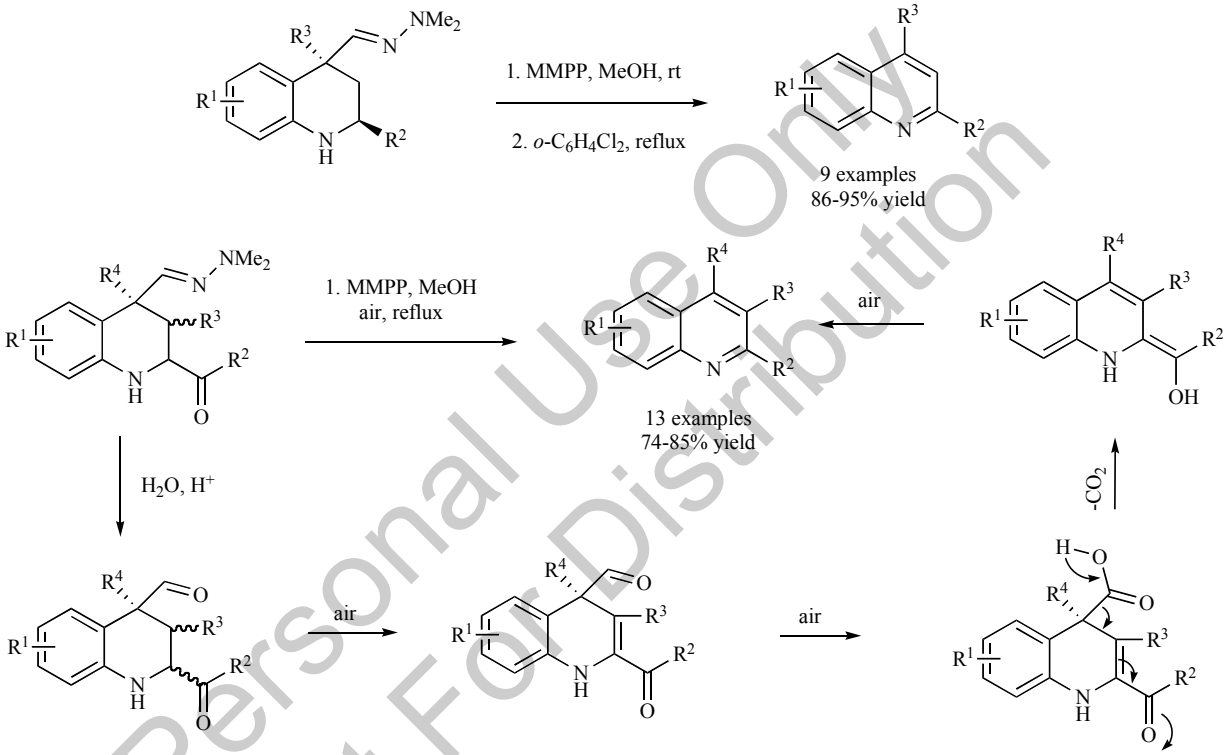


Scheme 72.



Scheme 73.



Scheme 74.

the synthesis of 2- alkylaminoquinolines through direct α-C(sp^3)-H amination of 1,2,3,4-tetrahydroquinolines catalyzed by copper iodide was conducted by Zhang *et al.* (Scheme **72**). The reduction reaction used O_2 as the oxidant under mild conditions with operational simplicity and suitability for functional groups [96]. In Stahl and Iosub research, Co_3O_4-NGr/C was employed as the catalyst for quinoline synthesis through aerobic dehydrogenation of different 1,2,3,4-tetrahydroquinolines (Scheme **73**) [97]. Menéndez *et al.* described a method for the synthesis of multi-substituted quinolines from 2-acyl-4-alkyl-4-dimethylhydrazonomethyl-1,2,3,4-tetrahydroquinolines through a sequence of the oxidative generation of a C-4 nitrile group and its elimination under thermal conditions (Scheme **74**). The transformation gave quinoline derivatives in very good yields [98].

3.2. Two-component Reaction

Wang *et al.* explored an efficient and practical method for the synthesis of quinoline involving alkylation of *N*-propargylanilines with ethers mediated by TBPB (Scheme **75**). The metal-free synthesis by a domino radical addition/cyclization reaction gave 3-alkylated quinolines in one step in moderate yields [99]. In a similar study, Sun *et al.* employed *fac*-Ir(ppy)$_3$ as the catalyst for the synthesis of 3-difluoroacetylated quinolines and 3-fluoroacetylated quinolines from *N*-propargyl aromatic amine and ethyl bromodi-fluoroacetate through a cascade addition/cyclization induced by visible light (Scheme **76**). The reactions occurred under mild conditions affording quinoline derivatives in good yields for most substrates [100]. From *N*-propargyl aromatic amine derivatives and arylsulfonylhydrazides, Tang *et al.* established a new method for the synthesis of 3-arylsulfonylquinoline derivatives through a sequence of sulfonylation, cyclization, aromatization mediated by TBHP without using any metals (Scheme **77**). The synthesis was suitable for a wide range of substrates and gave quinoline derivatives in high yields [101]. Guan *et al.* developed a protocol for the synthesis of quinoline-3-carboxylic esters from N-(3-phenylprop-2-ynyl)anilines *via* regioselective cyclocarbonylation with carbon monoxide and alcohols catalyzed by palladium complex (Scheme **78**) [102]. Zhang *et al.* reported the synthesis of 3-vinylquinolines from the dimerization of *N*-arylpropargylamines (Scheme **79**). The quinoline products were formed through the Pd-

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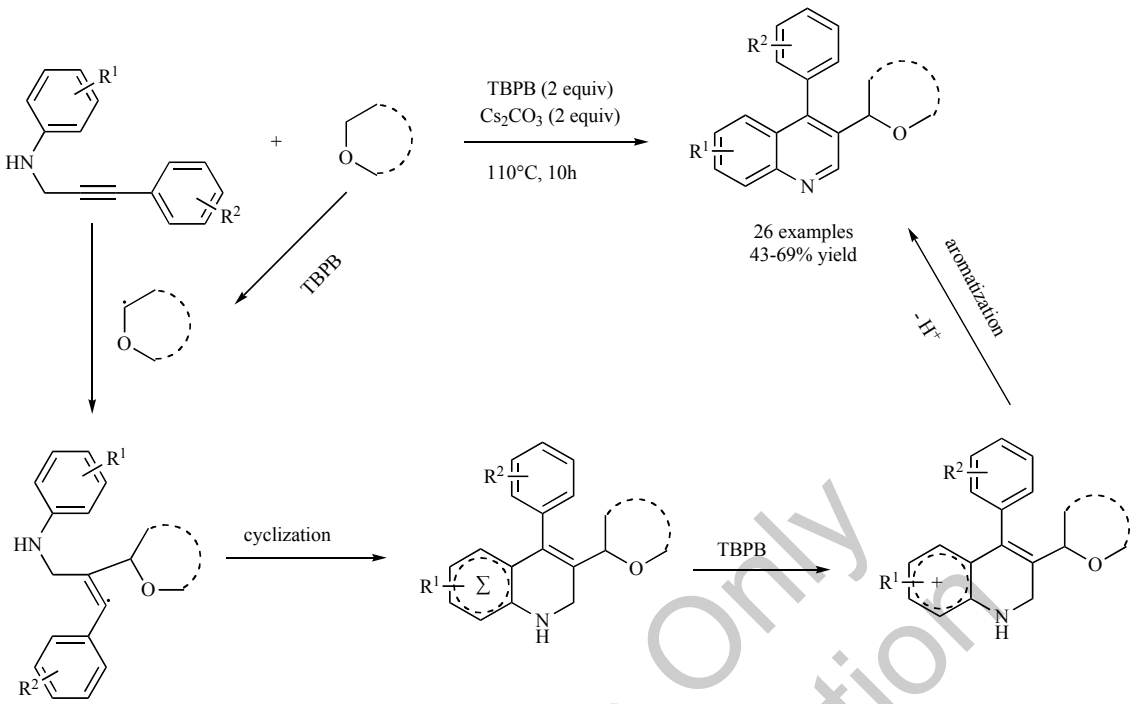
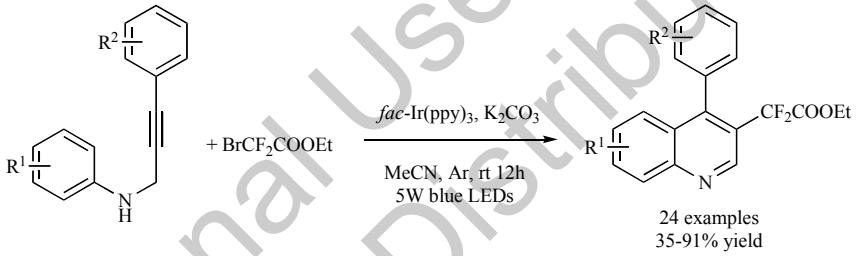
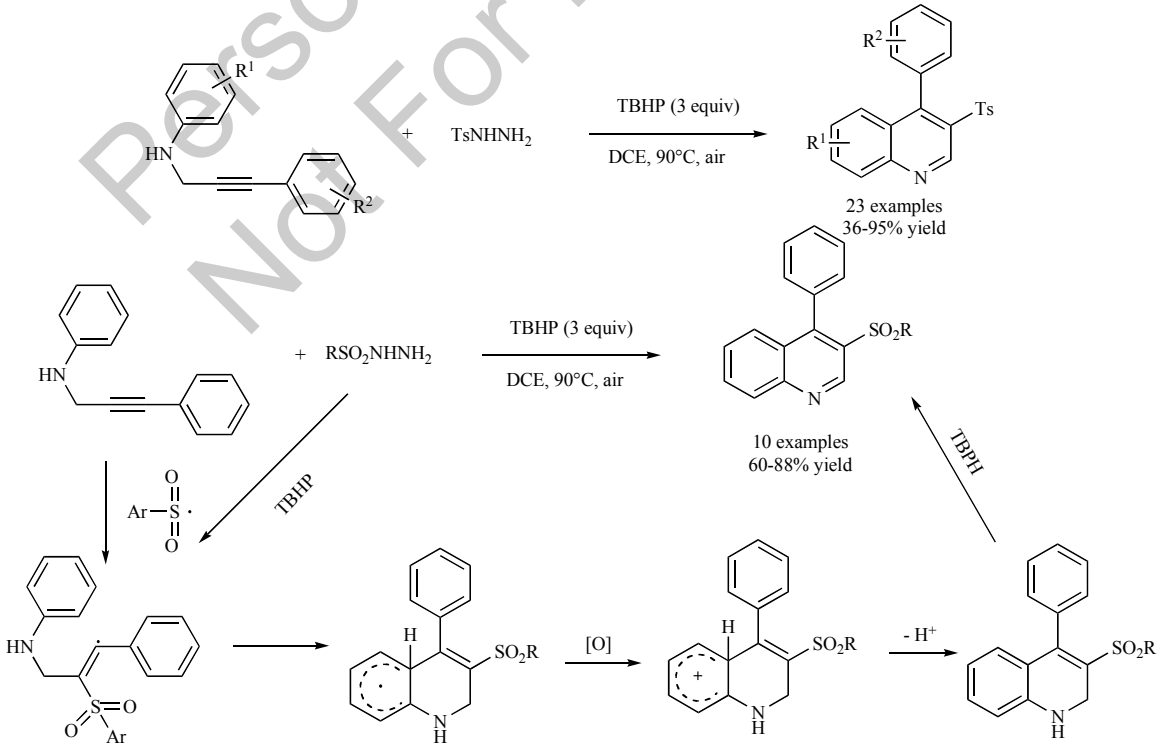


Scheme 75.



Scheme 76.



Scheme 77.

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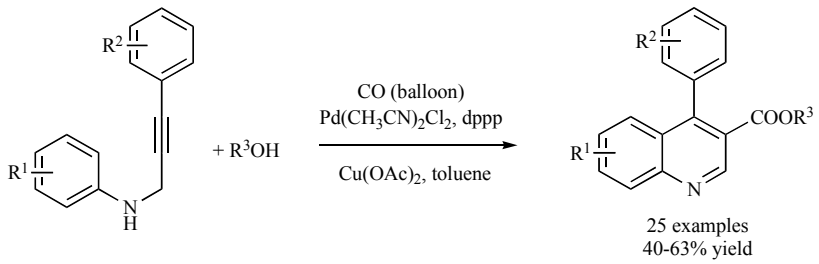
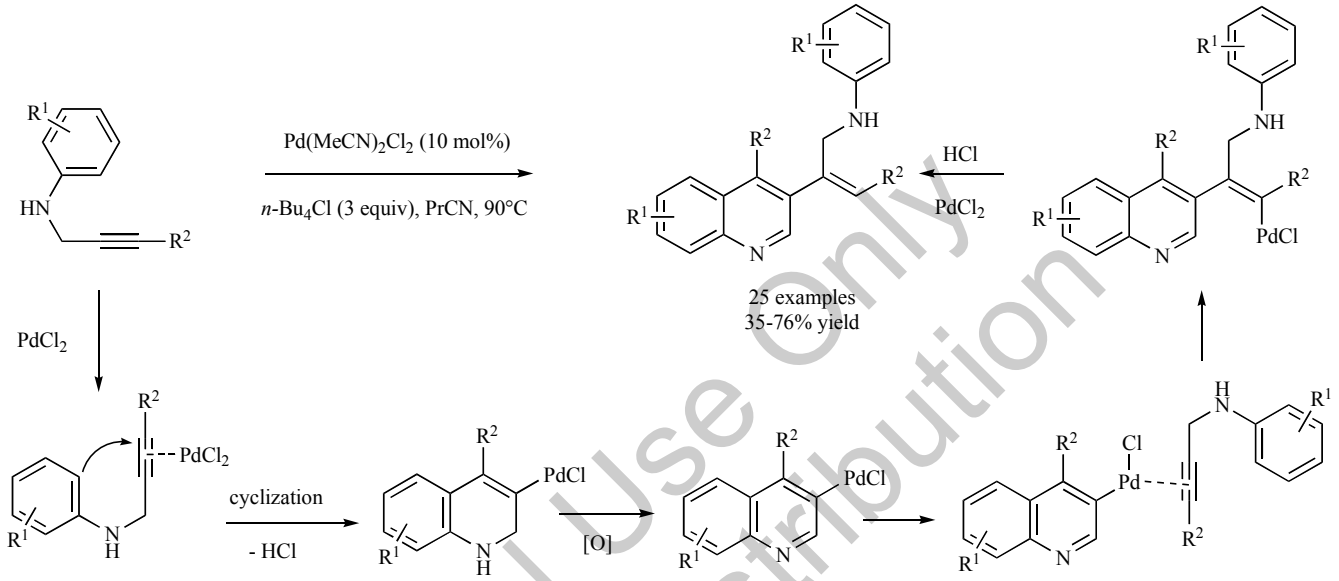
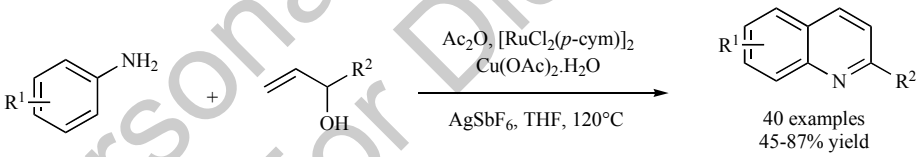


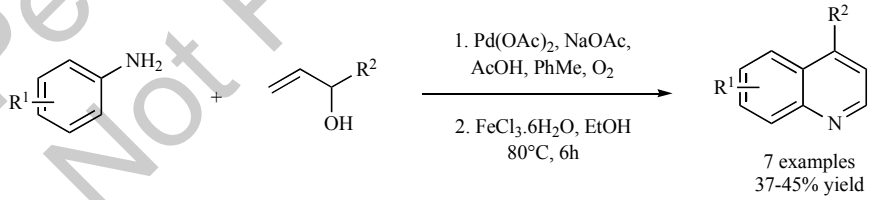
Scheme 78.



Scheme 79.



Scheme 80.



Scheme 81.

catalyzed electrophilic cyclization of the amine substrates, followed by hydroarylation process through trapping of the σ-quinolinylpalladium intermediate. Products were obtained in moderate to good yields and are suitable for many functional groups [103].

A unique [3 + 3] annulation of anilines with allyl alcohols to prepare quinoline derivatives catalyzed by Ru complex was discovered by Kapur *et al.* (Scheme **80**). A sequence of installation of the directing group, oxidation of the allyl alcohol, ortho-C-H functionalization, annulation, removal of the directing group, and oxidation/ aromatization was supposed to occur in one-pot reaction giving quinoline products [104]. The intermediate **A** could be isolated in separate experiments. Later, Kapur *et al.* employed Pd catalyst for this transformation (Scheme **81**). The mechanism proposed that firstly β-amino ketones were formed by the oxidative coupling of allyl alcohols with anilines from catalyzation by [Pd], and then these intermediates were converted into substituted quinolines [105].

Sudalai *et al.* presented a simple annulation strategy for the synthesis of quinoline carboxylates through rhodium-catalyzed cyclization from anilin derivatives and propiolate esters (Scheme **82**). This reaction might proceed through a rhodacycle of *in situ* generated amide and enamine ester followed by *ortho* C-H activation of arylamines with rhodium catalyst [106]. In a mechanistic study, the intermediate amide reacts with ethyl propiolate to form the same product. The reaction of electron-rich anilines and ethyl propiolates furnished 2,3-disubstituted quinoline carboxylates [106]. In Dai *et al.*, research, the reaction of primary

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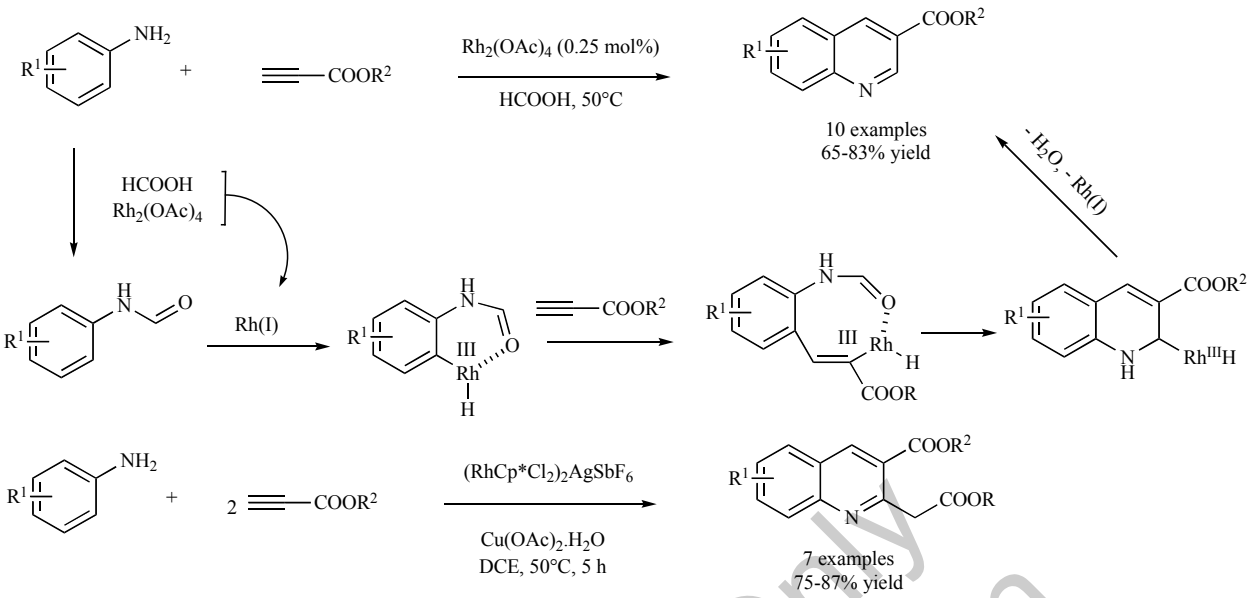
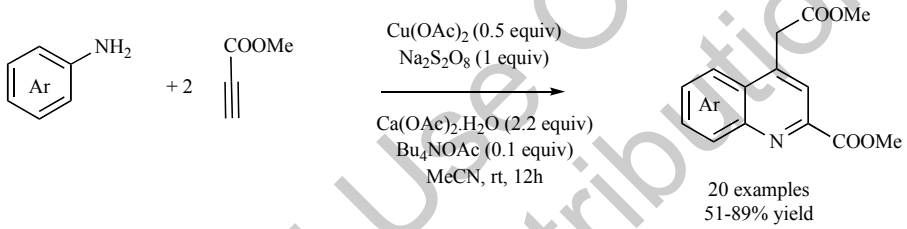
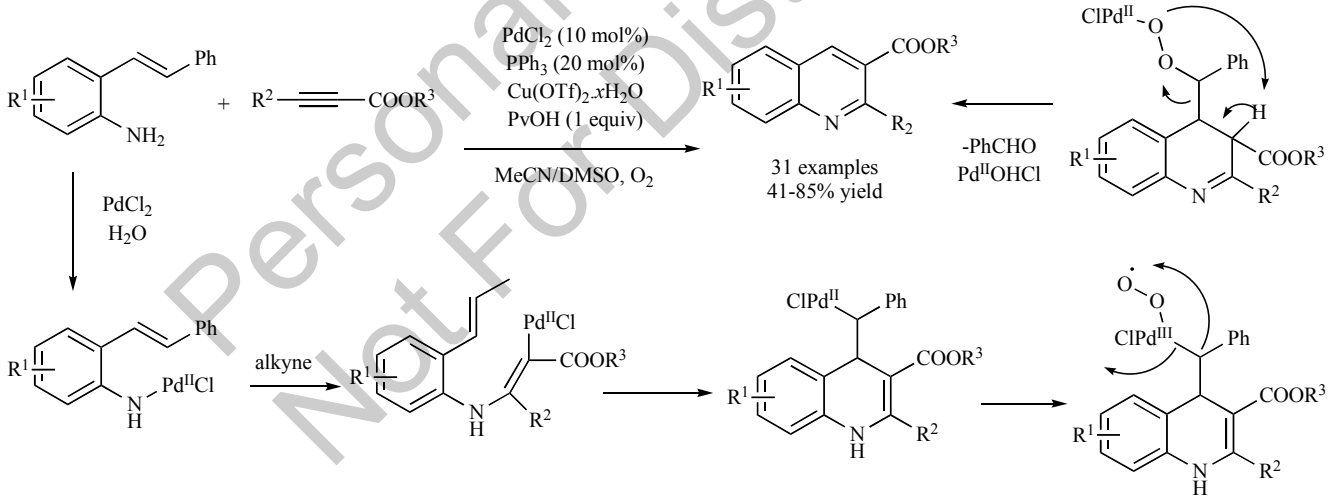


Scheme 82.



Scheme 83.



Scheme 84.

arylamines and 2 equivalents of electron-deficient terminal alkynes provided 2,4-disubstituted quinoline derivatives under $Cu(OAc)_2 \cdot H_2O$ catalyst (Scheme **83**) [107].

Jiang *et al.* developed a Pd-catalyzed oxidative annulation between *o*-alkenylanilines and alkynes for the synthesis of 2,3-disubstituted quinolines (Scheme **84**). A sequence of amination of alkyne, alkenyl migration insertion, and aerobic C-C bond cleavage was supposed to occur and the proposed reaction mechanism is illustrated below. Good functional group tolerance and high regioselectivity are the merits of the synthesis [108].

Prathapan *et al.* reported a simple method for the synthesis of substituted quinolines without using metal under mild conditions from nitrones and acetylenes (Scheme **85**). They employed oxalic acid adsorbed on silica gel as a catalyst and the reaction was performed in MeCN at room temperature [109].

In work done by Roschenthaler, 2-difluoromethyl-4-aryl-, alkyl- or perfluoroalkylquinolin-3-ylphosphonates were obtained through regioselective heterocyclization of XCF_2-alkynylphosphonates with ortho-aminoaryl ketones mediated by K_2CO_3 or Li_2CO_3/TMEDA (Scheme **86**). A series of quinolines were prepared in moderate to excellent yields [110].

Zhang *et al.* developed a new strategy for the synthesis of quinolines from benzamidine precursors and alkynes (Scheme **87**). The reaction underwent a sequence of C–C coupling and cycli-

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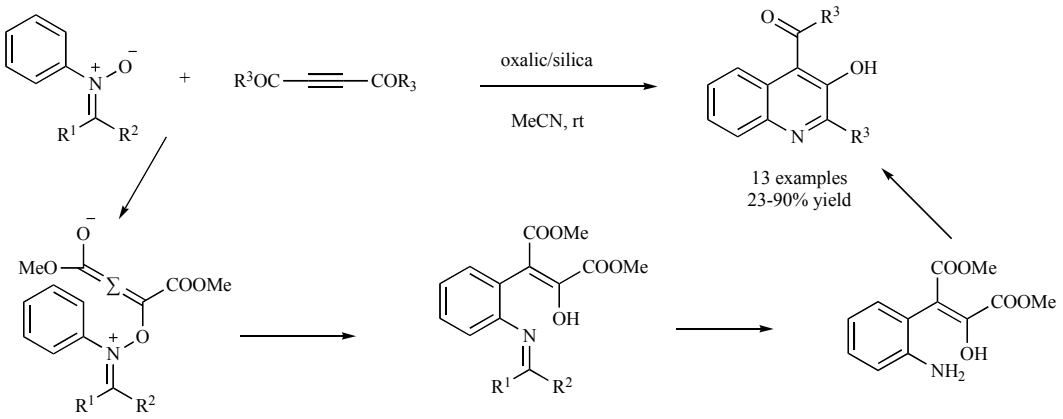
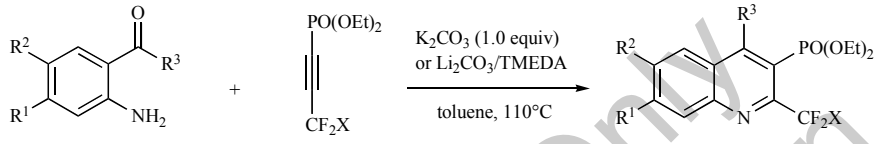
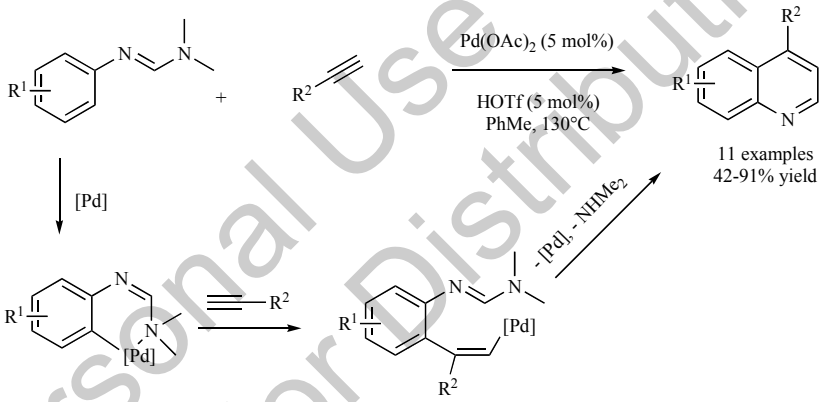


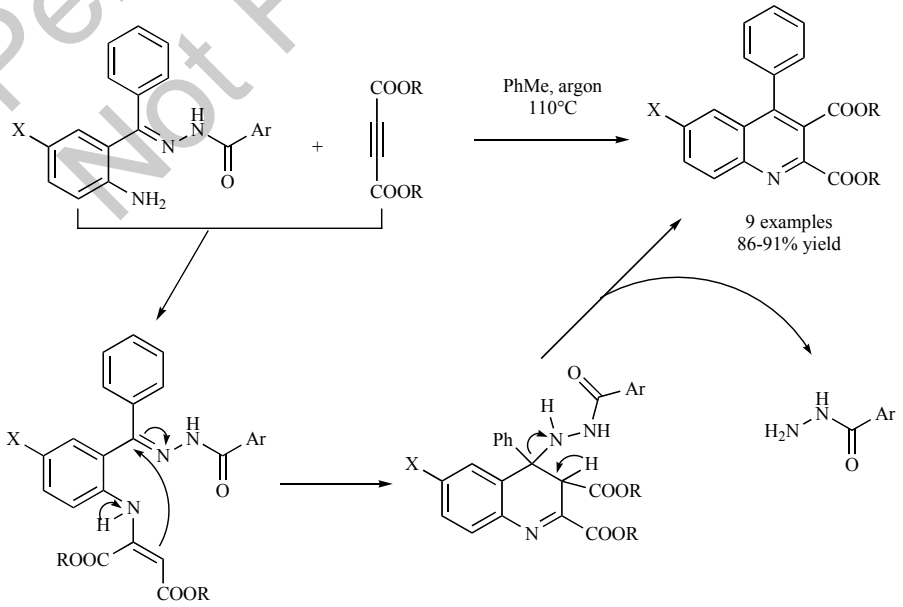
Scheme 85.



Scheme 86.



Scheme 87.



Scheme 88.

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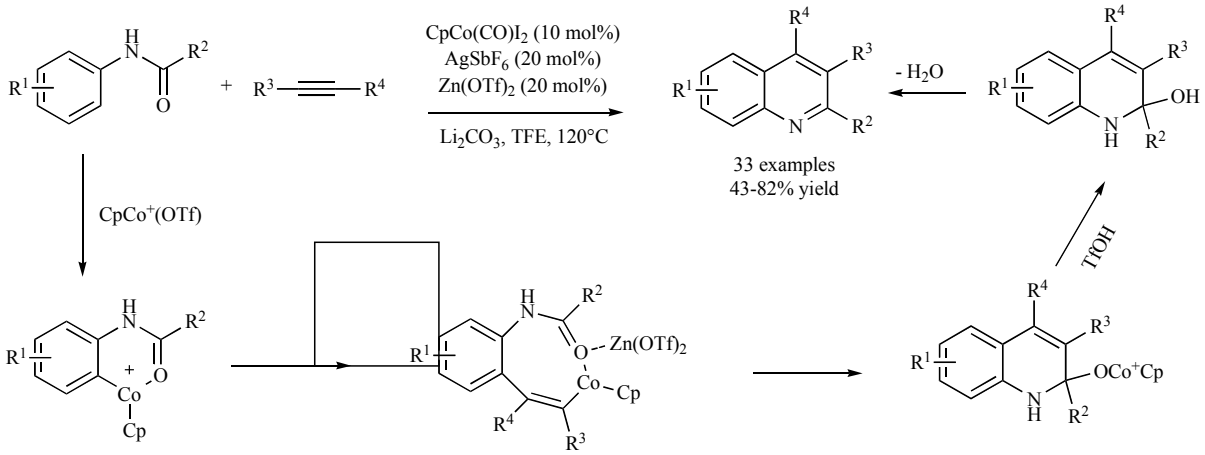
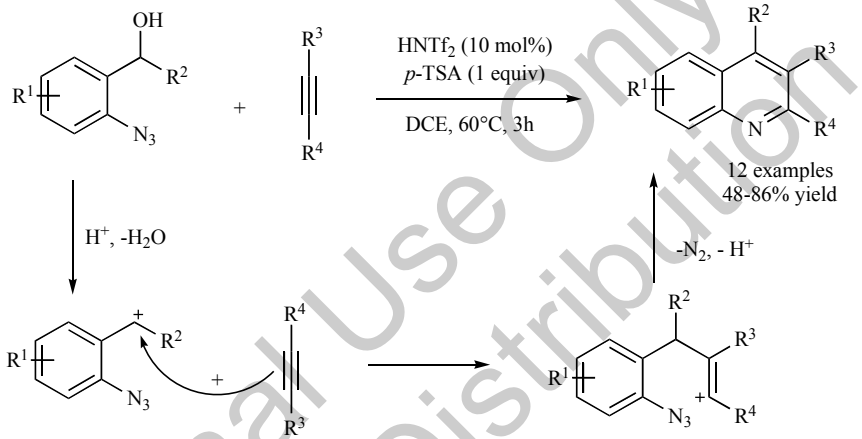
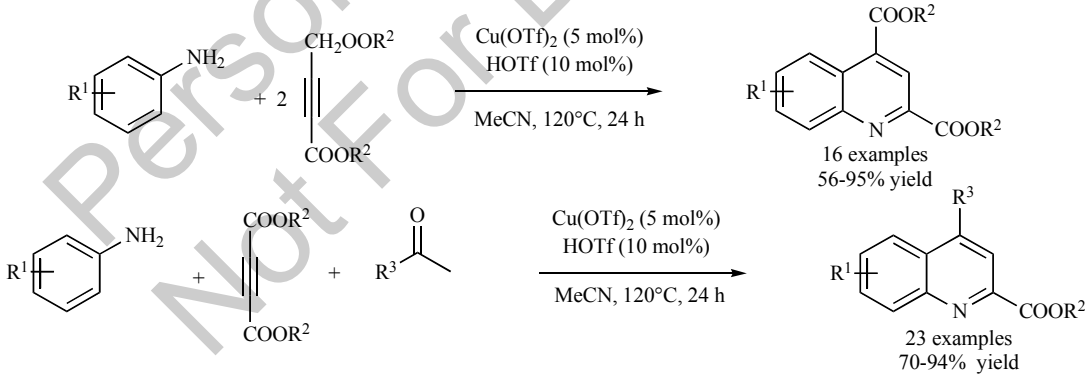


Scheme 89.



Scheme 90.



Scheme 91.

zation reaction by directed C–H activation of benzamidine and terminal alkynes catalyzed by Pd(II). The transformation was suitable for a broad range of functional groups [111].

Imanzadeh reported the synthesis of quinoline-2,3-dicarboxylates from a reaction of *N*'-((2-aminophenyl)(phenyl) methylene) benzohydrazides with acetylenic esters without using any catalysts under mild conditions (Scheme **88**). In short reaction time, nine quinolines were obtained in excellent yields with simple operation [112].

Zhang *et al.* reported the synthesis of quinolines from acetanilide and internal alkynes (Scheme **89**). The transformation might undergo the *ortho* C-H activation and nucleophilic addition of C-Co species toward the amides. Advantages of the synthesis include high yields of products, wide substrate compatibility and good functional group tolerance [113].

A straightforward procedure for the synthesis of polysubstituted quinolines from 2-azido phenylethanols and internal alkynes was developed by Niggemann and Stopka (Scheme **90**). The reaction was supposed to proceed through a highly reactive benzyl cation in a C-C bond formation - Schmidt sequential reaction [114].

A cascade annulation of anilines with internal alkyne esters catalyzed by copper (II) for the synthesis of 2,4-disubstituted quinolines in one-pot reaction was reported by Yi *et al.* (Scheme **91**). The reactions showed exclusive regioselectivity, broad

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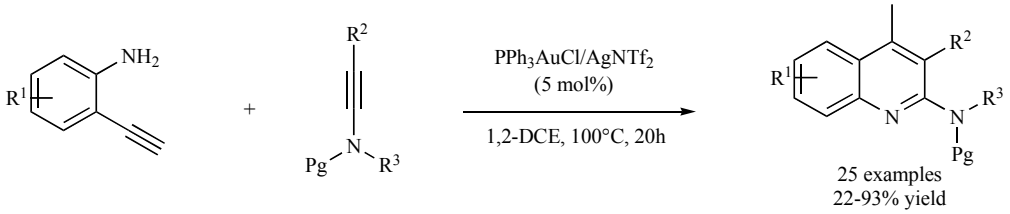
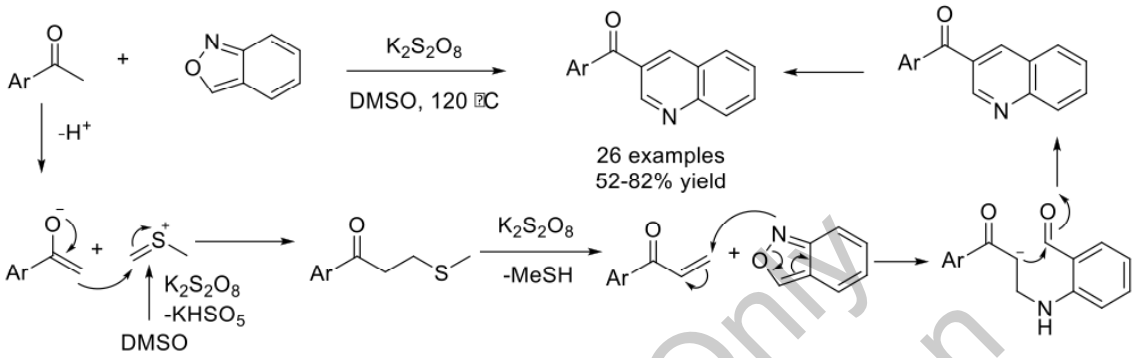
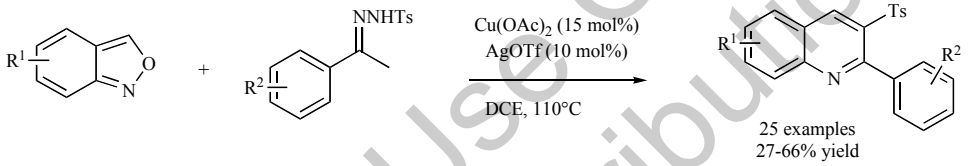


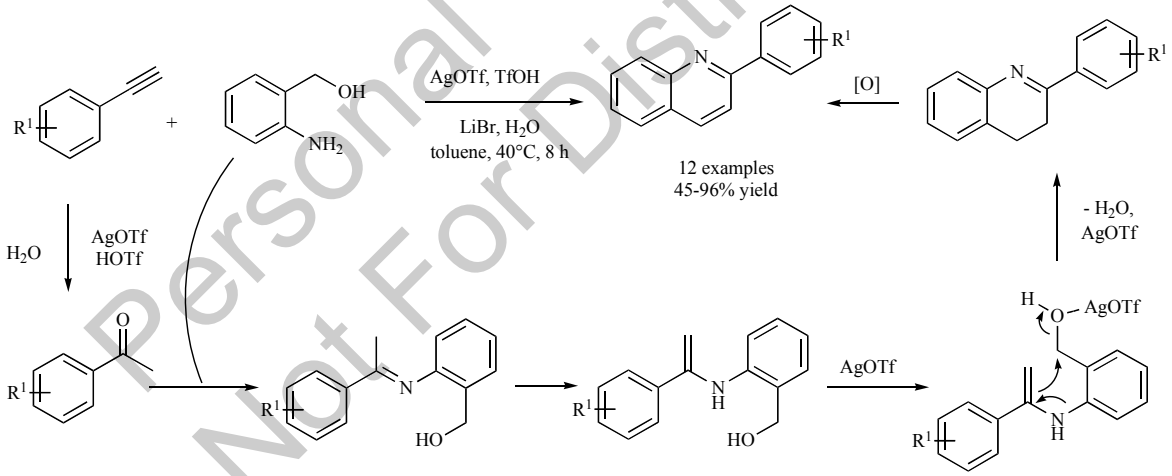
Scheme 92.



Scheme 93.



Scheme 94.



Scheme 95.

substrate scope, wide functional group tolerance and produced quinolines in good to excellent yield. Furthermore, the second molecule of alkyne esters in the reaction could be replaced by (hetero)aryl- or cycloalkyl-ketone substrates [115].

Hashmi *et al.* developed an efficient synthesis of 2-aminoquinolines through one-step intermolecular [4+2] annulation of 2-ethynylanilines with ynamides catalyzed by gold complex (Scheme **92**). Good substrate scope, high regioselectivity, good functional group tolerance, mild reaction conditions and good yield of products are the advantages of the synthesis [116].

In a study by Tiwari *et al.*, 3- ketoquinolines were synthesized from acetophenones, anthranils and DMSO and the reaction was catalyzed by $K_2S_2O_8$ (Scheme **93**). The mechanistic study proposed that α,β-unsaturated ketones generated *in situ* from the acetophenone by one-carbon homologation by DMSO were afforded first, and then the products were formed by the aza-Michael addition of anthranils and subsequent annulation. The plausible reaction mechanism is also displayed [117].

A domino reaction of *p*-toluenesulfonylhydrazone with anthranils to form 2,3- quinoline derivatives catalyzed by Cu(II)/Ag(I) was achieved by Ji *et al.* (Scheme **94**). New C-C, C-N, and C-S bonds were formed in one step through free-radical cyclization under mild conditions resulting in quinolines in moderate yields [118].

Zhang *et al.* described an approach for the synthesis of 2-substituted quinolines from reactions between 2- aminobenzyl alcohol and alkyne/ketone or 2-aminophenethyl alcohol and aldehyde catalyzed by AgOTf (Scheme **95**). The reaction occurred

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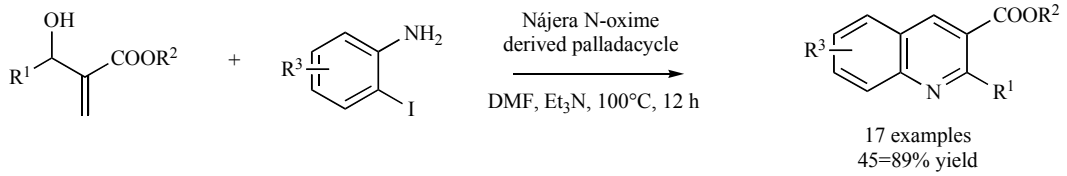
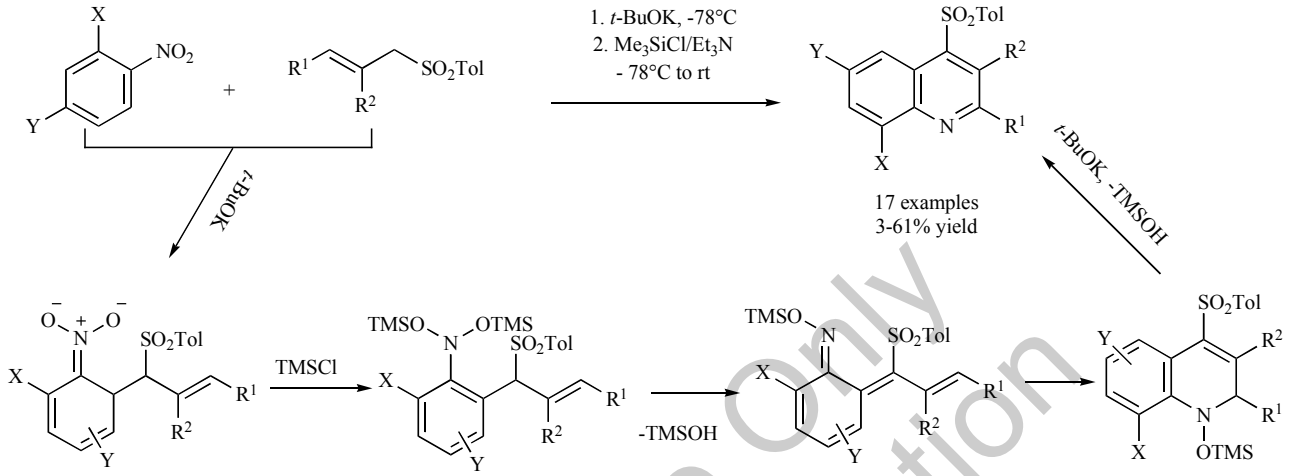
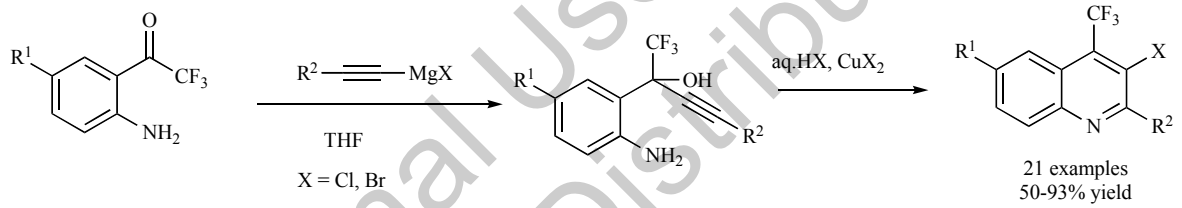


Scheme 96.



Scheme 97.



Scheme 98.

at mild conditions and could tolerate both electron-donating and electron-withdrawing substituents in the alkyne moiety [119].

A chemoselective and regioselective strategy for the synthesis of multi-substituted quinolines starting from the Morita-Baylis-Hillman adducts and anilines was developed by Coelho *et al.* (Scheme **96**). The products were afforded in good to excellent yields (industrial-scale 89 tons) with simple operations applied for one substrate [120].

From nitroarenes and allyl tolyl sulfone carbanions, which were formed when treated with base and silylating agents, Wojciechowski *et al.* obtained 4-toluenesulfonyl quinolines *via* a step-by-step procedure (Scheme **97**) [121].

A mild, efficient and highly regioselective method for the preparation of 3-chloride or 3-bromide substituted quinoline derivatives through cyclization–halogenation tandem reaction was described by Cheng *et al.* (Scheme **98**). *o*-Trifluoroacetyl anilines were treated with alkynyl Grignard reagents to form propargylic alcohols, and then halogen sources (HCl or HBr) were directly introduced into the one-pot system catalyzed by Cu(II) to afford final products [122].

In a study by Marinelli *et al.*, 4-sulfonylquinolines and 4-nitroquinolines were synthesized through a sequence of addition and annulation reactions of sulfinate anions with β-(2-aminophenyl)-α,β-ynones, which were prepared from Sonogashira coupling between phenyl iodide and propargyl alcohol, followed by MnO_2-mediated oxidation (Scheme **99**). Multi-substituted quinolines were produced in good to excellent yields under mild conditions [123].

From Δ2-isoxazolines, Lal *et al.* investigated a new approach for the synthesis of quinolines under reductive conditions (Scheme **100**). High yields of 2-substituted quinolines were obtained with simple purification [124].

In a study by Orellana *et al.*, quinolines were synthesized through a coupling of *ortho*-bromoaniline derivatives with substituted cyclopropanols in a single step (Scheme **101**). The reaction underwent a sequence of intermolecular condensation and oxidation catalyzed by palladium(II) with good functional group tolerance [125].

From indoles and ethyl halodiazoacetates, Hansen *et al.* investigated a mild and efficient method for the preparation of ethyl quinoline-3-carboxylates. A cyclopropanation-ring expansion pathway was proposed to occur (Scheme **102**). N-substituted indole might follow a different reaction pathway and the quinolines products were not formed [126].

A Knoevenagel/Staudinger/aza-Wittig sequence reaction was developed by Wu *et al.* for the synthesis of quinolines from 2-azidobenzaldehyde and carbonyl compounds (Scheme **103**). The reaction showed many merits such as mild reaction conditions, high yields of disubstituted quinoline products and simple purification [127].

Rajanna *et al.* discovered a method for quinoline synthesis using 2,4,6-trichloro-1,3,5-triazine and trichloroisocyanuric acid as

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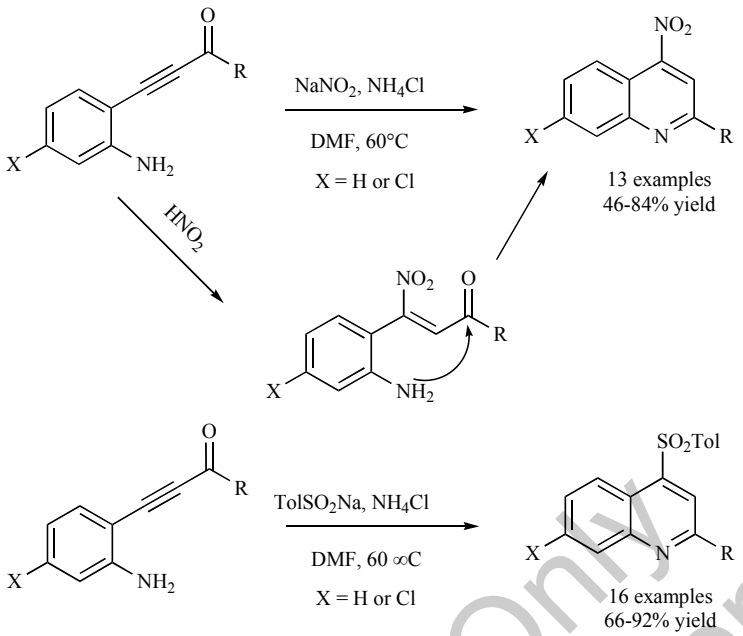
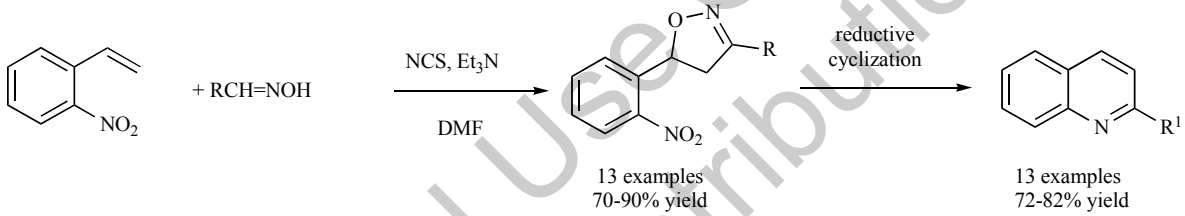
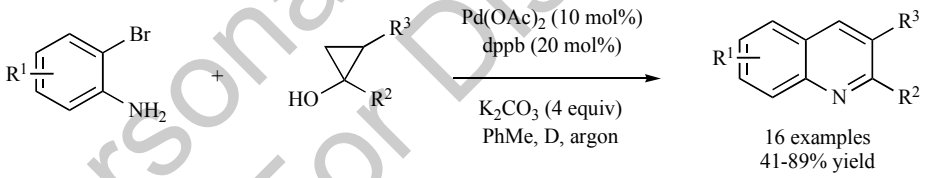


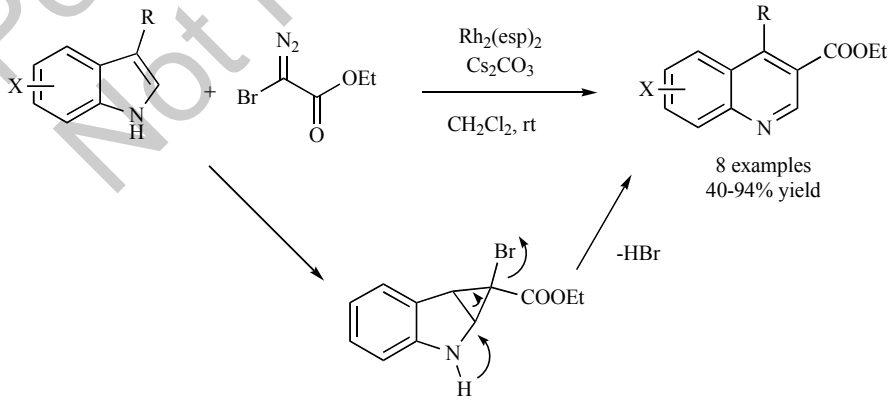
Scheme 99.



Scheme 100.



Scheme 101.



Scheme 102.

catalysts under conventional heating or ultrasonication (Scheme **104**). Higher yields of the products and considerably shorter reaction time were observed with ultrasonication design [128].

From vinyl azides and α -carbonyl benzyl bromides, Zhou reported the synthesis of quinolines through sequential C-C and C-N bond formation with the assistance of visible light (Scheme **105**). Moderate to good yields of products with good functional group tolerance were obtained [129].

Jiang *et al.* discovered an approach for the synthesis of disubstituted quinolines from vinyl azides and anilines in a one-step procedure (Scheme **106**). In this approach, vinyl azides played as a dual synthon *via* C-C and C−N bond cleavage as well as two C-C

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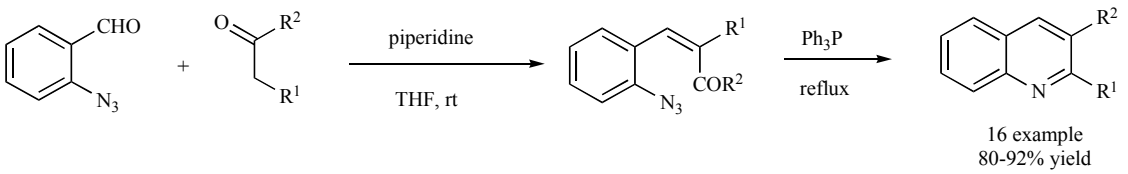
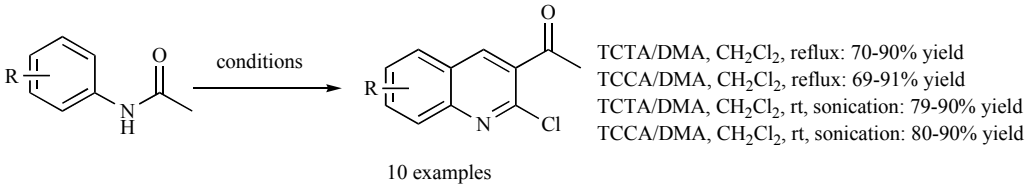
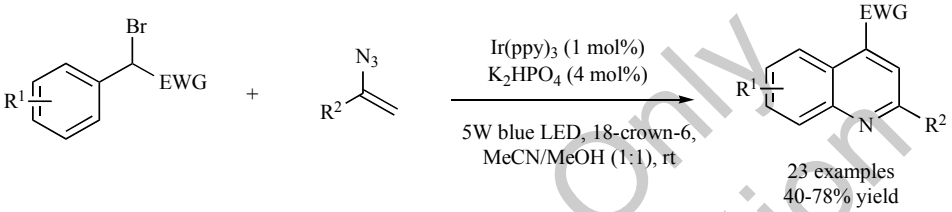


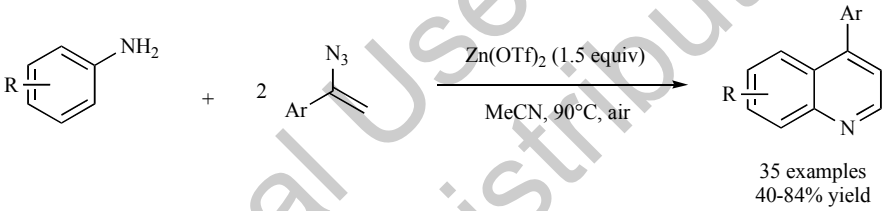
Scheme 103.



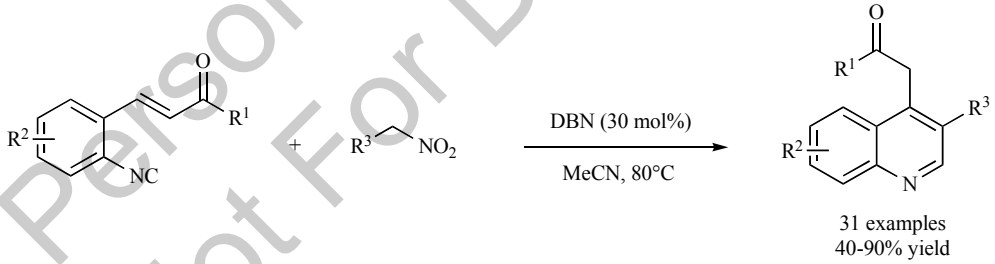
Scheme 104.



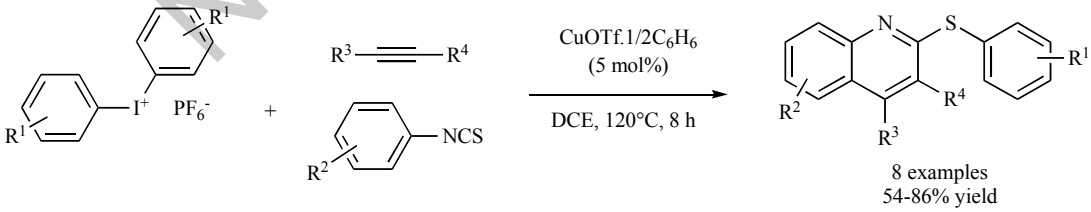
Scheme 105.



Scheme 106.



Scheme 107.



Scheme 108.

bonds and one C-N bond formation. The use of air as the sole oxidant and a broad range of functional group tolerance are attractive features of the synthesis [130].

A new DBN-catalyzed [5+1] annulation between 2-isocyanochalcones and nitroalkanes was developed by Xu *et al.* for the synthesis of aromatic quinolines and 3-nitrodihydroquinolines (Scheme **107**). Merits of the synthesis include mild reaction conditions, and high yields of products in most cases [131].

3.3. Three-component Reaction

An efficient, CuOTf-catalyzed, three-component approach for the synthesis of quinoline derivatives was established by Zhang *et al.* (Scheme **108**). A [2 + 2 + 2] annulation between hetero-cumulenes, alkynes and diaryliodonium salts was proposed to occur through a cation intermediate providing quinolines in good yields with the formation of two C-C bonds and one C-N or C-S bond in the one-pot reaction. Good regioselectivity was achieved when

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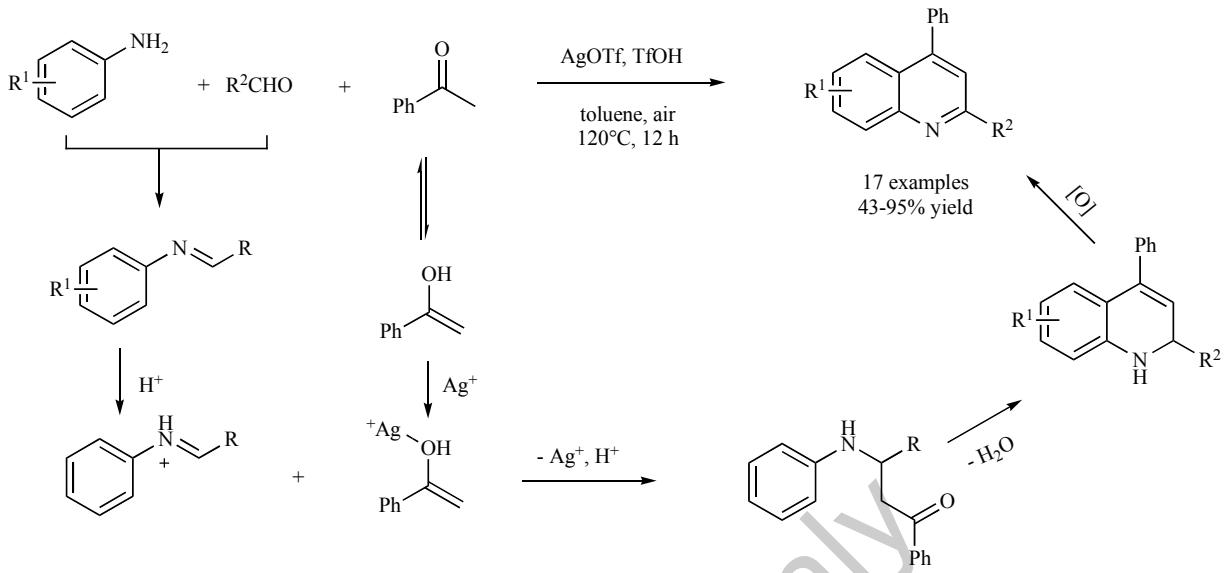
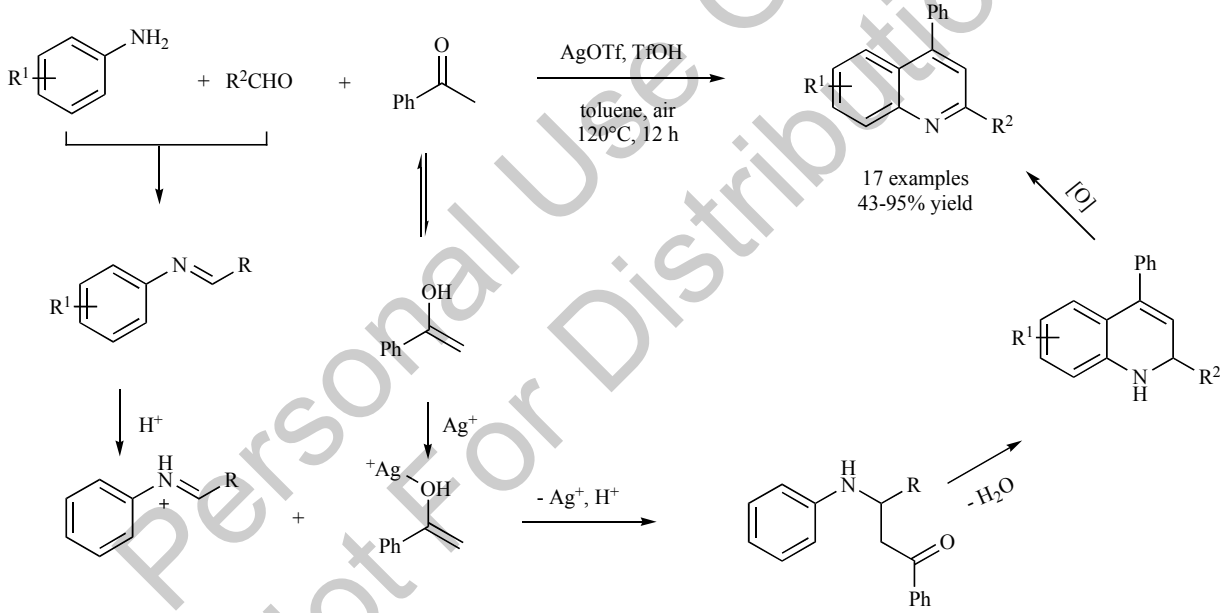


Scheme 109.



Scheme 110.

unsymmetrical alkynes were employed due to electronic effect [132].

An efficient and regioselective synthesis of multiply substituted quinolines from aldehyde, aniline, and carbonyl compounds, or aniline and 1,3-diketones was reported by Zhang *et al.* (Scheme **109**). The synthesis proceeded by the formation of a silver-catalyzedC-C bond. Good to excellent yields of quinolines were obtained in most cases with a broad range of substrates and good functional group tolerance [133].

Kumar *et al.* disclosed a regioselective synthesis of 2-aminoquinolines and 2-arylquinoline-3-carbonitriles mediated by copper iodide from ortho-bromobenzaldehyde and active methylene nitriles (Scheme **110**). The synthesis involved Knoevenagel condensation of the reactants to form the intermediate **A**, which then underwent reductive amination catalyzed by copper iodide and intramolecular cyclization. Moderate to good yields of products were obtained through a one-pot tandem reaction with broad substrate scope and good functional group tolerance. In separate experiments, intermediates such as **A**, **B**, **C** could be isolated by changing reaction conditions [134].

The synthesis of polysubstituted quinolines from anilines, aldehydes, and alcohols under mild conditions catalyzed by Ag(OTf) in the presence of air was achieved by Zhang *et al.* (Scheme **111**). The synthesis showed good substrate scope,good functional group tolerance and gave products in good yields for most substrates [135].

Orru *et al.* introduced a novel synthesis of 4-aminoquinolines through a sequence of imidoylative Sonogashira cross-coupling and cyclization mediated by an acid in one-pot reaction (Scheme **112**). The reaction was compatible with various substituents on arene as well as a wide range of isocyanides [136].

The synthesis of quinolines from arylisothiocyanate, alkyltriflate, and alkynes in one-pot protocol was presented by Xi *et al.* (Scheme **113**). The reaction underwent alkyltriflate triggered

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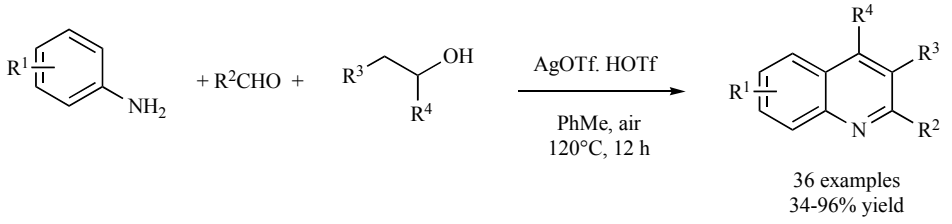
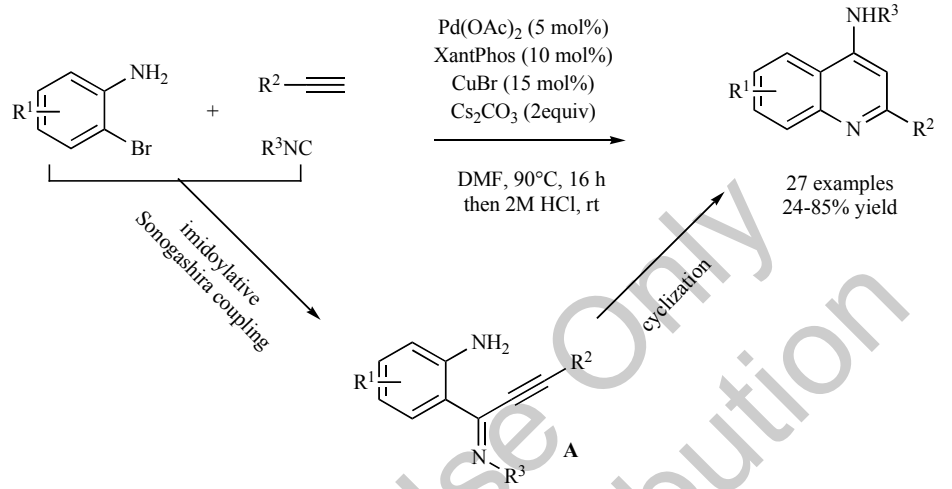
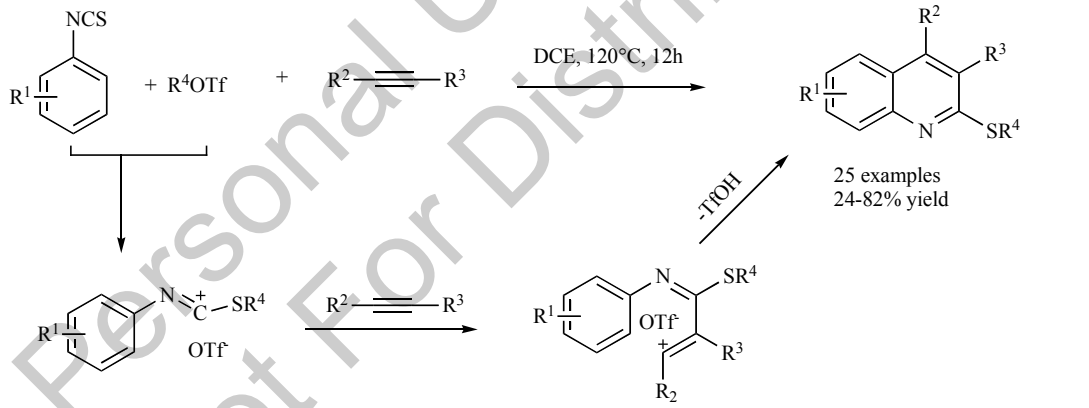


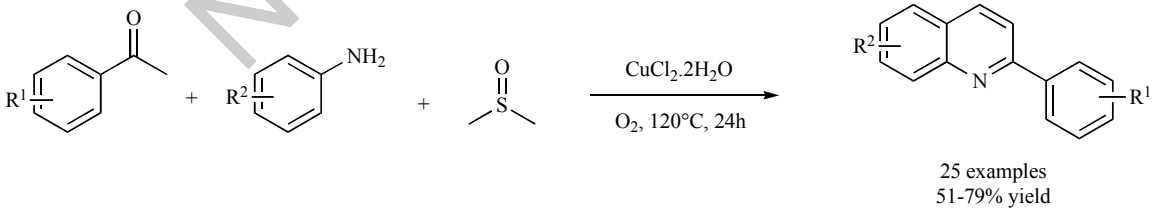
Scheme 111.



Scheme 112.



Scheme 113.



Scheme 114.

domino electrophilic activation. Good functional group tolerance, complete regioselectivity, and high yields of products are the advantages of the synthesis [137].

Guo *et al*. synthesized 2-arylquinolines through Cu-catalyzed C–H cyclization of aryl ketones, anilines, and DMSO (Scheme **114**). The synthesis employed O_2 as an oxidant and DMSO as a carbon source resulting in quinolines adducts in moderate to good yields [138].

CONCLUSION

Many methods for the synthesis of substituted quinoline rings have been developed recently. Over the past five years, the majority of those reports have been based on cycloisomerization and cyclization processes. Undoubtedly, more imaginative approaches to quinoline synthesis will appear in the literature in the near future. Application of known methods to natural product synthesis is probably the next challenge in the field. Improving the efficiency

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and versatility as well as the use of environmentally friendly methods and economical procedures for quinoline synthesis will attract more attention of the chemists. Another direction will be the employment of established or new methods to the synthesis of bioactive quinoline derivatives which can be used as drugs. Industrial-scale synthesis of commercially and medicinally important quinolines will possibly be developed. In medicinal chemistry, more and more quinoline-containing compounds with valuable bioactivities will be discovered. The relationship between structure and bioactivities of quinoline derivatives might also be the next challenge to the field.

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CONFLICT OF INTEREST

The author declare no conflict of interest, financial or otherwise.

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