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Metal-free domino one-pot protocols for quinoline synthesis

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Quinoline is one of the most widely investigated scaffolds by synthetic chemists because of its medicinal importance. A wide range of metal-catalyzed, metal-free, multi-step or domino one-pot protocols are reported in the literature for construction of this scaffold. Several reviews have appeared on synthetic aspects of this scaffold, however there is no focused review on metal-free domino one-pot protocols. Domino one-pot protocols offer an opportunity to access highly functionalized final products from simple starting materials. Because of this unique feature of domino protocols, in recent years their utility for generation of molecular libraries has been widely appreciated. In this review, all contributions till March 2015 are surveyed with particular emphasis on

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Ram Vishwakarma studied chemistry at the Central Drug Research Institute (CDRI), Lucknow and completed Ph.D. in 1986 under joint supervision of Drs SP Popli and RS Kapil. After working for few years as research scientist at CIMAP, Lucknow, he moved to the Cambridge University in 1991 to work with Sir Alan Battersby on biosynthesis of cyanocobalamin (vitamin B_{12}) and related porphyrins/corrins. In the end of 1993, he joined as staff-scientist at the National Institute of Immunology at New Delhi and initiated a research program on chemical biology of Glycosyl Phosphatidyl Inositol (GPI) anchors of parasitic protozoa (Leishmania and Malaria). In 2005, he moved to Piramal Life Sciences (Mumbai) as vice-president and head of medicinal chemistry & natural product groups. During this period, he worked on the clinically validated disease targets relevant to cancer (PI3K/mTOR, IGFR1), diabetes (DGAT1) and infection (VRE/MRSA), learnt the "intricacies" of drug-discovery under guidance of Dr Somesh Sharma, and realized the potential of marine natural products. In 2009, he joined as Director of Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research) at Jammu, where his primary focus remain natural-products driven drug discovery for cancer and infection. His scientific work has been published in over 200 papers and >40 patent applications filed. Ram Vishwakarma is an elected Fellow of the National Academy of Sciences, India.

metal-free domino reactions for quinoline ring construction and are discussed herein along with mechanistic aspects.

1. Introduction

Quinoline (1-aza-napthalene or benzo[*b*]pyridine) is a weak tertiary base. It was first extracted from coal tar in 1834 by Friedlieb Ferdinand Runge and this source still remains the principal source of commercial quinoline. This scaffold has found many applications in diverse chemical domains. This scaffold has wide occurrence among natural products (alkaloids)[1] and is a key structural component of several pharmaceuticals, agrochemicals, dyestuffs, and materials. In coordination chemistry, quinolines are used to chelate metallic ions as N-donor ligands.[2] The quinoline scaffold has been reported to possess diverse range of pharmacological activities[3–14] including antiprotozoal,[15–20] antitubercular,[21,22] anticancer,[4,23,24] antipsychotics,[25] antiinflammatory,[26,27] antioxidant,[3] anti-HIV,[28] antifungal,[29] as efflux pump inhibitors,[30] and for treatment of neurodegenerative diseases,[19] and treatment of lupus,[31] *etc.*

The well known antimalarial natural products quinine and quinidine alkaloids isolated from Cinchona bark comprises quinoline scaffold.[32,33] Camptothecin is a quinoline alkaloid discovered in 1966 by Wall and Wani through systematic screening of natural products for anticancer drugs. Two camptothecin analogues namely topotecan and irinotecan have been approved for clinical use for cancer chemotherapy,[34] and another analog exatecan is under clinical studies. A fused quinoline natural product mappicine ketone is an antiviral lead compound with selective activities against herpes viruses HSV-1 and HSV-2 and human cytomegalovirus (HCMV).[35] A fused quinoline alkaloid cryptolepine isolated from *Cryptolepis* sp. is an antimalarial natural product possessing cytotoxic properties.[36] Its structural isomers isocrytolepine and neocryptolepine also possesses antimalarial activity.[37] The chemical structures of quinoline class of natural products are shown in Fig. 1.

Quinoline is also part of several clinically used drugs, where their major occurrence is among antimalarial drugs. The aminoquinoline scaffold has been a backbone of antimalarial drugs since 1940s. In this class, chloroquine was the first drug discovered in 1934 by Hans Andersag and coworkers at the Bayer laboratories.[38] With the emergence of resistance to chloroquine, a series of its analogs (*e.g.* amodiaquine, primaquine, mefloquine, tafenoquine, bulaquine, NPC-1161B, AQ-13, IAAQ) were discovered. Other antimalarial quinolines include piperaquine and pyronaridine. Quinoline has also been a part of drugs used for other diseases. This includes fluoroquinolone antibiotic ciprofloxacin (and its analogs), pitavastatin (cholesterol lowering agent), lenvatinib (kinase inhibitor for cancer) and its other structural analogs (such as carbozantinib, bosutinib), tipifarnib (farnesyl transferase inhibitor for leukemia), saquinavir (antiretroviral), bedaquiline (anti-TB), *etc.* The 2-(2-fluorophenyl)-6,7-methylenedioxy quinolin-4-one monosodium phosphate (CHM-1-P-Na) is a preclinical anticancer agent, showing excellent antitumor activity in a SKOV-3 xenograft nude mice model.[39,40] The chemical structures of above discussed representative quinoline based drugs are shown in Fig. 2a. Several quinoline based compounds showed inhibition of kinases involved in cancer progression.[4] The chemical structures of representative kinase inhibitors are shown in Fig. 2b.

Sandip B. Bharate obtained B. Pharm. degree from the University of Pune in 2001 and received a M.S. (Pharm.) degree from the National Institute of Pharmaceutical Education and Research (NIPER), Mohali (India), in 2002. In 2003, he worked in the discovery research unit of Dr Reddy's Laboratories, Hyderabad, for six months before commencing his Ph.D., which he completed under the supervision of Dr Inder Pal Singh at NIPER Mohali in January 2007. Subsequently, he worked as a Research Scientist in the Department of Medicinal Chemistry, Piramal Life Sciences Ltd, Mumbai (formerly, Nicholas Piramal Research Center), for 1.5 years. He subsequently pursued postdoctoral studies (2008–2010) at the University of Montana (USA) with Professor Charles M. Thompson in the area of neuroscience. Presently, he is working as a Senior Scientist in the Medicinal Chemistry Division of the Indian Institute of Integrative Medicine (Council of Scientific and Industrial Research), Jammu, India. His current research interests are in the field of development of new tandem one-pot protocols for construction of medicinally important scaffolds and medicinal chemistry of marine natural products. He is recipient of several innocentive awards in the area of new drug discovery.

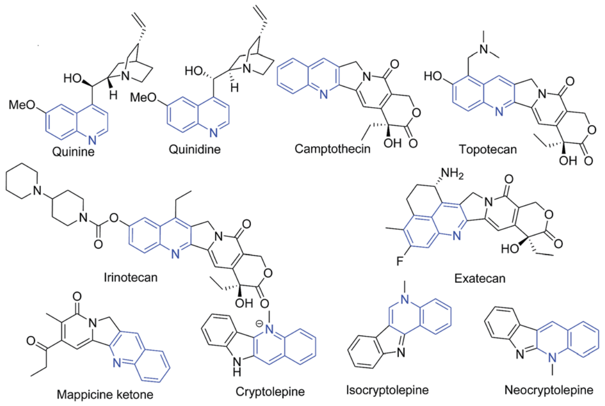


Fig. 1 Structures of quinoline ring containing natural products and their analogs.

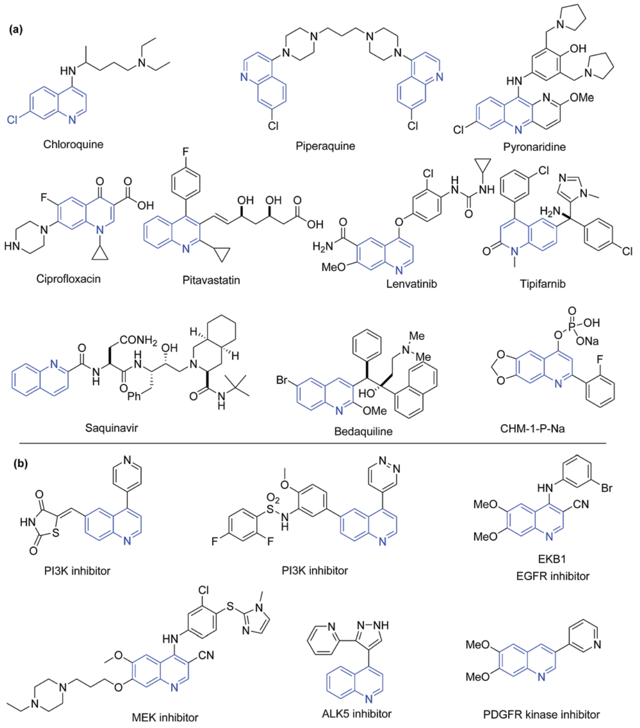


Fig. 2 Chemical structures of (a) quinoline containing drugs and clinical candidates; and (b) quinoline-based kinase inhibitors.

As a consequence of their tremendous biological importance, chemists have developed a plethora of methods to elaborate this structure, and most of them have been compiled in a series of reviews.[41–47] Recently, Patel's group (2014)[41] have reviewed advances in the synthesis of quinolines, which covered very broadly various reports on quinoline synthesis and cited 57 references. Koorbanally's group (2014)[42] have reviewed synthesis and anti-cancer activity of 2-substituted quinolines. Nammalwar and Bunce (2014)[45] have reviewed recent syntheses of 1,2,3,4-tetrahydroquinolines, 2,3-dihydro-4(1*H*)-quinolinones and 4(1*H*)-quinolinones using domino reactions. Alam's group (2013)[47] have briefly discussed various synthetic and biological aspects of this scaffold and cited total of 75 references. Hassanin *et al.* (2012)[44] reviewed synthesis and chemical reactivity of pyrano[3,2-*c*]quinolinones. Mekheimer *et al.* (2012)[46] reviewed recent developments in the chemistry of pyrazolo[4,3-*c*]quinolines. Barluenga *et al.* (2009)[43] reviewed advances in the synthesis of indole and quinoline derivatives through cascade reactions and cited total of 46 references.

Despite of the fact that large number of metal-free domino one-pot protocols for quinoline synthesis have been published; this has never been reviewed. The metal-free domino protocols provide rapid access to structural diversity, and metal-free nature of the reaction makes these protocols environmentally friendly. Therefore, a critical review on such protocols for synthesis of this medicinally important scaffold is highly desirable. The present review provides a comprehensive compilation of synthetic approaches involving specifically metal-free one-pot domino and multicomponent reactions (MCRs) for quinolines and related fused skeletons.

2. Classical methods for quinoline synthesis

There exist several classical methods (name reactions) for synthesis of quinolines. Most of the methods involve simple arylamines as starting materials. The 'name reactions' involving arylamines as one of the starting material includes: (a) Combes quinoline synthesis (from anilines and β-diketones); (b) Skraup synthesis (from ferrous sulfate, glycerol, aniline, nitrobenzene, and sulfuric acid); (c) Conrad–Limpach synthesis (from anilines and β-ketoesters); (d) Povarov reaction (from aniline, benzaldehyde and an activated alkene); (e) Doebner reaction (from anilines, aldehyde and pyruvic acid); (f) Doebner–Miller reaction (from anilines and α,β-unsaturated carbonyl compounds); (g) Gould–Jacobs reaction (from aniline and ethyl ethoxymethylene malonate); and (h) Reihm synthesis (from aniline and acetone).

A number of other name reactions exists, which require specifically substituted anilines or related substrates. These includes: (i) Knorr quinoline synthesis (from β-ketoanilide and sulfuric acid); (j) Pfitzinger reaction (from an isatin with base and a carbonyl compound); (k) Friedländer synthesis (from 2-aminobenzaldehyde and carbonyl compounds); (l) Niementowski quinoline synthesis (from anthranilic acid and carbonyl compounds); (m) Meth-Cohn synthesis (from acylanilides and DMF/$POCl_3$); and (n) Camps quinoline synthesis (from an *o*-acylaminoacetophenone and hydroxide). The synthetic schemes of these classical methods are summarized in Fig. 3.

Despite of the availability of several classical methods for quinoline synthesis, extensive efforts have been made on the development of new metal-free domino protocols for preparation of quinolines, which are described in this review.

3. Metal-free domino one-pot or multicomponent protocols for synthesis of quinolines and related quinoline fused heterocycles

Development of domino reactions for the concise construction of diverse heterocyclic architectures is of a tremendous importance in synthetic organic and medicinal chemistry.[48] Extensive amount of efforts have been made in this area towards development of domino one-pot protocols or multicomponent reactions (MCRs) for construction of heterocycles.[49–58] Few specific reviews on multicomponent synthesis of particular heterocycles such as pyrroles,[50,59] indoles,[60] and pyridines[61] have been published. Such domino reactions achieve high level of atom-efficiency, and avoids time-consuming isolation and purification of intermediates. Reduction in number of steps is the major advantage with these protocols, thus reduces manpower and avoids waste production.[62] This section discusses all reported metal-free one-pot protocols for quinoline synthesis. Most of the metal-free protocols discussed herein, comprises simple acid catalysts, bases, molecular iodine, ionic liquids or

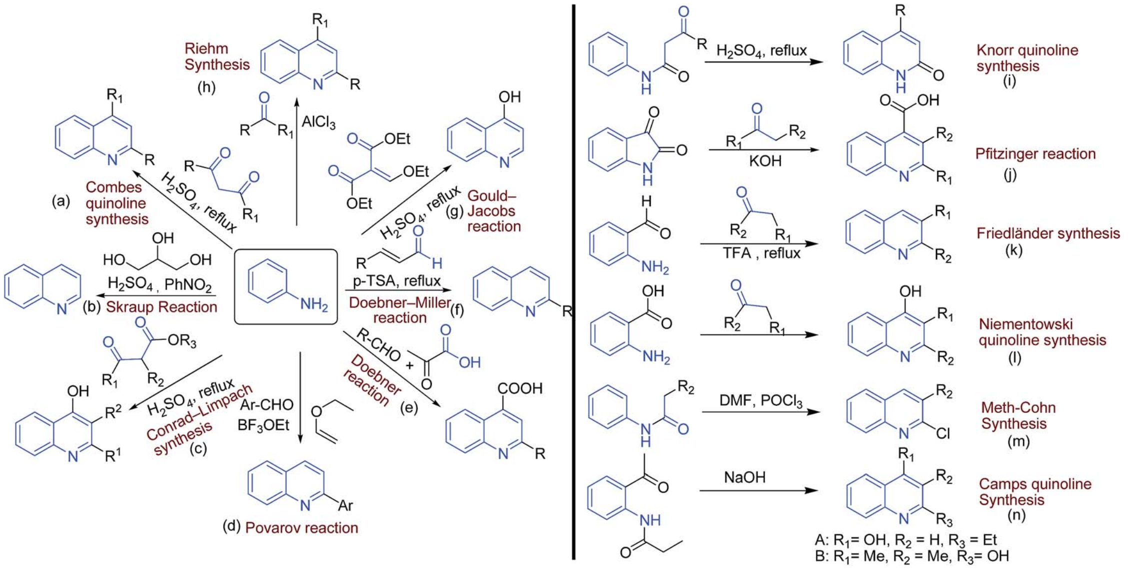


Fig. 3 Classical methods ("Name Reactions") for quinoline synthesis.

organocatalysts, and few methods are catalyst-free. In this section, these protocols have been discussed according to the use of different non-metal reagents/catalysts: (a) acid catalyzed protocols; (b) base catalyzed protocols; (c) molecular iodine catalyzed protocols; (d) ionic liquid mediated quinoline synthesis; (e) organocatalysis for quinoline synthesis; (f) catalyst-free reactions; and (g) miscellaneous reactions.

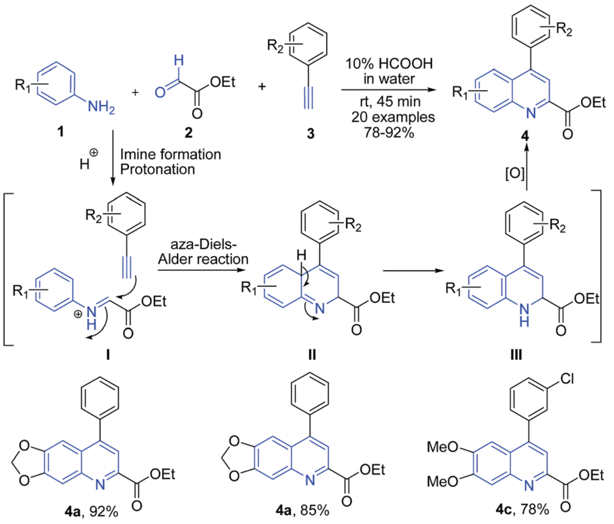
3.1. Acid catalyzed protocols

Acids have been widely used as simple and ecofriendly catalysts and promoters for various organic reactions. Acid catalysts which are routinely used in various organic transformations include trifluoroacetic acid (TFA), formic acid, acetic acid, triflic acid, and pTSA. Acetic acid and formic acid are the two most common reagents available in most of the chemistry laboratories and their use for quinoline synthesis has been well documented. Among various starting materials, arylamines are among most widely used precursors for quinoline synthesis.

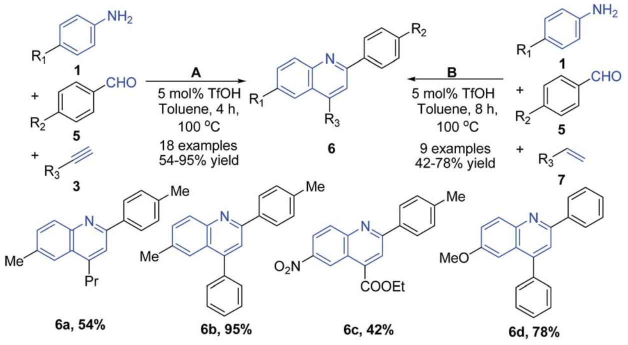
Many acid catalyzed protocols are based on the traditional name reactions. Povarov reaction is one of the most widely investigated reaction for quinoline synthesis, comprising the aza Diels–Alder cycloaddition as the key step. Recently our group[63] have developed an efficient formic acid catalyzed one-pot synthesis of 4-arylquinoline 2-carboxylates **4** in water *via* three-component Povarov reaction of arylamines **1**, glyoxylates **2** and phenylacetylenes **3** (Scheme 1). The reaction mechanism involves a cascade of reactions involving initial condensation of arylamine **1** and ethyl glyoxylate **2** to form imine intermediate **I**. Next, there is a protonation of the nitrogen of the imine which facilitates the attack by phenylacetylene, resulting in cyclization to produce dihydroquinoline **III**, which on oxidation produces 4-arylquinoline 2-carboxylates **4**. These compounds displayed neuroprotective, antioxidant and Pgp-induction activities.

Zhang *et al.*[64] reported a three-component Povarov reaction between aryl aldehydes **5**, arylamines **1**, and alkynes **3** in presence of triflic acid leading to formation of 2,4-disubstituted quinolines **6** (path A of Scheme 2). Interestingly, the use of alkenes **3** instead of alkynes **7** with the increase in reaction time (from 4 h to 8 h) produced same quinoline products **6** (path B of Scheme 2).

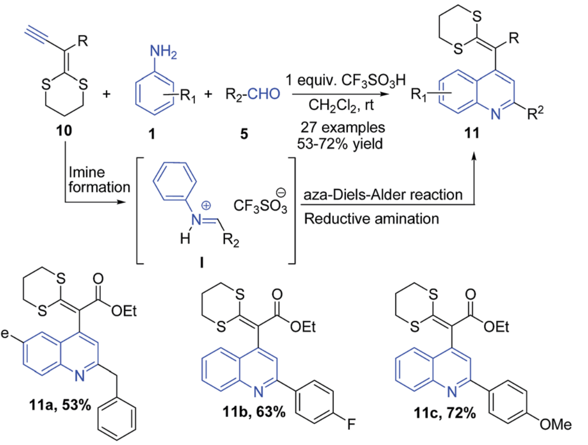
Majumdar *et al.*[65] reported another Povarov-type three-component domino reaction of heterocyclic amines **8**, aldehydes **5**, and terminal alkynes **3** in the presence of $BF_3\cdot OEt_2$, which led to formation of pyrano[3,2-*f*]quinolines **9a** and phenanthrolines **9b**. The imine intermediate **I** undergoes intermolecular concerted type aza-Diels–Alder reaction with an alkyne **3** leading to formation of quinoline skeleton **II**, which on aromatization produces **9** (Scheme 3).



Scheme 1 Formic acid-catalyzed synthesis of quinoline-2-carboxylates **4**; some representative examples are shown.



Scheme 2 TfOH-catalyzed synthesis of 2,4-disubstituted quinolines **6**; some representative examples are shown.



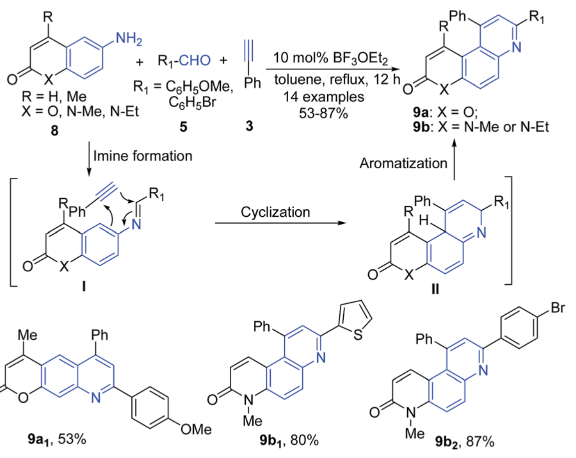
Scheme 4 Triflic acid-catalyzed synthesis of 2,4-disubstituted quinolines **11** *via* three-component aza Diels–Alder reaction; some representative examples are shown.

Ketene-dithioacetals have been used as important building blocks for construction of heterocycles.[66] Ethynyl-*S*,*S*-acetals **10** are highly reactive electron-rich dienophiles which undergo regiospecific aza-Diels–Alder (Povarov) reaction with arylimines to produce quinoline skeleton. A triflic acid mediated three-component reaction between ethynyl-*S*,*S*-acetals **10**, arylamines **1** and aldehydes **5** produced quinoline skeleton **11** *via* consecutive arylimine **I** formation, regiospecific aza-Diels–Alder reaction, and reductive amination (Scheme 4).[67]

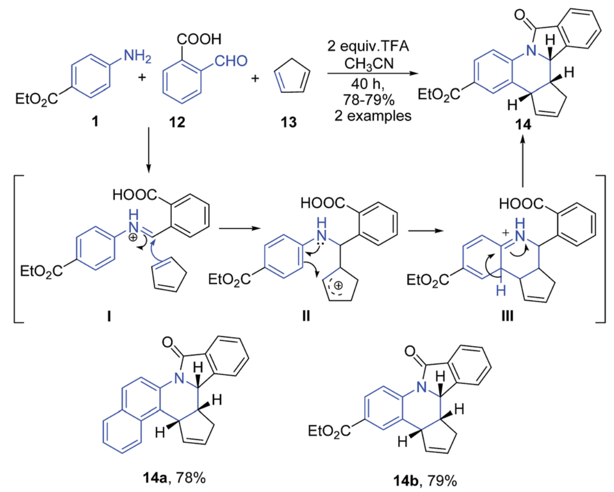
An interesting utility of Povarov reaction for construction of pentacyclic quinoline based fused heterocycles has been recently reported by Khadem *et al.*[68] This protocol implies the three component reaction between arylamine **1**, 2-carboxy benzaldehyde **12** and cyclopentadiene **13** in presence of TFA to furnish isoindolo[2,1-*a*]quinoline **14** (Scheme 5). The Schiff's base **I** undergoes a step-wise aza Diels–Alder reaction with cyclopentadiene **13** to produce isoindolo[2,1-*a*]quinolines **14**. Authors mentioned that the concerted [4 + 2] cycloaddition route would afford a mixture of regio-isomeric products due to free N–Ar bond rotation prior to addition.

Borel *et al.*[69] reported a three-component Povarov reaction of pyridine aldehydes **15** and arylamines **1** with ethyl vinyl ether **16** in presence of boron trifluoride methyl etherate producing 2-(2-pyridyl)quinolines **17** (Scheme 6).

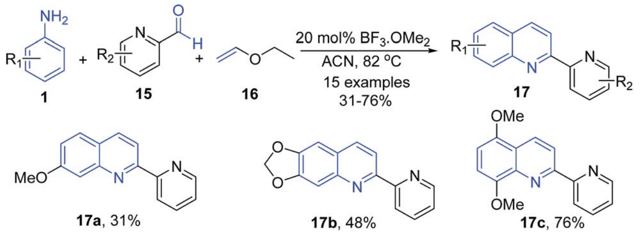
Shindoh *et al.*[70] reported triflic imide and triflic acid catalyzed Povarov-Hydrogen-Transfer cascade reaction to produce quinolines **20**. The reaction between electron-rich olefins **19** and excess amount of imines **18** in the presence of triflic imide



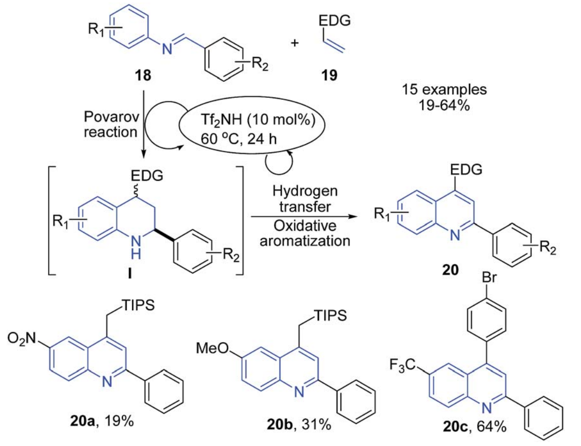
Scheme 3 $BF_3 \cdot OEt_2$-catalyzed synthesis of pyrano[3,2-*f*]quinolines **9a** and phenanthrolines **9b**; some representative examples are shown.



Scheme 5 TFA catalyzed synthesis of pentacyclic isoindoloquinolines **14**; some representative examples are shown.



Scheme 6 $BF_3 \cdot OMe_2$-catalyzed synthesis 2-(2-pyridyl)quinolines **17**; some representative examples are shown.

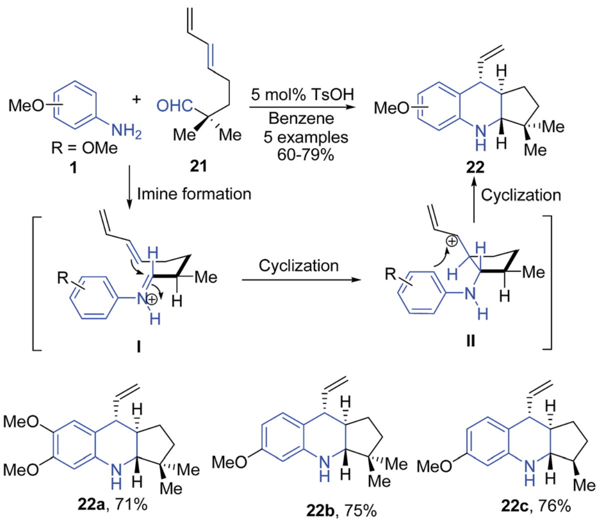


Scheme 7 Triflic imide-catalyzed synthesis of imidazopyrrolo-quinolines **20**; some representative examples are shown.

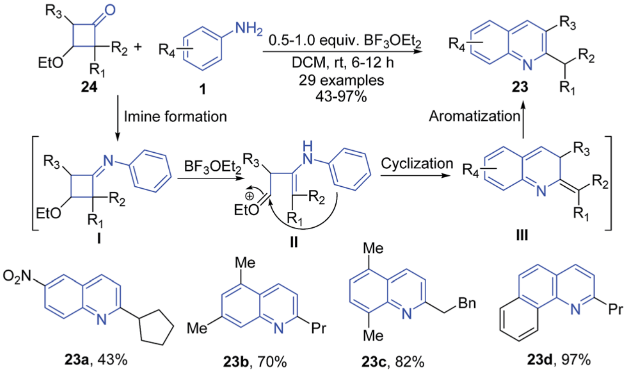
in DCM at 60 °C afforded substituted quinolines **20** in one-pot (Scheme 7).

para-Toluene sulfonic acid (*p*TSA) catalyzed condensation of aromatic amines **1** with δ,ε-unsaturated aldehydes **21**, followed by intramolecular formal hetero Diels–Alder reaction produced cyclopenta[*b*]quinolines **22**.[71] Mechanistically, reaction proceeds through the iminium ion transition state **I** which further undergoes ring closure *via* intramolecular Diels–Alder reaction to produce **II** with a *trans*-arrangement of allylic cation and an amine. The electrophilic aromatic substitution reaction between allylic cation and aniline moiety then leads to formation of stable cyclopenta[*b*]quinoline **22** (Scheme 8).

Boron trifluoride etherate is a widely used Lewis acid catalyst in various reactions. Shan *et al.*[72] reported boron trifluoride etherate catalyzed single-step approach toward the regioselective synthesis of 2-alkylquinolines **23** from 3-ethoxycyclobutanones **24** and aromatic amines **1**. The imine intermediate **I** formed from two substrates undergoes intramolecular cyclization followed by aromatization to produce quinoline product **23** (Scheme 9).



Scheme 8 *p*TSA catalyzed synthesis of cyclopenta[*b*]quinolines **22** from δ,ε-unsaturated aldehydes **21**; some representative examples are shown.

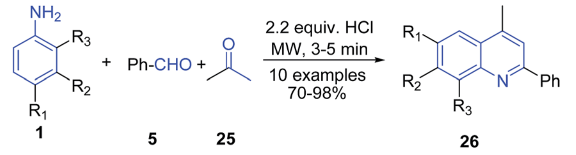


Scheme 9 $BF_3 \cdot OEt_2$-catalyzed synthesis of alkyl quinolines **23** from 3-ethoxycyclobutanones **24** and aromatic amines **1**; some representative examples are shown.

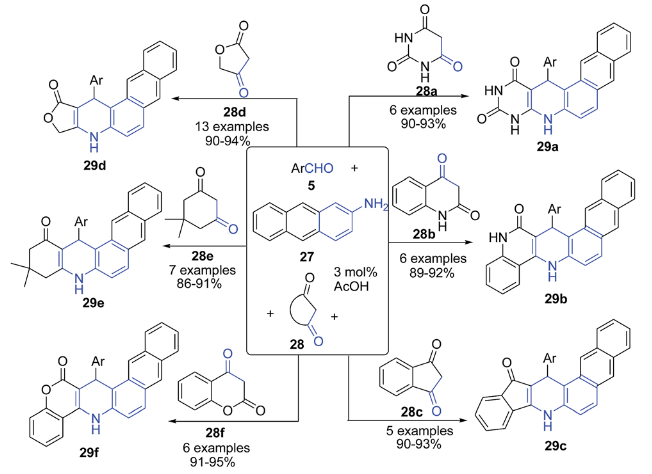
Apart from the Povarov reaction, arylamines are also one of the key precursors in several other protocols. There are several reports on the three-component reaction of arylamines, aryl aldehydes and active methylene compounds leading to formation of a quinoline skeleton. Mirza and Samiei[73] reported Doebner type multicomponent reaction of arylamine **1**, acetone **25** and benzaldehyde **5** without any solvent under microwave irradiation on the surface of alumina impregnated with hydrochloric acid to produce substituted quinolines **26** (Scheme 10).

Tu's group[74] established a sequential three-component reaction between 2-aminoanthracene **27**, aromatic aldehyde **5** and cyclic 1,3-dicarbonyl compounds **28** (such as tetronic acid **28d**, 5,5-dimethyl,3-cyclohexanedione **28e**, 1,3-indanedione **28c**, 3*H*-chromene-2,4-dione **28f**, quinoline-2,4(1*H*, 3*H*)-dione **28b** and barbituric acid **28a**) in acidic medium under microwave irradiation to produce a series of unusual fused heterocyclic compounds, naphtho[2,3-*f*]quinoline derivatives **29** (Scheme 11). This scaffold exhibited good luminescent properties with emission wavelengths in the blue region.

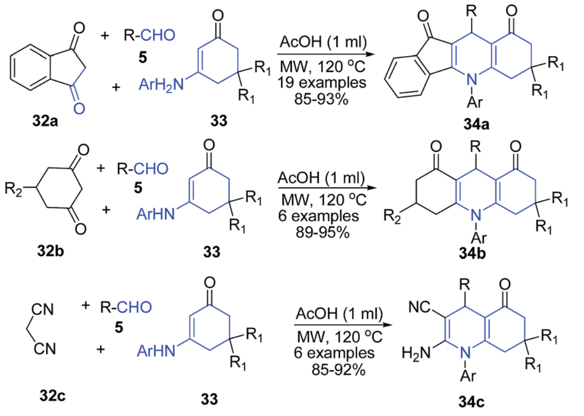
Khan and Das[75] utilized 3-aminocoumarins **30** as the arylamine precursor for synthesis of chromeno[3,4-*b*]quinolines **31**. The *p*TSA catalyzed one-pot three component reaction between aryl aldehydes **5**, 3-aminocoumarins **30**, and cyclic 1,3-diketones **28e** (Scheme 12) produced chromeno[3,4-*b*]quinolines **31**. The reaction proceeds through the key intermediate **I** which on cyclization produces chromeno[3,4-*b*]quinoline **31**.



Scheme 10 HCl-catalyzed synthesis of 4-methyl quinolines **26**.



Scheme 11 AcOH-catalyzed synthesis of naphtho[2,3-*f*]quinoline derivatives **29a–f**.



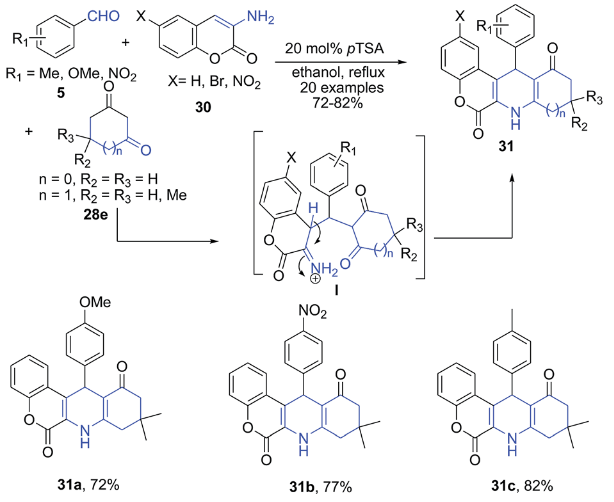
Scheme 13 AcOH-catalyzed synthesis of imidazopyrrolo-quinolines **34a–c**.

Tu and coworkers[76] employed the use of enaminones **33** as the amine precursor and 1,3-indanedione **32a** as an active methylene precursor for preparation of quinoline skeleton. The three component one-pot protocol involving treatment of aldehydes **5**, 1,3-indanedione **32a** and enaminone **33** in presence of acetic acid produced indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-diones **34a**. Authors also used other active methylene compounds such as 5-substituted-cyclohexane-1,3-dione **32b** or malononitrile **32c** in this protocol to produce acridine-1,8(2*H*,5*H*)-diones **34b** or multi-substituted quinolines **34c** (Scheme 13). The reaction mechanism involves Michael addition as the key step; and the protocol was found to work both by microwave irradiation and conventional heating.

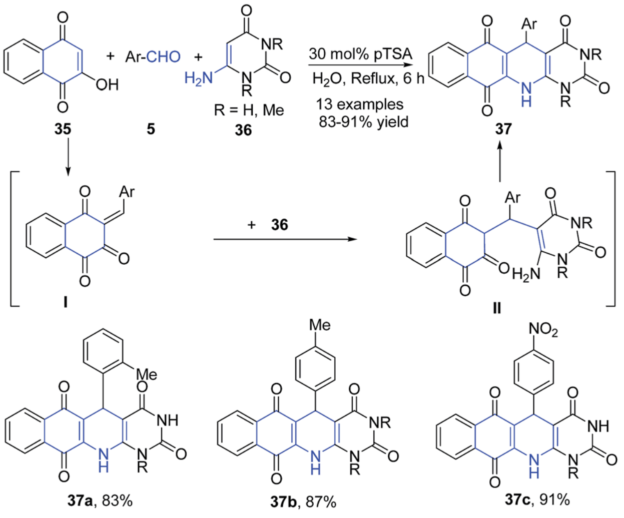
Azizian *et al.*[77] also utilized enaminones as amine precursors for quinoline synthesis. A three-component reaction between 2-hydroxynaphthalene-1,4-dione **35**, 6-amino-uracils **36**, and aromatic aldehydes **5** in presence of *p*TSA in aqueous media produced pyrimido[4,5-*b*]quinoline-tetraones **37**. This reaction has been proposed to proceed by first condensation of 2-hydroxynaphthalene-1,4-dione **35** and aldehyde **5** followed by coupling with 6-amino-uracil **36** and then cyclization of **II** to yield **37** (Scheme 14).

The four-component reaction between naphthylamines **41**, phenylhydrazine **39**, isatins **40** and 3-ketoesters **38** in presence of *p*TSA under solvent-free conditions afforded spiro[1*H*-pyrazolo[3,4-*b*]benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] **42a–b** (Scheme 15). Authors also employed this 4-CR protocol for anilines instead of naphthylamines, which produced 4-substituted pyrazolo[3,4-*b*]quinoline derivatives.[78]

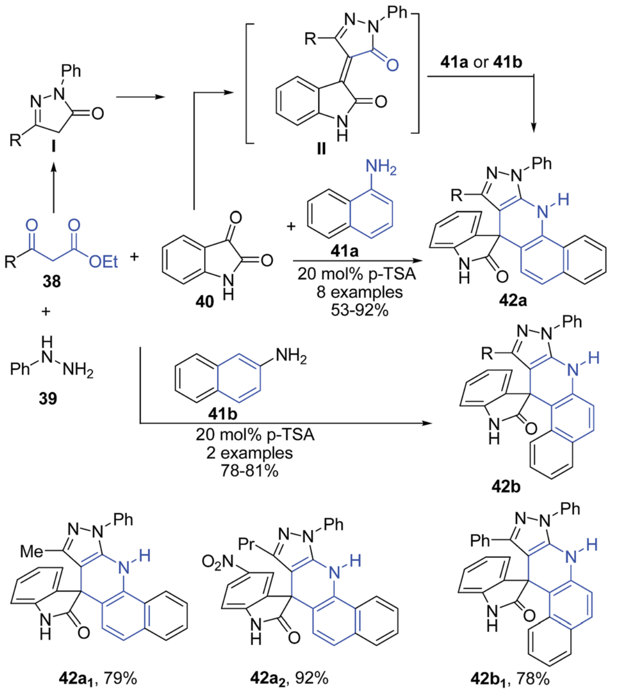
Yu *et al.*[79] reported acetic acid catalyzed three-component reaction between aryl aldehyde **5**, β-naphthylamine **41b**, and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione **44** in the presence of acetic acid leading to formation of benzo[*f*]thiopyrano[3,4-*b*]quinolin-11(8*H*)-ones **43** (Scheme 16).



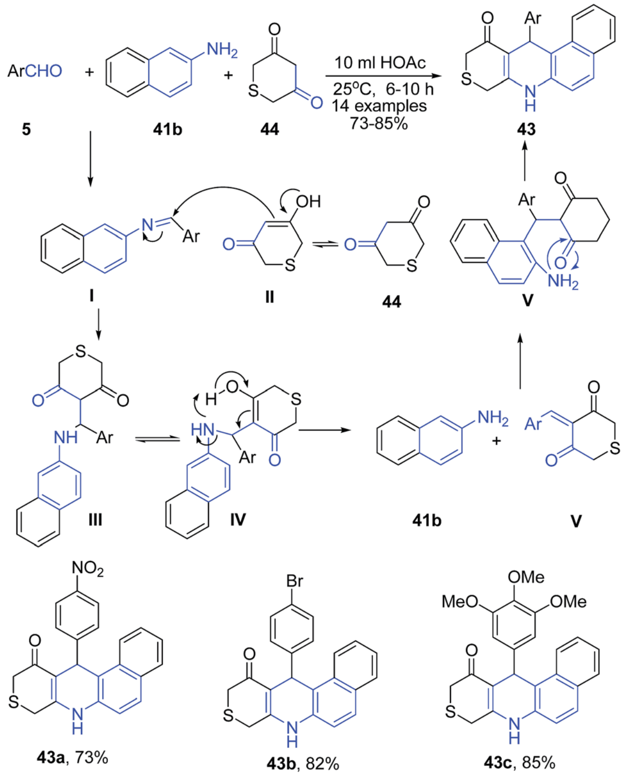
Scheme 12 *p*TSA-catalyzed synthesis of chromeno[3,4-*b*]quinolines **31**; some representative examples are shown.



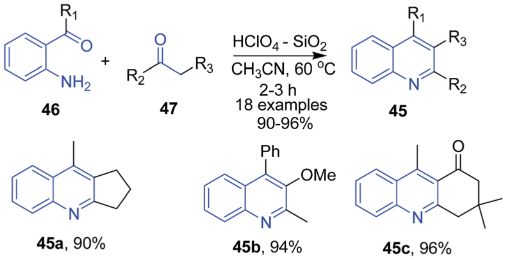
Scheme 14 *p*TSA-catalyzed synthesis pyrimido[4,5-*b*]quinoline-tetraones **37**; some representative examples are shown.



Scheme 15 *p*TSA-catalyzed synthesis of spiro[1*H*-pyrazolo[3,4-*b*]-benzo[*h*]dihydroquinolin-4,3-indolin-2-ones] **42** using 4-CR; some representative examples are shown.



Scheme 16 AcOH catalyzed synthesis of benzo[*f*]thiopyrano[3,4-*b*]quinolin-11(8*H*)-ones **43**; some representative examples are shown.



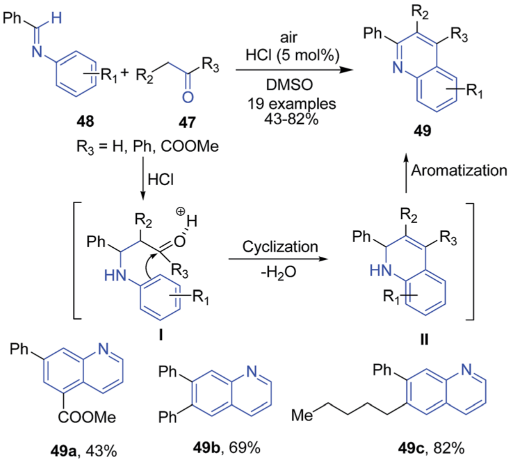
Scheme 17 Silica supported perchloric acid-catalyzed synthesis of poly-substituted quinolines **45**; some representative examples are shown.

Narasimhulu *et al.*[80] used silica supported perchloric acid as a heterogeneous recyclable catalyst for synthesis of various poly-substituted quinolines **45** using Friedlander condensation of 2-aminoarylketones **46** with carbonyl compounds **47** and α-keto esters at ambient temperature (Scheme 17).

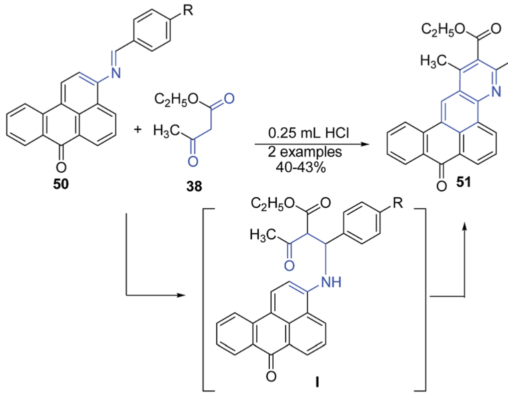
The quinoline synthesis through condensation of benzylideneanilines with active methylene compounds has been reported by two groups. Tanaka *et al.*[81] reported the condensation of benzylideneanilines **48** with carbonyl compounds (aldehydes or ketones or diketones) **47** in presence of catalytic HCl leading to formation of quinolines **49.** The enol form of carbonyl compound reacts with imine to form quinoline ring **II** *via* intramolecular cyclization, which further on aromatization produces **49** (Scheme 18).

Bojinov and Grabchev[82] reported cyclization of 3-(arylideneamino)-benzo[*de*]anthracen-7-ones **50**, with 3-oxo-butyric acid ethyl ester **38** in presence of catalytic amount of HCl to produce fluorescent ethyl 3-aryl-1-methyl-8-oxo-8*H*-anthra[9,1-*gh*]quinoline-2-carboxylates **51** in 40–43% yields (Scheme 19). The reaction proceeds through key amine intermediate **I,** which on cyclization produces **51.**

Apart from the above discussed protocols involving either arylamine, enaminone or benzylimine as one of the key precursor, several groups have established protocols involving



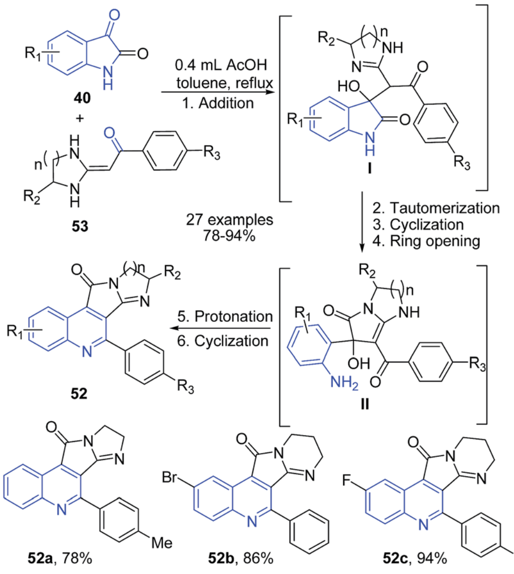
Scheme 18 HCl-catalyzed synthesis of substituted quinolines **49**; some representative examples are shown.



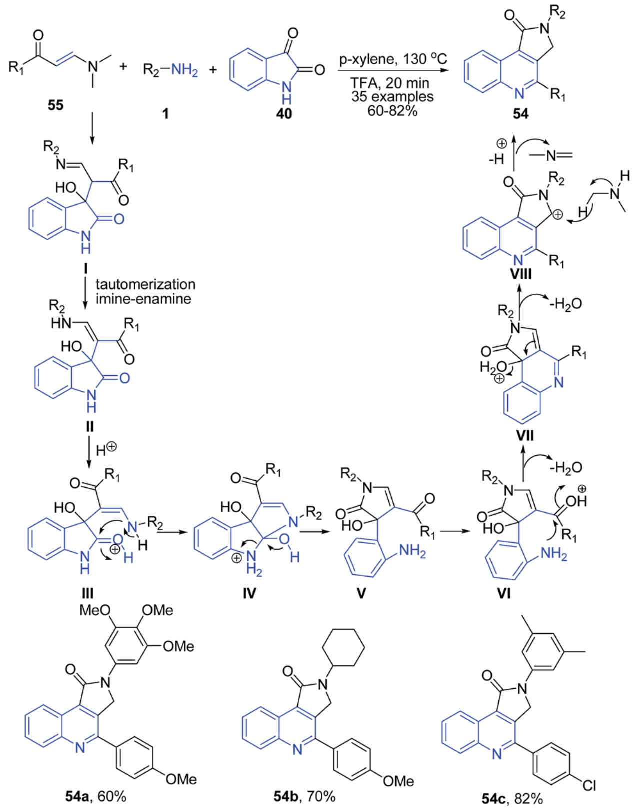
Scheme 19 HCl-catalyzed synthesis of anthra[9,1-*gh*]quinoline-2-carboxylates **51** by cyclization of 3-(arylidene-amino)-benzo[*de*]-anthracen-7-ones **50**.

precursors other than those involved in conventional name reactions. Yu *et al.*,[83] established a domino one-pot protocol for the synthesis of highly substituted imidazopyrroloquinolines **52** by simply refluxing a reaction mixture of different types of isatins **40** and heterocyclic ketene aminals **53** in presence of acetic acid. The reaction mechanism involves cascade of reaction involving first addition of ketene *N*,*N*-acetals to the carbonyl group of isatin **40.** This was followed by imine-inamine tautomerization, intramolecular cyclization, dehydration and ring opening to produce amino intermediate **II.** This intermediate on protonation followed by cyclization leads to the formation of imidazopyrroloquinoline **52** (Scheme 20).

Yu *et al.*[84] described a three-component reaction of enaminones **55,** amines **1**, and isatin **40** under acidic condition. The reaction proceeds through an unusual hydride transfer from *in situ* formed dimethylamine to a carbocation intermediate **VIII** to produce structurally diverse pyrrolo[3,4-*c*]quinoline-1-ones **54** (Scheme 21).

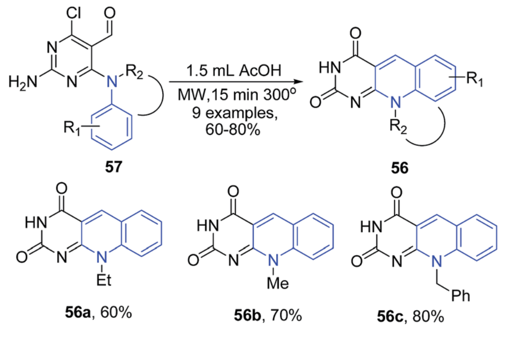


Scheme 20 AcOH-catalyzed synthesis of imidazopyrrolo-quinolines **52** *via* cascade of reactions; some representative examples are shown.

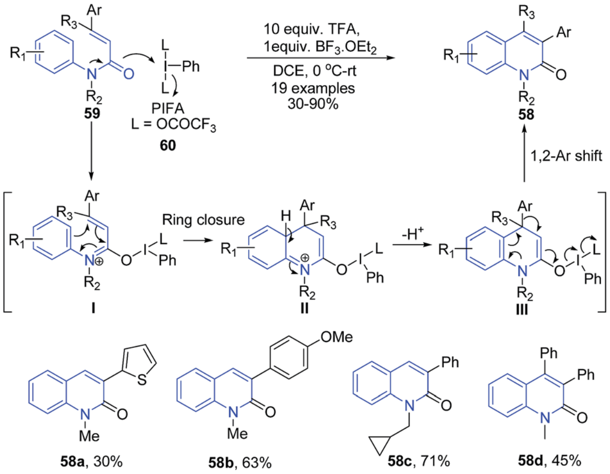


Scheme 21 TFA-catalyzed synthesis of pyrrolo[3,4-*c*]quinoline-1-ones **54**; some representative examples are shown.

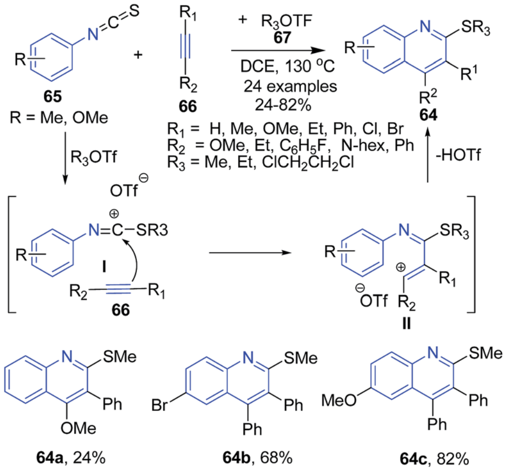
Quiroga *et al.*,[85] showed that microwave-assisted intramolecular cyclization of *N*-4-substituted 6-chloropyrimidine-5-carbaldehydes **57** in acetic acid leads to formation of pyrimido[4,5-*b*]quinolines **56** (deazaflavin analogs), which exhibited excellent fluorescence properties (Scheme 22). The reaction process involves removal of the both Cl and NH_2 groups of the starting material, as these groups are not present in the final products.



Scheme 22 Synthesis of pyrimido[4,5-*b*]quinolines **56** *via* intramolecular cyclization of *N*-4-substituted 6-chloropyrimidine-5-carbaldehydes **57**; some representative examples are shown.



Scheme 23 TFA catalyzed synthesis of 3-arylquinolin-2-ones **58** from *N*-methyl-*N*-phenylcinnamamides **59**; some representative examples are shown.



Scheme 25 Alkyl triflate triggered-synthesis of quinolines **64** from arylisothiocyanates **65**; some representative examples are shown.

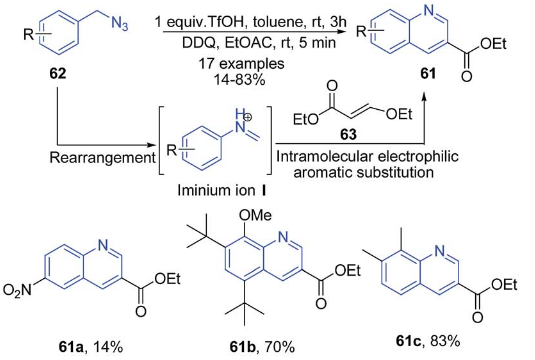
The reaction of *N*-methyl-*N*-phenylcinnamamides **59** with phenyliodine bis(trifluoroacetate) (PIFA) in the presence of TFA produced 3-arylquinolin-2-one compounds **58**. First, the nucleophilic attack on the iodine center by the carbonyl oxygen of the amide moiety in **59** affords 3-azatriene **I** which undergoes an electrocyclic ring closure and the subsequent proton elimination to give intermediate **III**. Next, the 1,2-aryl shift followed by the breakage of the O–I bond gives 3-phenylquinolin-2-one **58** (Scheme 23).[86]

Arylmethyl azides **62** undergo rearrangement to produce *N*-aryl iminium ion intermediate **I** which can be trapped with a variety of nucleophiles.[87] Tummatorn *et al.*[88] utilized arylmethyl azides as the precursors to give an *N*-aryl iminium ion intermediate. Following the addition of ethyl 3-ethoxyacrylate **63**, the 2-substituted quinoline products **61** were obtained in moderate to excellent yields (Scheme 24), *via* a cascade of reactions including intramolecular electrophilic aromatic substitution, elimination and subsequent oxidation.

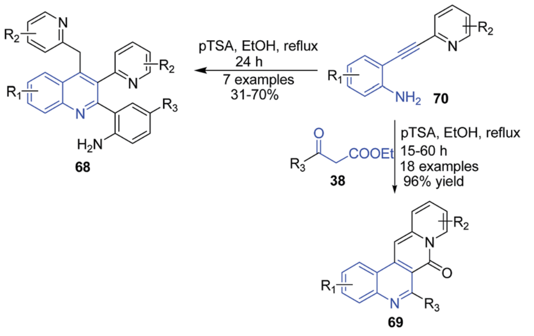
A three-component reaction between arylisothiocyanate **65** alkyltriflate **67**, and alkynes **66** led to the formation of substituted quinolines **64** in high yields. The reaction undergoes alkyltriflate triggered domino electrophilic activation and avoids the use of a transition-metal catalyst. This transformation consisted of a cascade reaction of the arylisothiocyanate **65** with alkyltriflate **67** to form alkylthiosubstituted carbenium ion **I**, which followed the reaction with alkyne **66** to form intermediate **II** and subsequent electrophilic annulation to give quinoline **64** (Scheme 25).[89]

The reaction between pyridine-substituted *o*-alkynylanilines **70** and β-keto esters **38** in presence of *p*TSA in ethanol produced quinoline-based tetracyclic scaffold **69**. Reaction proceeds through sequential hydration-condensation-double cyclization reactions. Interestingly, in the absence of β-keto esters, multisubstituted quinolines **68** were formed *via* condensation of two molecules of *o*-alkynylanilines **70** in reasonable yields (Scheme 26).[90]

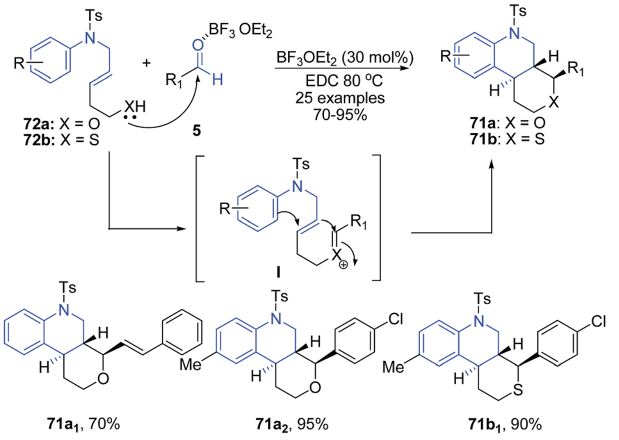
A cascade reaction of (*E*)-5-(arylamino)pent-3-en-1-ols **72a** and thiols **72b** with various aldehydes **5** in the presence of 30 mol% $BF_3 \cdot OEt_2$ in 1,2-dichloroethane at 80 °C afforded *trans*-fused hexahydro-1*H*-pyrano[3,4-*c*]quinolines **71a** and hexahydro-1*H*-thiopyrano[3,4-*c*]quinolines **71b** in good yields with high selectivity.[91] The reaction proceeds *via* formation of an oxocarbenium ion **I** from the hemiacetal that is formed *in situ*



Scheme 24 Triflic acid catalyzed domino synthesis of quinolines **57** from arylmethyl azides **62**; some representative examples are shown.



Scheme 26 *p*TSA-catalyzed synthesis of quinoline-based tetracyclic scaffolds **69** and multisubstituted quinolines **68** from *o*-alkynylanilines.

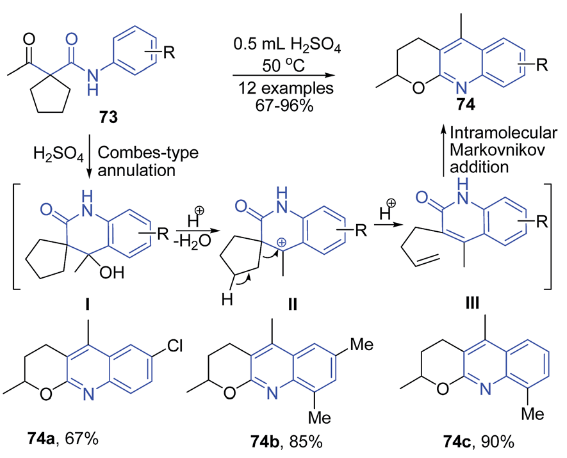


Scheme 27 $BF_3 \cdot OEt_2$-catalyzed synthesis of hexahydro-1*H*-pyrano-[3,4-*c*]quinolines **71a–b**; some representative examples are shown.

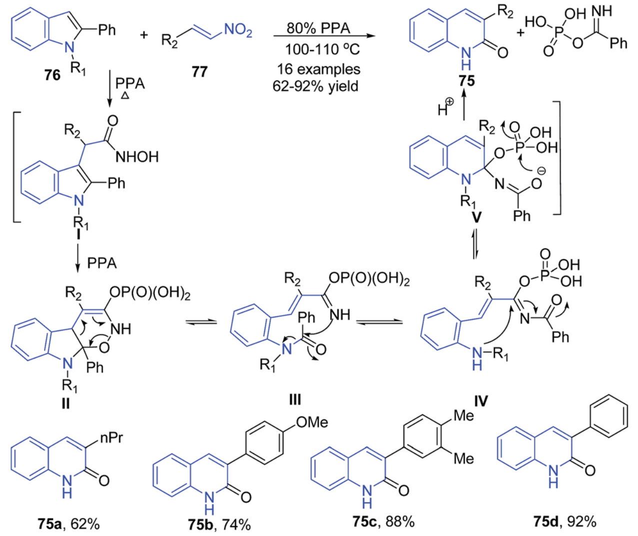
from the aldehyde and a homoallylic alcohol likely after activation with $BF_3 \cdot OEt_2$. The oxocarbenium ion is attacked by an internal olefin resulting in the formation of a carbocation that is simultaneously trapped by a tethered aryl group, leading to the formation of hexahydro-1*H*-pyrano[3,2-*c*]quinolines **71** (Scheme 27).

Zhang *et al.*[92] developed an efficient synthesis of pyrano-[2,3-*b*]quinolines **74** *via* the H_2SO_4-mediated domino cyclization/ring-opening/recyclization reaction of readily available activated cyclopentanes **73.** This transformation commences from a H_2SO_4-mediated Combes-type annulation of cyclopentane to provide an alcohol intermediate **I**, which on elimination of water, produces a tertiary benzylic cation intermediate **II.** The elimination of a proton from intermediate **II** directly provide a terminal alkene intermediate **III**, which undergoes an intramolecular Markovnikov addition to produce pyrano[2,3-*b*]quinoline **74** (Scheme 28).

Aksenov *et al.*[93] reported synthesis of 3-aryl-2-quinolones **75** from indoles **76** *via* a metal-free transannulation reaction of 2-substituted indoles **76** with 2-nitroalkenes **77** in polyphosphoric acid. The conjugation of nitroalkene with indole in presence of PPA produces hydroxamic acid intermediate **I.** Next the intramolecular nucleophilic attack by the *N*-hydroxyl moiety at the C-2 of indole followed by tautomerization affords cyclized enamine **II.** Retro-Diels–Alder reaction followed by migration of acyl group from aniline to the more nucleophilic imine nitrogen produces **IV**, followed by the nucleophilic attack by the aniline at the acyliminium moiety in **IV** affords aminoquinoline **V**, which further on hydrolytic cleavage produces 3-aryl-2-quinolones **75** (Scheme 29).



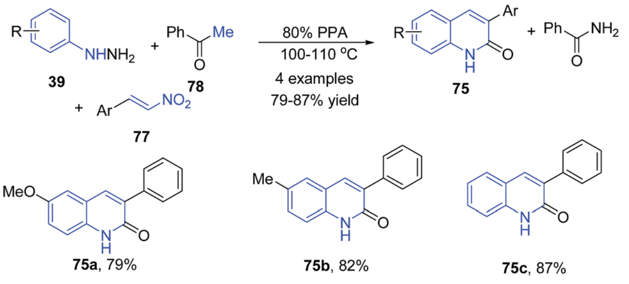
Scheme 28 H_2SO_4-mediated synthesis of pyrano[2,3-*b*]quinolines **74**; some representative examples are shown.



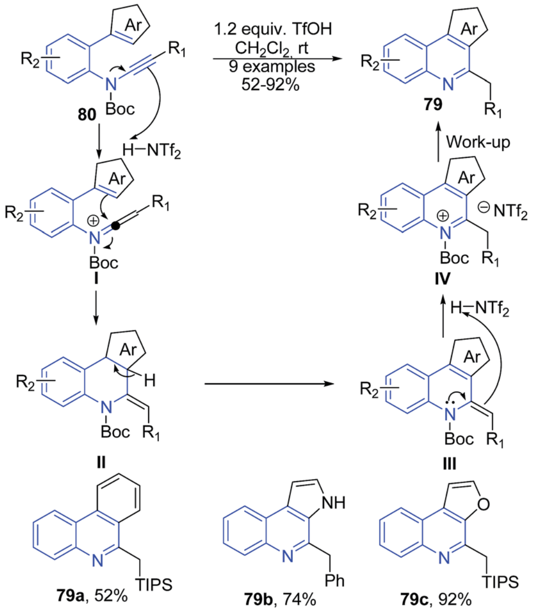
Scheme 29 PPA-catalyzed synthesis of 3-aryl-2-quinolones **75** from 2-substituted indoles **76** and nitroalkenes **77**; some representative examples are shown.

Aksenov *et al.*[93] also reported a three-component condensation of arylhydrazines **39**, 2-nitroalkenes **77** and acetophenone **78** to produce 3-aryl 2-quinolones **75** (Scheme 30).[93]

Yamaoka *et al.*[94] reported a Brønsted acid-promoted arene-ynamide cyclization reaction to construct 3*H*-pyrrolo[2,3-*c*]-quinolines **79.** This reaction involves generation of a highly reactive keteniminium intermediate **IV** from arene-ynamide activated by a Brønsted acid and electrophilic aromatic substitution reaction to give arene-fused quinolines **79** in high yields (Scheme 31).



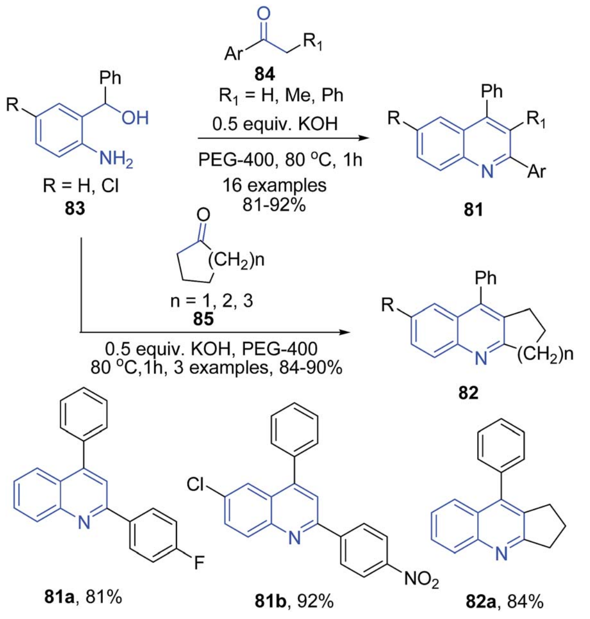
Scheme 30 PPA-catalyzed synthesis of 3-aryl-2-quinolones **75** from arylhydrazines **39**; some representative examples are shown.



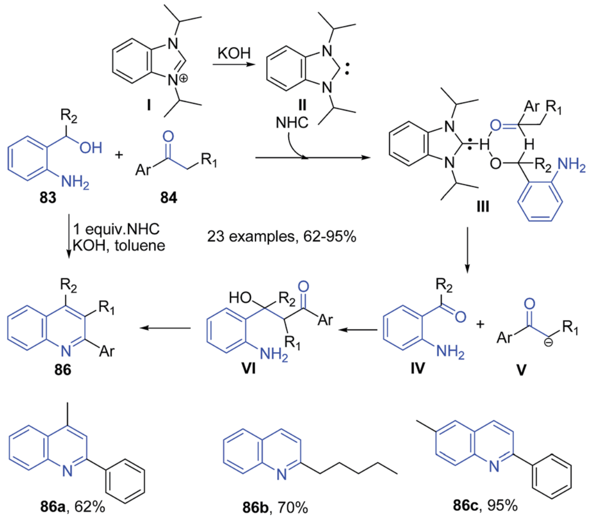
Scheme 31 TfOH catalyzed synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines **79**; some representative examples are shown.

3.2. Base catalyzed protocols

Like acids, various simple and commonly used bases have been employed to catalyze several important organic transformations. This has opened up a way to greener routes for synthesis of heterocyclic structures. Wu *et al.*[95] reported synthesis of substituted quinolines **81** *via* direct reaction between the corresponding aminoalcohol **83** and ketone **84** using PEG-400 as reaction medium in the presence of a base (Scheme 32). This method was also effective for cyclic ketones **85** such as cyclopentanone, cyclohexanone and cycloheptanone producing corresponding substituted quinolines **82**.



Scheme 32 KOH-catalyzed synthesis of quinolines **81–82**; some representative examples are shown.

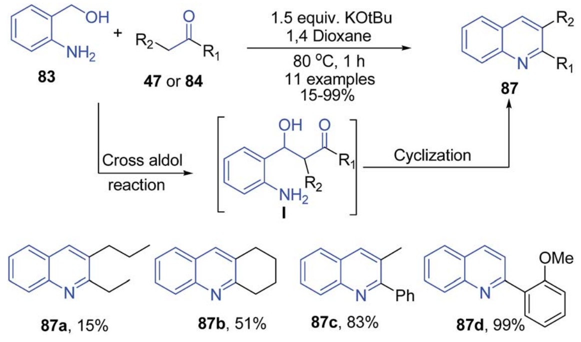


Scheme 33 N-heterocyclic carbene and KOH catalyzed synthesis of quinolines **86**; some representative examples are shown.

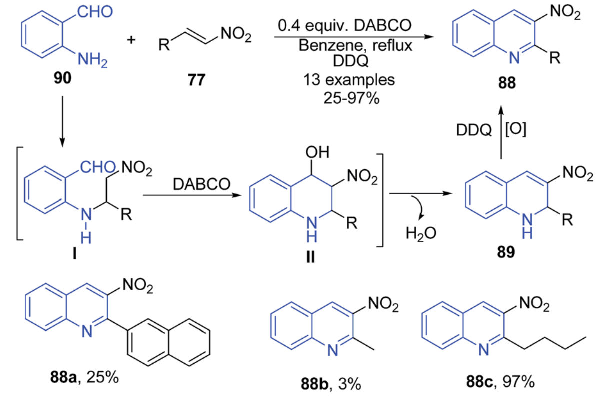
Zhu and Cai[96] reported similar protocol for synthesis of quinolines **86** using N-heterocyclic carbene as a catalyst. The reaction between 2-aminobenzyl alcohol **83** and ketones **84** proceeds *via* two tandem reactions – alpha-alkylation and indirect Friedländer annulation. The base deprotonates N-heterocyclic carbene salt **I** to generate a free carbine **II**. A cross aldol reaction between keto-intermediate **IV** and deprotonated ketone **V**, followed by a cyclization leads to formation of quinoline **86** (Scheme 33).

Using similar starting materials (aminobenzylalcohol **83** and ketones **47** or **84**), Mierde *et al.*[97] have accomplished the synthesis of 2,3-disubstituted quinolines **87** in the presence of potassium *tert*-butoxide (Scheme 34). In the same year, Yus and coworkers[98] have reported exactly same protocol, with the inclusion of 100 mol% benzophenone as an additive.

Yan *et al.*[99] employed the use of alkyl or aryl nitro olefins **77** and 2-aminobenzaldehydes **90** in the presence of DABCO for synthesis of 2-substituted-3-nitro-1,2-dihydroquinolines **89**. The amino group of **90** attacks the aryl nitro olefin **77** to form



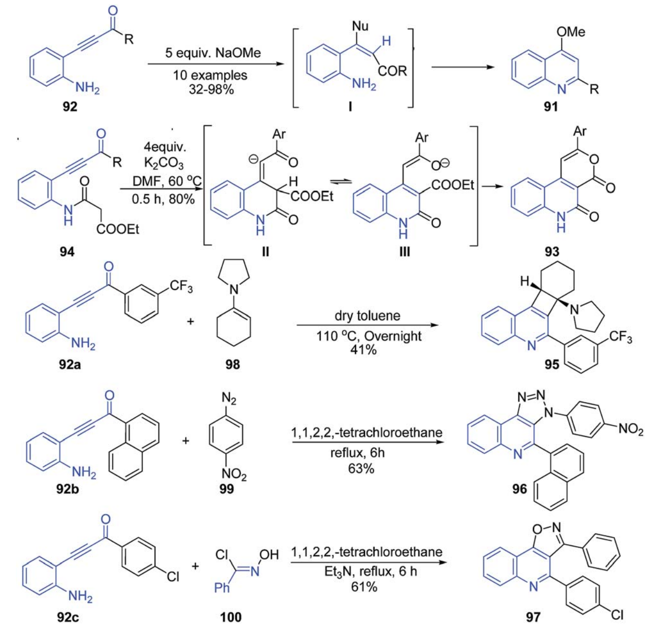
Scheme 34 KO*t*Bu-catalyzed synthesis of quinolines **86** from amino benzyl alcohols **83**; some representative examples are shown.



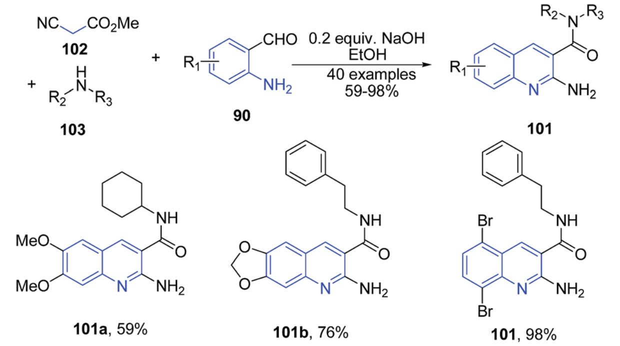
Scheme 35 DABCO-catalyzed synthesis of 3-nitro quinolines **88**; some representative examples are shown.

1,4-addition intermediate **I**, which on cyclization followed by dehydration gives product **88**. After oxidation with DDQ, high yields of 2-alkyl-3-nitroquinolines **88** were obtained (Scheme 35).

Base-catalysed cyclization of β-(2-aminophenyl)-α,β-ynones **92** led to formation of 2,4-disubstituted quinolines **91** through tandem nucleophic addition annulations reactions.[100] Interestingly, the exposure of the β-(2-malonylamidophenyl)-α,β-ynone **94** to K_2CO_3 accomplished the synthesis of fused quinolones **93** through an intramolecular Michael addition/tautomerisation and *trans*-esterification cascade reaction. Similarly, other fused quinolines **95–97** were also obtained (Scheme 36) from β-(2-aminophenyl)-α,β-ynones.



Scheme 36 Base-catalyzed synthesis of 2,4-disubstituted quinolines **91** and fused quinolines **93**, **95–97** from β-(2-aminophenyl)-α,β-nones.



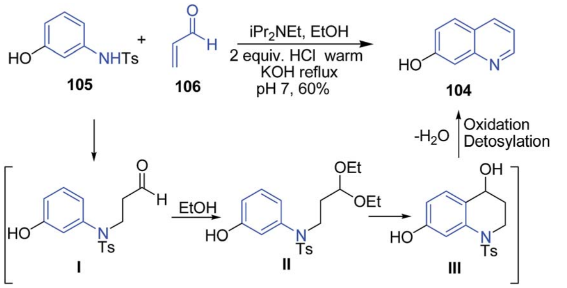
Scheme 37 Base catalyzed one-pot three-component synthesis of 2-aminoquinoline-3-carboxamides **101**; some representative examples are shown.

Wang and coworkers[101] reported a three-component reaction between cyanoacetic acid methyl ester **102**, substituted secondary amine **103** and 2-aminobenzalehyde **90** in the presence of NaOH in ethanol as a solvent produced 2-aminoquinoline-3-carboxamides **101** in good yields (Scheme 37).

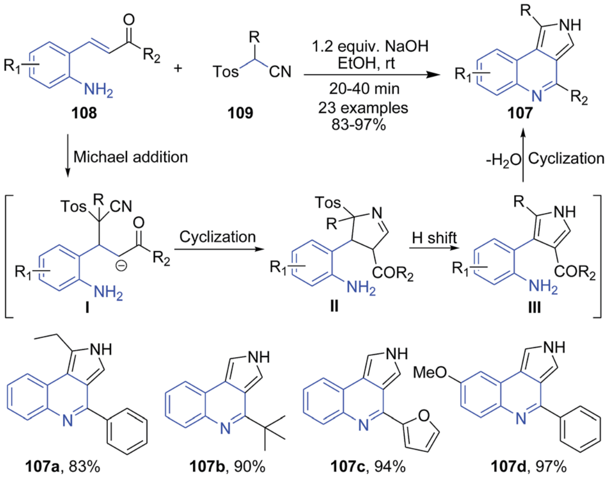
Cameron *et al.*[102] described an efficient one-pot procedure for the four-step preparation of 7-hydroxyquinoline **104** from 3-*N*-tosylaminophenol **105** in presence of diisopropylethylamine in 60% isolated yield. This one-pot procedure has reduced the risk of exposure to acrolein. The 3-*N*-tosylaminophenol **105** on condensation with acrolein **106** produces intermediate **I**. In ethanol, this intermediate **I** is readily converted to the stable acetal **II**, which further on intramolecular Friedel–Craft reaction, followed by dehydration, oxidation and detosylation produces 7-hydroxyquinoline **104** (Scheme 38).

The reaction of aminochalcones **108** with tosylmethyl isocyanide **109** in presence of NaOH produced tricyclic pyrrolo[3,4-*c*]quinolines **107**. In this domino process, three new bonds and two rings are successively formed at ambient conditions.[103] The overall reaction process involves (i) Michael addition of **109** to aminochalcone **108** under basic conditions that provides the carbanion intermediate **I**; (ii) intramolecular cyclization of the resulting anion **I** to form the imidoyl anion intermediate **II** followed by hydrogen shift and elimination of tosylic acid to give the pyrrole intermediate **III**; and finally (iii) intramolecular condensation of ketone with amine to furnish pyrrolo[3,4-*c*]quinoline **107** (Scheme 39).

Rehan *et al.*[104] reported synthesis of 2-aryl 4-substituted quinolines **110** from *O*-cinnamylanilines **111** (which are



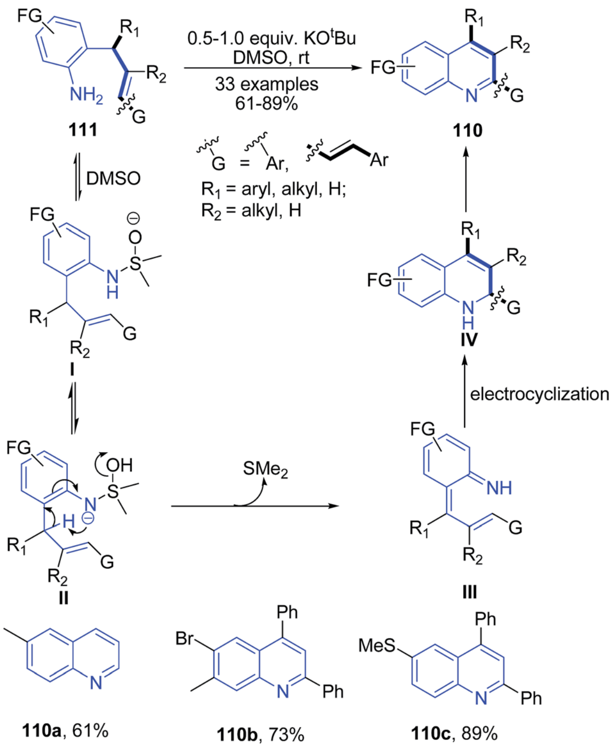
Scheme 38 Diisopropylethylamine catalyzed synthesis of 7-hydroxyquinoline **104** from 3-*N*-tosylaminophenol **105**.



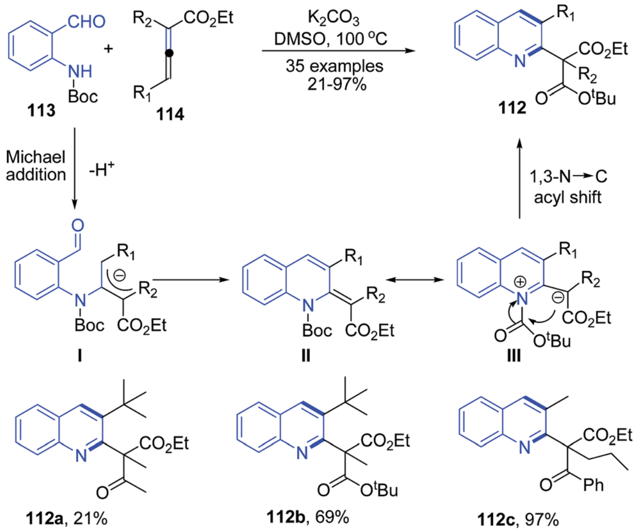
Scheme 39 Synthesis of pyrrolo[3,4-*c*]quinolines **107** in presence of base in ethanol; some representative examples are shown.

prepared from anilines and cinnamylalcohols). The reaction occurs *via* a regioselective 6-endo-trig intramolecular oxidative cyclization using KO*t*Bu as a mediator and DMSO as an oxidant at room temperature (Scheme 40).

The N-protected *O*-aminobenzaldehydes **113** in presence of K_2CO_3 in DMSO smoothly react with α,γ-dialkylallenoates **114** under Brønsted basic conditions to yield 2,3-disubstituted quinolines **112.** This transformation involves a three-step reaction cascade of Michael addition, aldol condensation, and 1,3-N → C rearrangement (Scheme 41).[105]



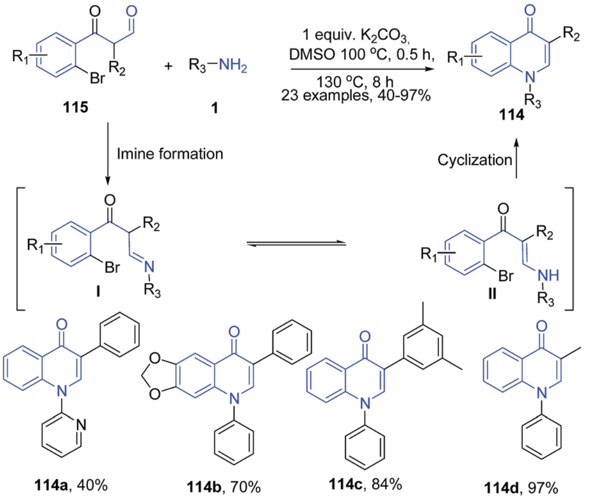
Scheme 40 Potassium *tert*-butoxide catalyzed synthesis of 2-aryl 4-substituted quinolines **110**; some representative examples are shown.



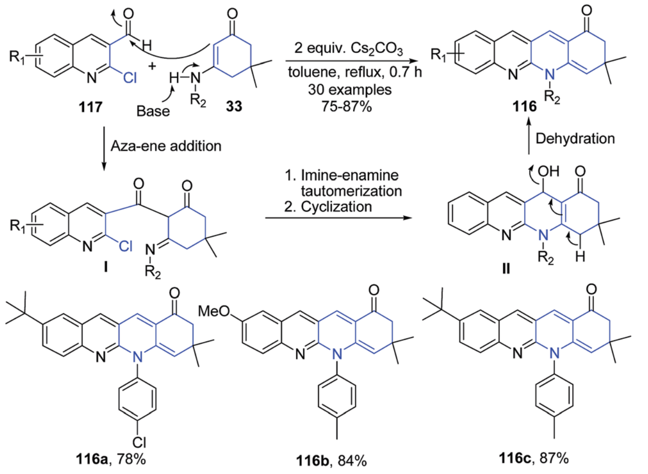
Scheme 41 K_2CO_3 catalyzed synthesis of 2,3-disubstituted quinolines **112**; some representative examples are shown.

The treatment of 3-(2-bromophenyl)-3-oxopropanals **115** with amines **1** in presence of K_2CO_3 in dimethylsulfoxide led to formation of 3-substituted 4-quinolones **114.**[106] Reaction cascade involves base promoted enamine **I** – imine **II** transformation followed by dehydrobromination leading to cyclization to yield quinolone **114** (Scheme 42). In this reaction, weaker bases failed to function in either of the processes and stronger base triggered aldol condensation, however K_2CO_3 was proved to be the most suitable base.

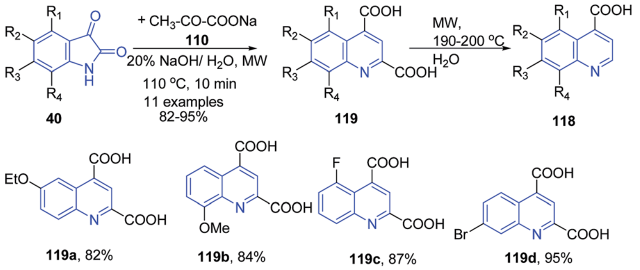
Fu *et al.*[107] have constructed another quinoline ring in the 2-chloroquinoline-3-carbaldehyde structure **117** by treatment with enaminones **33** in presence of Cs_2CO_3 catalyst, producing 1,8-naphthyridines **116.** Initially, the aza-ene addition of enaminones **33** to 2-chloroquinoline-3-carbaldehyde **117** catalyzed by base leads to the formation intermediate **I.** The



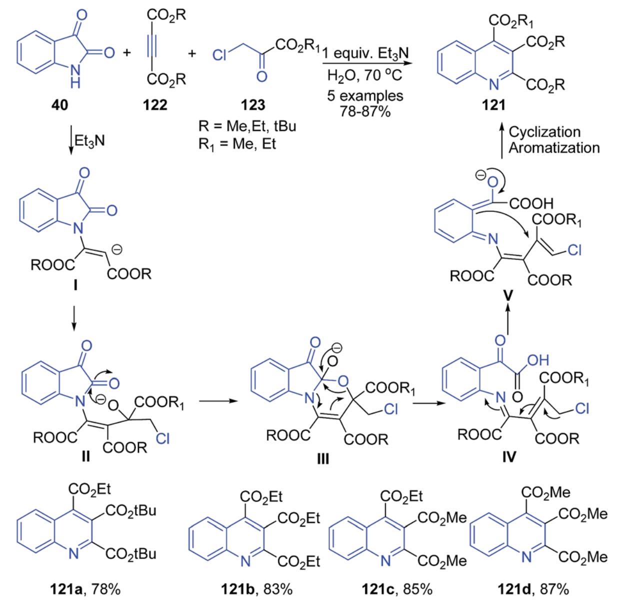
Scheme 42 K_2CO_3-catalyzed synthesis of 3-substituted 4-quinolones **114** in DMSO; some representative examples are shown.



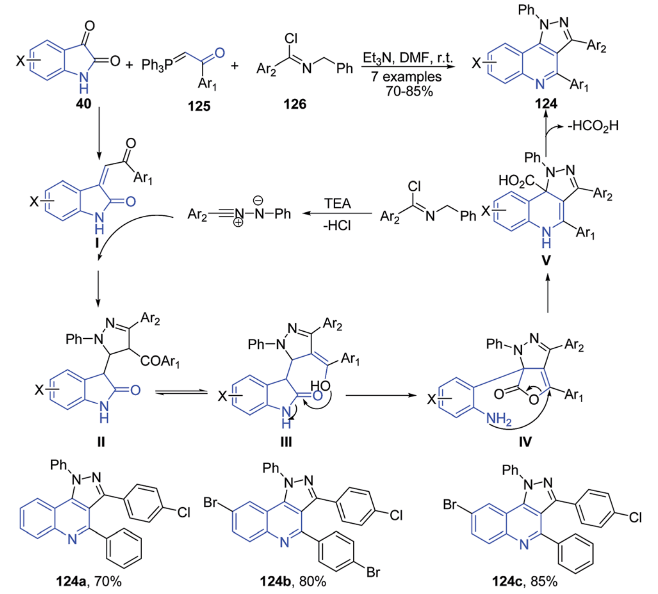
Scheme 43 Cs_2CO_3 catalyzed synthesis of 1,8-naphthyridines **116**; some representative examples are shown.



Scheme 44 Synthesis of quinoline-4-carboxylic acids **118–119** under basic condition; some representative examples are shown.



Scheme 45 Et_3N catalyzed synthesis of substituted quinolines **121** from isatins **40**; some representative examples are shown.



Scheme 46 Et_3N catalyzed synthesis of pyrazolo[4,3-*c*]quinolines **124** from isatins **40**; some representative examples are shown.

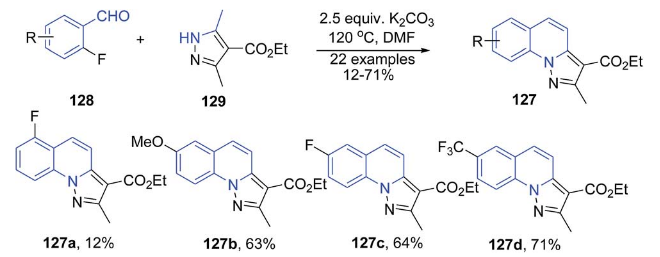
intermediate **I** then undergo an intramolecular cyclization to give intermediate **II**, which on elimination of water produces 1,8-naphthyridines **116** (Scheme 43).

Zhu and coworkers established a facile and efficient method for the preparation of 2-non-substituted quinoline-4-carboxylic acids **118** *via* the Pfitzinger reaction of isatins **40** with sodium pyruvate **120** following consequent decarboxylation under microwave irradiation (Scheme 44).[108]

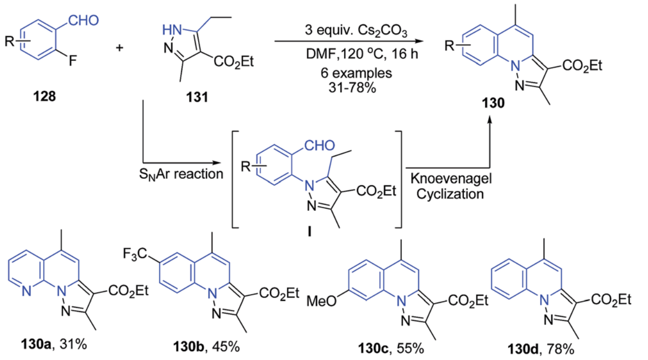
Rineh and coworkers[109] have established triethylamine mediated protocol for synthesis of quinolines **121** *via* reaction between ethyl chloropyruvate **123** and activated acetylenic compounds **122** in the presence of nucleophilic form of isatin in water as the solvent. Nucleophilic form of isatin is produced from the reaction of isatin **40** and triethylamine (Scheme 45).

Alizadeh *et al.*[110] reported three component reaction of isatins **40**, 1-aryl-2-(1,1,1-triphenyl-λ5-phosphanylidene)-1-ethanone **125** and hydrazonoyl chlorides **126** in the presence of Et_3N as a catalyst to produce pyrazolo[4,3-*c*]quinoline **124** (Scheme 46).

Kato *et al.*[111] developed a domino protocol for synthesis of pyrazolo[1,5-*a*]quinolines **127** starting from 2-fluorobenzaldehydes



Scheme 47 Base catalyzed synthesis of pyrazolo[1,5-*a*]quinolines **127**; some representative examples are shown.



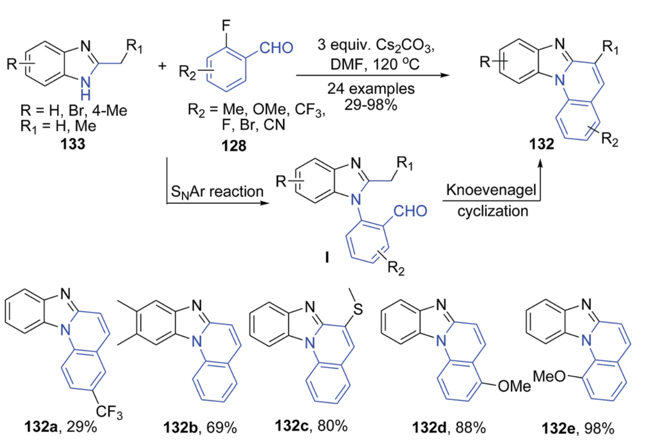
Scheme 48 Cs_2CO_3-catalyzed cascade synthesis of pyrazolo[1,5-*a*]-quinolines **130**; some representative examples are shown.

128 and substituted 3,5-dimethyl-1*H*-pyrazoles **129**. In this cascade reaction, the inactivated methyl group of the pyrazoles **129** participates in the Knoevenagel cyclization upon arylating at the nitrogen of the pyrazoles through the SNAr substitution (Scheme 47).

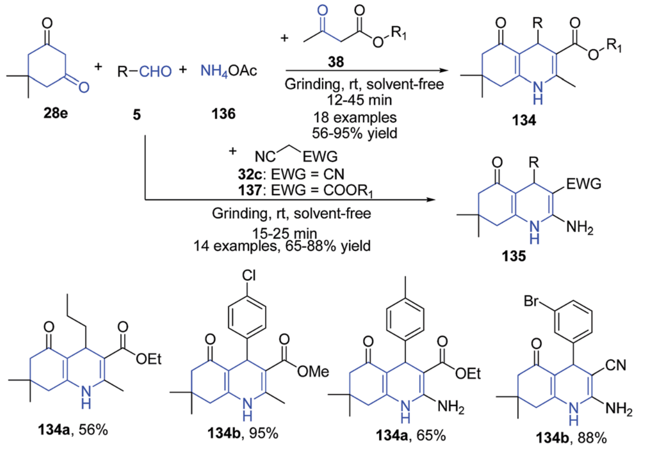
Kato *et al.*[112] reported another similar protocol for synthesis of pyrazolo[1,5-*a*]quinolines **130** from 2-fluoro aryl aldehydes **128** and pyrazole-3-carboxylic acid ester **131** using cesium carbonate base. This cascade reaction involves a sequential intermolecular aromatic nucleophilic substitution (SNAr) and intramolecular Knoevenagel condensation (Scheme 48).

The reaction of 2-methyl benzimidazole **133** with 2-fluorobenzaldehydes **128** in presence of cesium carbonate in DMF produces benzimidazo[1,2-*a*]quinolines **132** *via* a cascade reactions involving sequential aromatic nucleophilic substitution and intramolecular Knoevenagel condensation reactions (Scheme 49).[113]

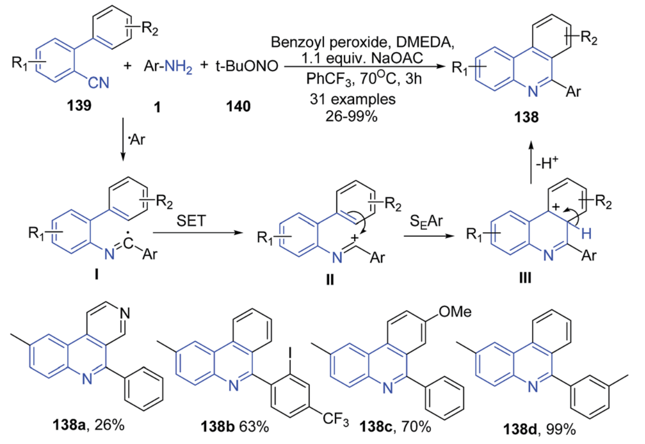
Kapoor and coworkers[114] have reported synthesis of polyhydroquinolines **134–135** *via* a four-component one-pot reaction of aldehydes **5**, dimedone **28e**, active methylene compounds **38** and ammonium acetate **136** under solvent-free conditions at room temperature *via* grinding. The products of



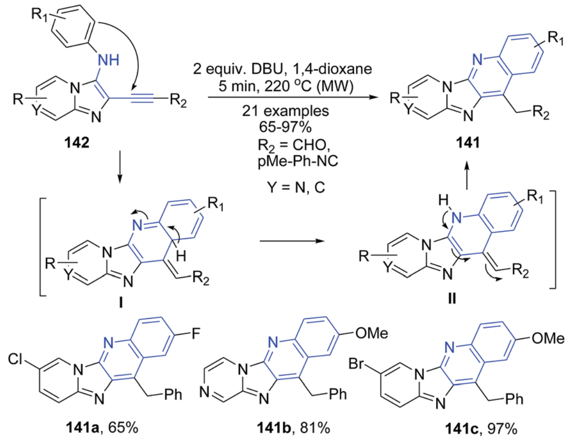
Scheme 49 CS_2CO_3 catalyzed synthesis of benzimidazo[1,2-*a*]quinolines **132**; some representative examples are shown.



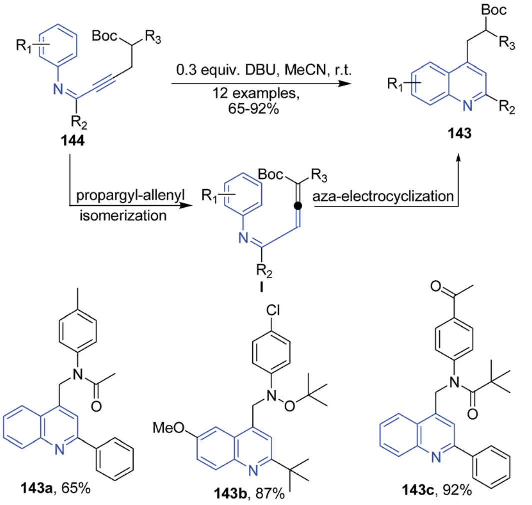
Scheme 50 Catalyst and solvent free synthesis of polyhydroquinolines **134–135** using a one pot four component reaction; some representative examples are shown.



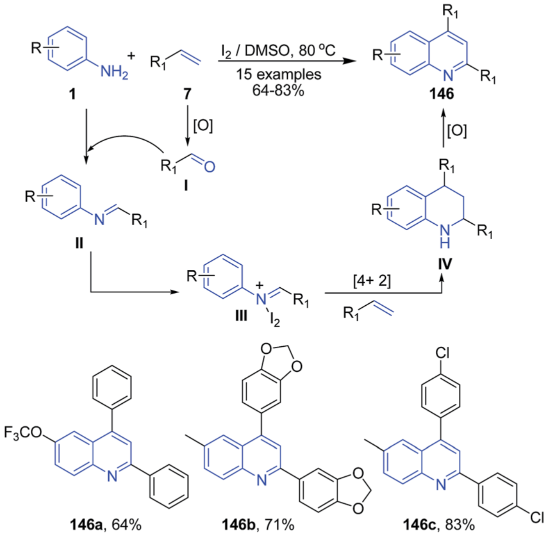
Scheme 51 Sodium acetate and benzoyl peroxide mediated synthesis of phenanthridine derivatives **138**; some representative examples are shown.



Scheme 52 DBU-catalyzed synthesis of pyrido[2′,1′:2,3]imidazo-[4,5-*b*]quinolines **141**; some representative examples are shown.



Scheme 53 DBU promoted synthesis of polyfunctionalized quinolines 143; some representative examples are shown.



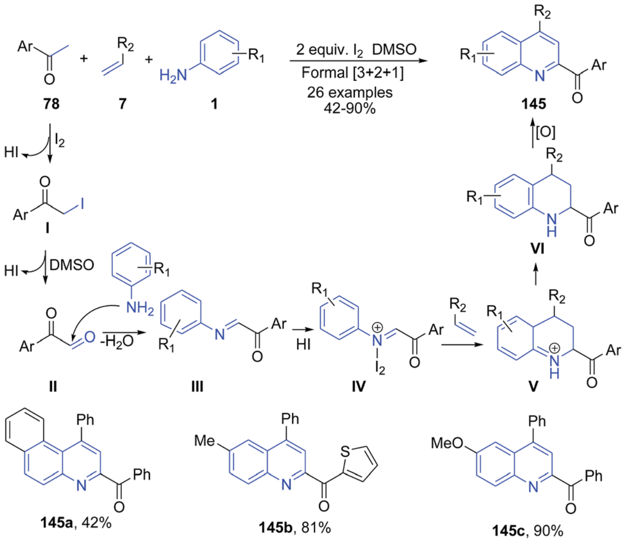
Scheme 55 Synthesis of 2,4-disubstituted quinolines 146; some representative examples are shown.

this protocol were obtained simply by recrystallization from ethanol (Scheme 50).

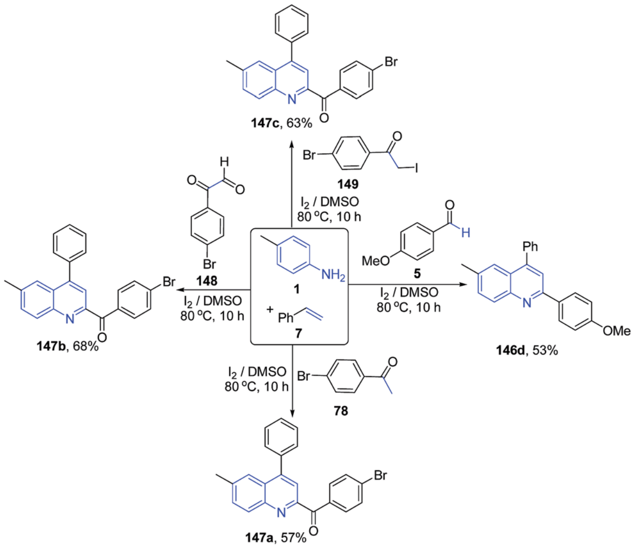
Zhu and coworkers[115] have developed a transition-metal-free method for the synthesis of C6 phenanthridine derivatives **138** by arylative cyclization of 2-isocyanobiphenyls **139** with arylamines **1** in presence of *tert*-butyl nitrite (*t*-BuONO) and using benzoyl peroxide as a promoter and sodium acetate as a base (Scheme 51). Initially, the anilines **1** reacts with *t*-BuONO to produce aryldiazonium ion which then gets decomposed (releasing N_2 and *t*-BuO$^•$) in presence of benzoyl peroxide to produce aryl radical. The resulting aryl radical gets added to the terminal divalent carbon of 2-isocyanobiphenyl **139**, to produce the *N*-biphenyl-2-yl imidoyl radical intermediate **I**. Next, the intramolecular hemolytic aromatic substitution of the imidoyl radical on the pending phenyl ring, forms the cyclohexadienyl radical intermediate **III**. Finally, deprotonation of the intermediate **III** produces **138**, as depicted in Scheme 51.

Berteina-Raboin and Guillaumet[116] described DBU catalyzed synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolines **141** from (ethynyl)*H*-imidazo[1,2-*a*]pyridin-3-amines **142**. The electron-rich secondary amine **142** assists in the hydroarylation of the triple bond after deprotonation by DBU. Next, aromatization leads to formation of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline **141** (Scheme 52).

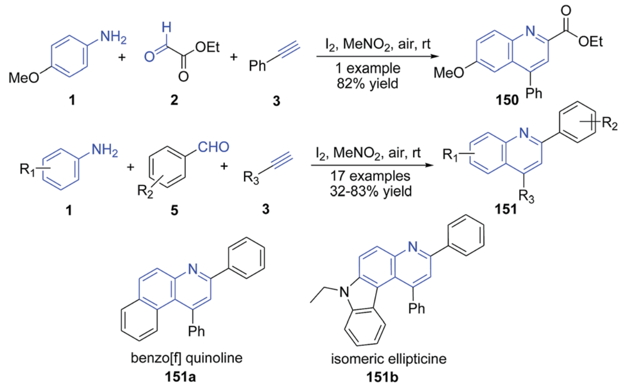
Zhou *et al.*[117] described synthesis of polyfunctionalized quinolines **143** *via* the sequence of propargyl-allenyl isomerization and aza-electrocyclization from but-2-yn-1-yl-phenylimines **144** (Scheme 53).



Scheme 54 Molecular iodine-catalyzed synthesis of 2-acyl quinolines 145 from a three-component reaction between methyl ketones 78, arylamines 1 and styrenes 7; some representative examples are shown.



Scheme 56 Synthesis of 2,4-disubstituted quinolines 146d and 147a–c.



Scheme 57 Molecular iodine catalyzed synthesis of 2,4-disubstituted quinolines **150–151**; some representative examples are shown.

3.3. Molecular iodine catalyzed protocols

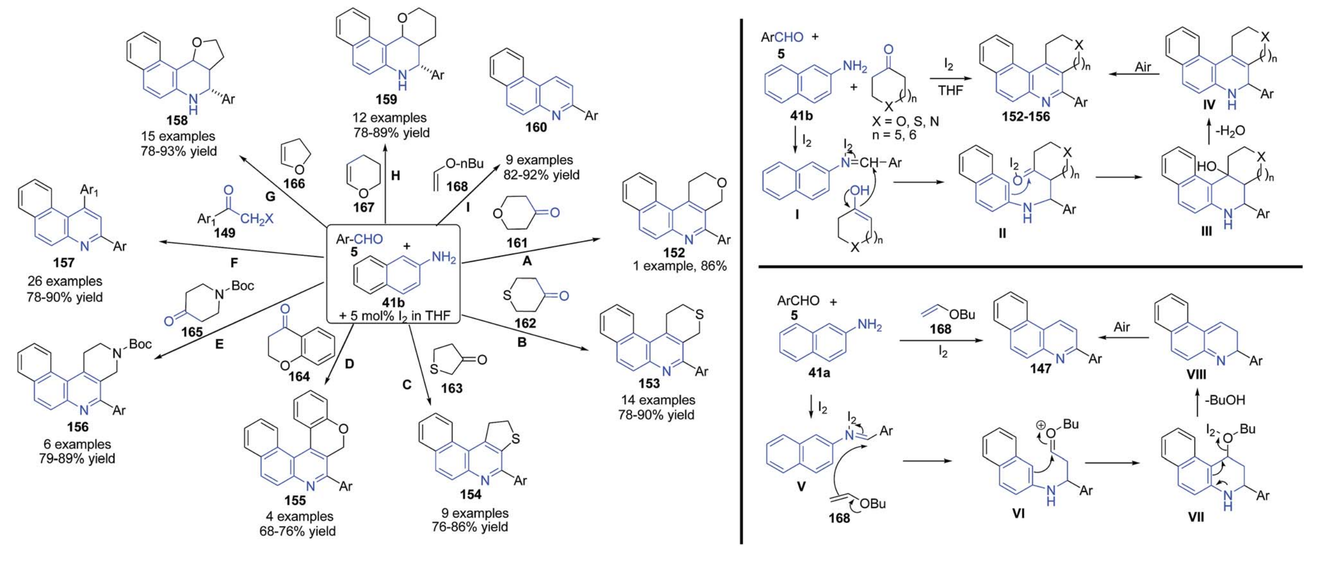
Iodine has been very extensively used in organic chemistry to catalyze diverse range of organic transformations including multicomponent reactions.[118] Gao *et al.*[119] developed a highly efficient molecular iodine mediated formal [3 + 2 + 1] cycloaddition reaction for the direct synthesis of substituted 2-acyl quinolines **145** from methyl ketones **78**, arylamines **1**, and styrenes **7**. Initial reaction of molecular iodine with acetophenone **78** leads to formation of the α-iodo ketone **I**, which gets converted to phenylglyoxal **II** by a subsequent Kornblum oxidation. The reaction of *p*-toluidine **1** with the aldehyde group of **II** then gives the C-acyl imine **III**, which reacts with HI to give the activated C-acyl imine ion **IV**. This activated C-acylimine species **IV** then undergoes cycloadition reaction with styrene (Povarov-type reaction) to give intermediate **V** in the presence of excess or regenerated iodine. Intermediate **V** then undergoes sequential oxidation and aromatization reactions to give **145** (Scheme 54).

Recently Deshidi *et al.*[120] reported molecular iodine catalyzed tandem reaction between styrenes **7** and anilines **1** producing 2,4-disubstituted quinolines **146**. Styrene **7** first gets oxidized to aldehyde **I** which on condensation with arylamine **1** produces imine **II**. Imine intermediate **II** then on coupling with iodine forms iminium ion intermediate **III** which undergoes aza-Diels–Alder cycloaddition reaction with styrene **7** to form **IV**. Intermediate **IV** on oxidation leads to formation of quinoline **146** (Scheme 55).

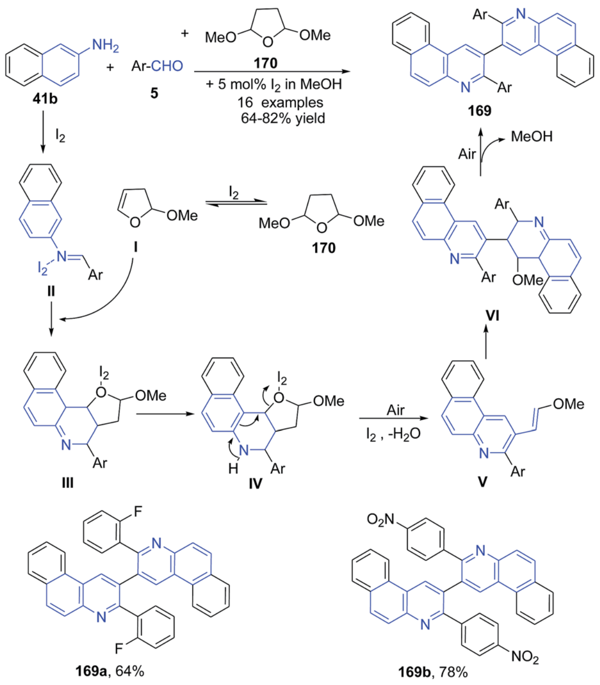
Deshidi *et al.*[120] also reported molecular iodine catalyzed three-component reaction between arylamines **1**, styrenes **7** and carbonyl compound **5**, **78**, **148–149** leading to formation of substituted quinolines **146a**, **1147a–c** (Scheme 56).

Lin's group have developed molecular iodine catalysed synthesis of quinolines **150–151** from aldehydes, amines, and alkynes at mild reaction conditions.[121] The method was also applicable for construction of benzo[*f*] quinolines **151a** (70% yield) and ellipticine **151b** (68% yield) (Scheme 57).

Wang's group[122–124] have developed a mild and efficient method for the synthesis of pyranoquinoline **152**, thiopyranoquinoline **153**, thienoquinoline **154**, chromanoquinolines **155** and naphtho[2,7]naphthyridine **156** derivatives *via* three-component reaction of aromatic aldehyde **5**, naphthalene-2-amines **41b**, and heterocycloketones **149** and **161–168** including tetrahydropyran-4-one **161**, tetrahydrothiopyran-4-one **162**, dihydrothiophen-3(2*H*)-one **163**, chroman-4-one **164** and *N*-Boc 4-piperidinone **165**, using iodine as catalyst (routes A–E).[122] On the use of 2-halogenated acetophenones **149** in the place of cyclic ketones, 1,3-diarylbenzo[*f*]quinolines **157** were obtained (route F).[123] Further same group explored the utility of this method for construction of several other fused quinolines *viz.* benzo[*f*]furo[3,2-*c*]quinoline **158** (route G), benzo[*f*]pyrano[3,2-*c*]quinoline **159** (route H), and benzo[*f*]quinolines **160** (route I) using dihydrofuran **166**, dihydropyran **167** and *n*-butylvinyl ether **168** as third coupling partners (Scheme 58).[124]



Scheme 58 Molecular iodine catalyzed synthesis of pyranoquinoline **152**, thiopyranoquinoline **153**, thienoquinoline **154**, chromanoquinolines **155** and naphtho[2,7]naphthyridine **156** derivatives.



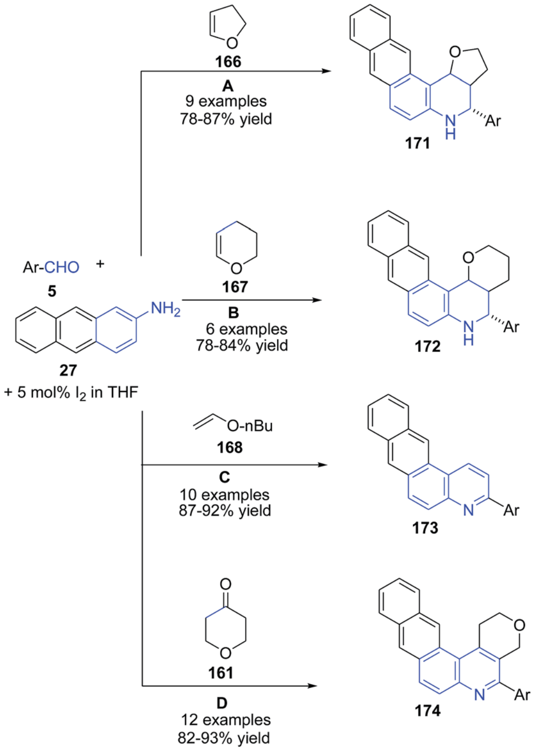
Scheme 59 Molecular iodine catalyzed synthesis of bis-benzoquinolines **169**; some representative examples are shown.

Wang's group[125] further investigated this reaction, wherein a three-component reaction of aromatic aldehyde **5**, naphthalene-2-amine **41b** and tetrahydro-2,5-dimethoxyfuran **170** in methanol catalyzed by iodine, produced 3-aryl-2-(3-arylbenzo[*f*]quinolin-2-yl)benzo[*f*]quinoline derivatives **169** *via* ring opening of furan (Scheme 59).

These authors[124,126] also investigated the utility of this method for preparation of naphtho[2,3-*f*]furo[3,2-*c*]quinolines **171** (route A),[124] naphtho[2,3-*f*]pyrano[3,2-*c*]quinolines **172** (route B)[124] and naphtho[2,3-*f*]quinolines **173** (route C)[124] and naphtho[2,3-*f*]pyrano[3,4-*c*]quinolines **174** (route D) (Scheme 60) from anthracen-2-amine **27**.[126] The mechanism involves the formation of imine **II** which undergoes covalent bond formation with iodine to produce intermediate **III**. This intermediate reacts with enol form **I** of tetrahydropyran-4-one **161** to produce cyclized intermediate **IV**, which on dehydration produces **V**. Finally air oxidation of **V** produces naphthoquinoline **174** (Scheme 61).

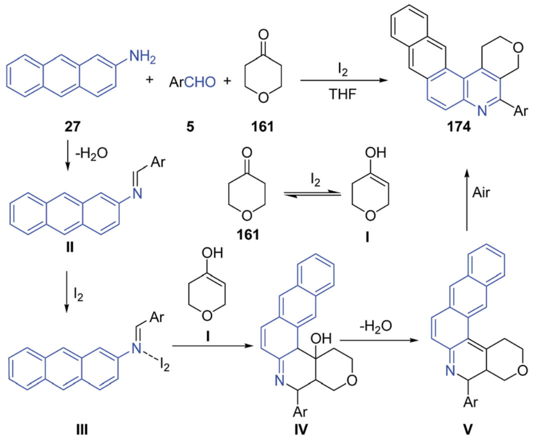
Molecular iodine catalyzed three-component imino Diels–Alder reaction of aromatic aldehyde **5**, anthracene-2-amine **27** or 1*H*-indazol-5-amine **177** and cyclopentanone **85** produced cyclopenta[*c*]naphtho[2,3-*f*]quinoline **175** and cyclopenta[*c*]-pyrazolo[4,3-*f*]quinoline **176** (Scheme 62).[127]

Anionic surfactant sodium dodecyl sulfate has also been employed in heterocycle synthesis.[128] Recently Ganguly and Chandra[129] have employed the use of molecular iodine and sodium dodecyl sulfate for the construction of quinoline skeleton using a three-component reaction. A three-component coupling of 6-aminocoumarin **8**, aromatic aldehyde **5** and an excess of styrene **7** in water in presence of molecular iodine and sodium dodecyl sulfate produced pyrano[3.2-*f*]quinolin-3-ones **178** and pyrano[2.3-*g*]quinolin-2-ones **179.** The reaction mechanism involves a cascade of two key transformations *viz.* Povarov reaction and hydrogen transfer (Scheme 63).

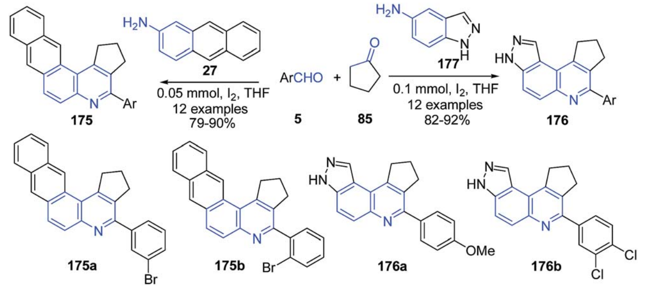


Scheme 60 Molecular iodine catalyzed synthesis of naphthoquinolines **171–174** from anthracenyl amines.

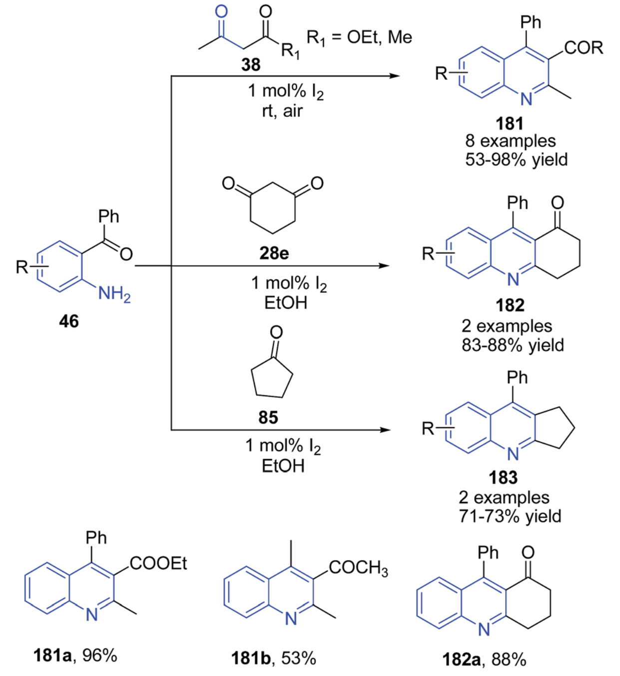
Wu and coworkers[130] reported a mild and efficient route for the synthesis of quinolines **181** and polycyclic quinolines **182–183** *via* Friedlander annulation utilizing molecular iodine (1 mol%). Treatment of 2-aminoaryl ketone **46** with α-methylene ketones **38** in ethanol in presence of molecular iodine produced quinolines **181**. Cyclic ketones such as cyclopentanone **85** and cyclohexadione **28e** also underwent smooth condensation with



Scheme 61 Reaction mechanism for molecular iodine catalyzed synthesis of naphthoquinolines **174**.



Scheme 62 Molecular iodine catalyzed synthesis of cyclopenta[*c*]-naphtho[2,3-*f*]quinoline **175** and cyclopenta[*c*] pyrazolo[4,3-*f*]quinolines **176**.



Scheme 64 Molecular iodine-catalyzed synthesis of 2,3,4-trisubstituted quinolines **181–183**; some representative examples are shown.

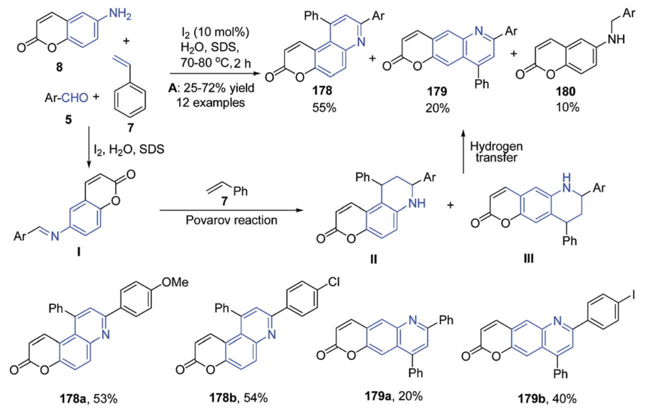
2-aminoaryl ketones to afford the respective tricyclic quinolines **182–183** (Scheme 64). The synthesis of **181** from 2-aminoaryl ketone **46** with α-methylene ketones **38** has also been reported using (bromodimethyl)sulfonium bromide[131] or cyanuric chloride[132] as a catalyst.

Zeng and Cai[133] reported a domino protocol for synthesis of benzo[*f*]quinolinyl acetamides **184** and benzo[*h*]quinolinyl acetamides **185** from diketene **186**, benzyl amines **187**, aromatic aldehydes **5** and naphthalene amines **41b** using molecular iodine as a catalyst (Scheme 65).

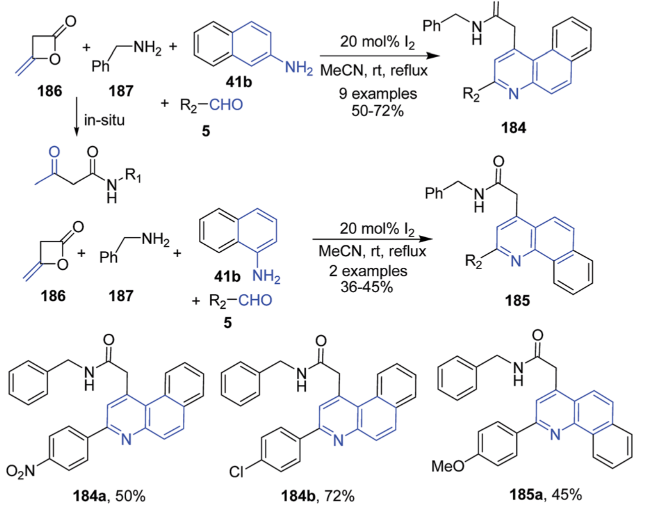
Fotie *et al.*[134] reported synthesis of a series of unusual 2,3,4,5-tetrahydro-4,4-tetramethylene-1*H*-cyclopenta[*c*] quinolines **188** through the Skraup-Doebner–Von Miller quinoline synthesis. The reaction mechanism involves three basic sequences: (a) the formation of a Schiff base **I** through a reaction between the ketone **85** and the aniline **1** in the first step, followed by (b) a cycloalkenylation at the *ortho*-position to the amine functional group of the aniline, and (c) an annulations in the final step to close the quinoline ring, leading to a dihydroquinoline derivative **188** as described in Scheme 66.

The oxidative cyclization of phenyl-*N*-(*o*-alkynylphenyl) imines **190** in presence of molecular iodine produced furanoquinolines **189** (Scheme 67).[135] The iodide cation on coupling with imine **190** generated iminium ion **I** which further undergoes intramolecular cyclization to produce quinoline **II**, which in elimination of HI produces **189.**

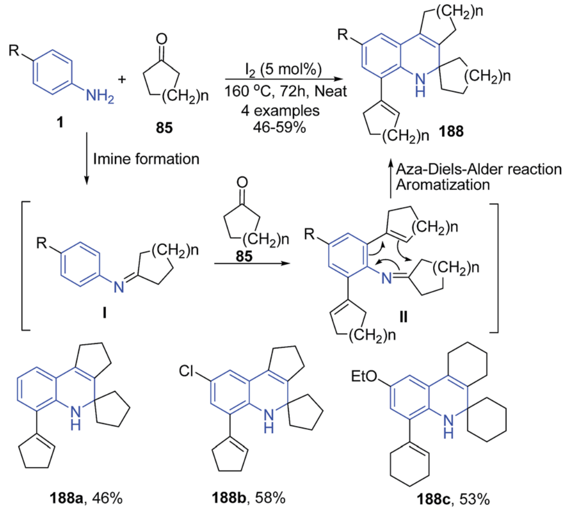
Batra's group[136] reported molecular iodine catalyzed synthesis of 2-substituted quinolines **191** from substituted primary allylamines **192.** Iodine initially activates the carbonyl group, which is then followed by electrophilic cyclization to produce dihydroquinoline **II.** The intermediate **II** on the subsequent elimination of two protons in the form of 2 HI molecules produces intermediate **V,** which finally oxidizes to the quinoline **191** (Scheme 68).



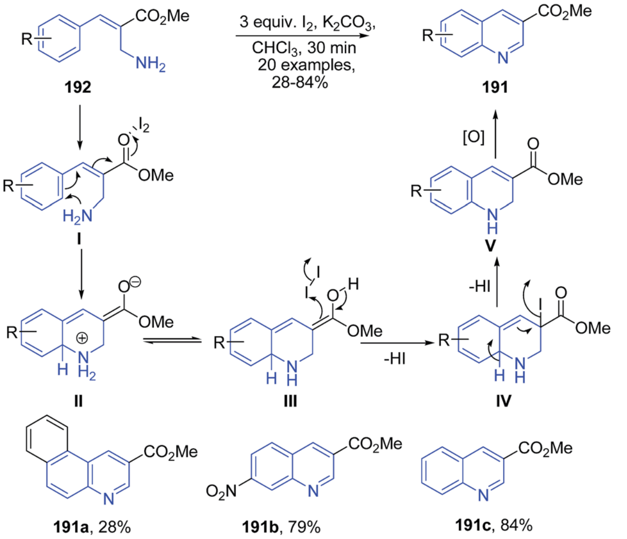
Scheme 63 Molecular iodine catalyzed synthesis of synthesis of pyrano[3.2-*f*]quinolin-3-ones **178** and pyrano[2.3-*g*]quinolin-2-ones **179**; some representative examples are shown.



Scheme 65 Molecular iodine catalyzed synthesis of benzo[*f*]quinolinyl and benzo[*h*]quinolinyl acetamides **184–185**; some representative examples are shown.



Scheme 66 I$_2$-catalyzed synthesis of cyclopenta[*c*]quinolines **188**; some representative examples are shown.

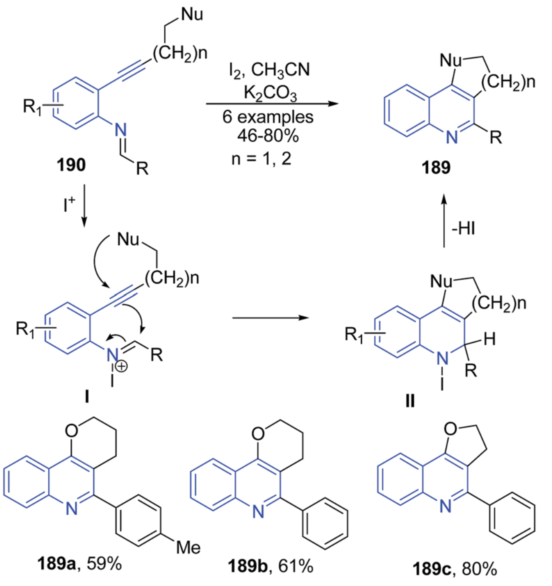


Scheme 68 Iodine-catalyzed synthesis of 2-substituted-quinolones **191** from allylamines **192**; some representative examples are shown.

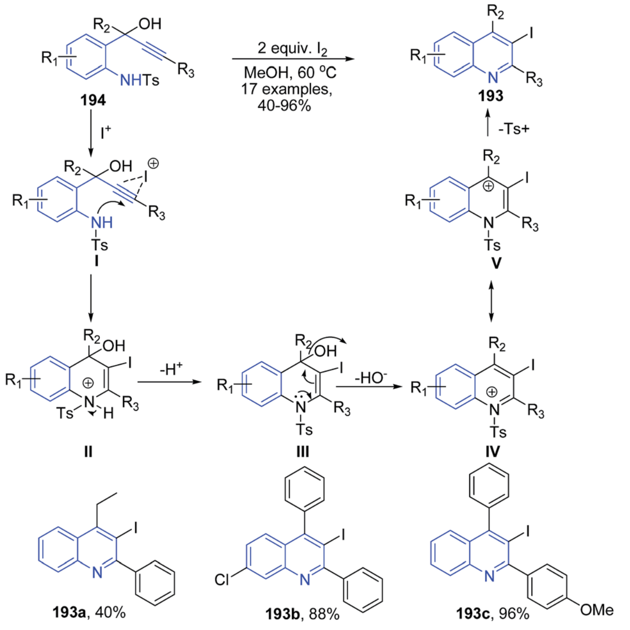
2-Tosylaminophenylprop-1-yn-3-ols **194** in the presence of molecular iodine undergoes 6-endo-dig iodocyclization leading to formation of substituted 3-iodoquinolines **193** (Scheme 69).[137] The mechanism involves anti-attack of the iodide cation and the nitrogen of the tosylated amino group on the alkyne moiety of **178** to produce an intermediate **II**, which further undergoes a proton removal by the iodide producing intermediate **III**. The intermediate **III** then loses hydroxyl ion to give cation **IV**, which finally on elimination of tosyl group leads to formation of quinoline **193**.

Activation of C2 and C3 of indoles **196** by molecular iodine and base followed by *in situ* reaction with 1-(2-tosylaminophenyl)ketones **197** or 2-tosylaminobenzaldehyde afforded highly substituted indolo(2,3-*b*)quinolines **195** in moderate to excellent yields.[138] This is a domino one-pot protocol involving cascade of three reactions – amination, alkylation and aromatization. The mechanism of this reaction involves electrophilic addition of iodonium to the 3-position of indole **196** to give cation **I**, which undergoes 2-amination with **197** to afford **II**. The intermediate **II** eliminates a molecule of HI in the presence of base to give **III**. Alkylation and subsequent detosylation of **III** in the presence of HCl gives **195** (Scheme 70).

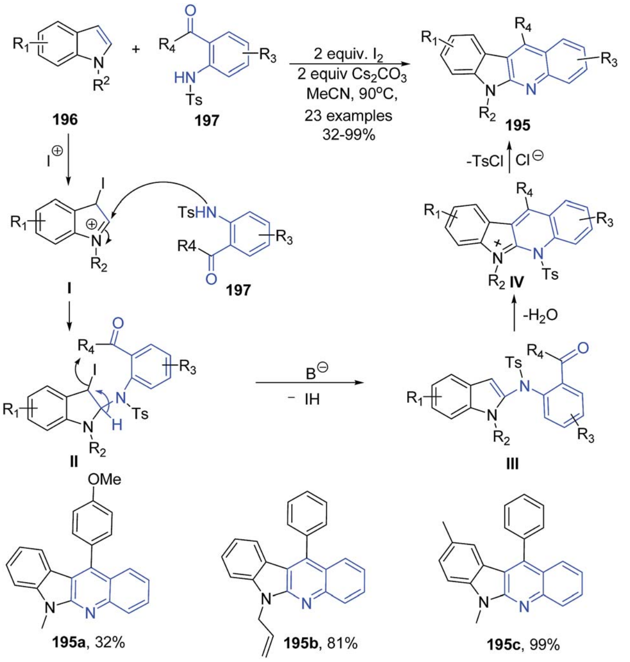
Isocyanides are one of the promising precursors for the preparation of N-heterocycles such as pyrroles, indoles, and



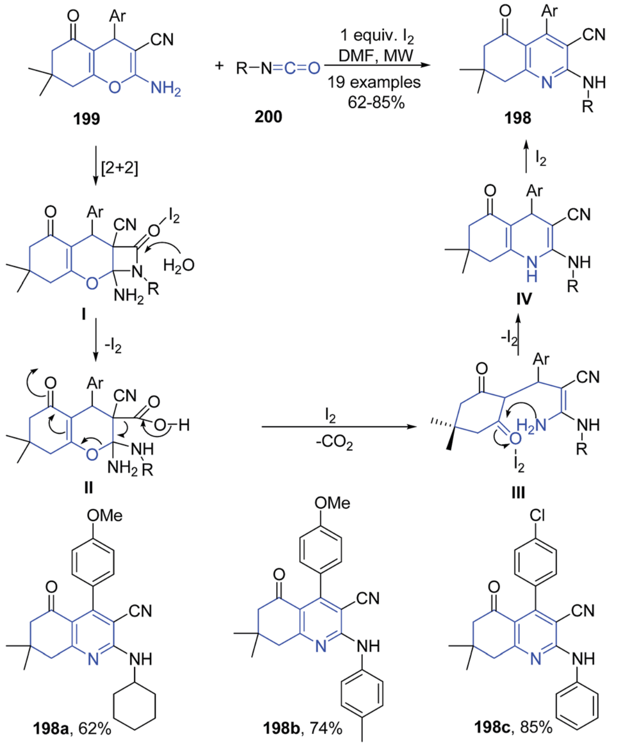
Scheme 67 I$_2$-catalyzed synthesis of furanoquinolines **189**; some representative examples are shown.



Scheme 69 Molecular iodine catalyzed synthesis of 2-aryl-3-iodoquinolines **193**; some representative examples are shown.



Scheme 70 I_2-catalyzed synthesis of indolo(2,3-*b*)quinolines **195**; some representative examples are shown.



Scheme 71 I_2-catalyzed synthesis of aminoquinoline-3-carbonitriles **198**; some representative examples are shown.

quinolines.[139–141] Tu and coworkers[142] have established a iodine-promoted domino reaction of 2-aminochromene-3-carbonitriles **199** with various isocyanates **200** for synthesis of poly-functionalized N-substituted 2-aminoquinoline-3-carbonitriles **198** with high regioselectivity under microwave heating. The reaction of phenyl isocyanate **200** with 2-aminochromene-3-carbonitrile **199** underwent [2 + 2] cyclization to produce β-lactam intermediate **I**, which then gets hydrolyzed forming a ring-opened intermediate **II**. Next, the intermediate **II** releases CO_2 to give intermediate **III**, which undergoes intramolecular cyclization to afford the 1,4-dihydropyridine **IV**. Finally, the aromarization of **IV** led to formation of **198** (Scheme 71).

Mitamura and Ogawa[143] found that upon photoirradiation of *O*-alkynylaryl isocyanides **202** in the presence of molecular iodine, it undergoes intramolecular cyclization to afford the corresponding 2,4-diiodoquinolines **201** in good yields. This reaction does not took place in the dark, indicating that the reaction requires photoirradiation (Scheme 72).

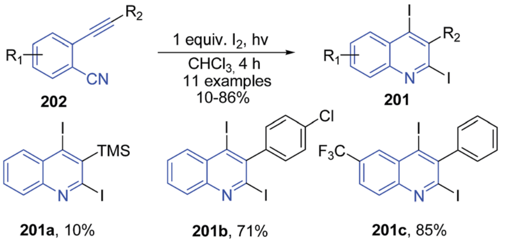
3.4. Ionic liquid mediated quinoline synthesis

Ionic liquid have been considered as a green reaction media with recyclability and this has been used as catalyst as well as reaction media.[55] Our group[144] have developed an expedient and metal-free synthetic protocol for construction of substituted quinolines **203–204** from anilines **1** and phenylacetaldehydes **205** using imidazolium cation-based ionic liquids as the reaction medium. [Bmim]BF_4 activates the aldehyde electrophile by interaction with the carbonyl oxygen. The ionic liquid [Bmim] BF_4 also enhances the nucleophilicity of the amine through interaction of tetrafluoroborate with N–H bond. The resulting imine intermediate **I** undergo self-condensation to generate **II** as a key intermediate. The C-2 benzyl moiety gets cleaved through radical mechanism by release of benzaldehyde, producing 3-substituted quinoline **204** (Scheme 73).

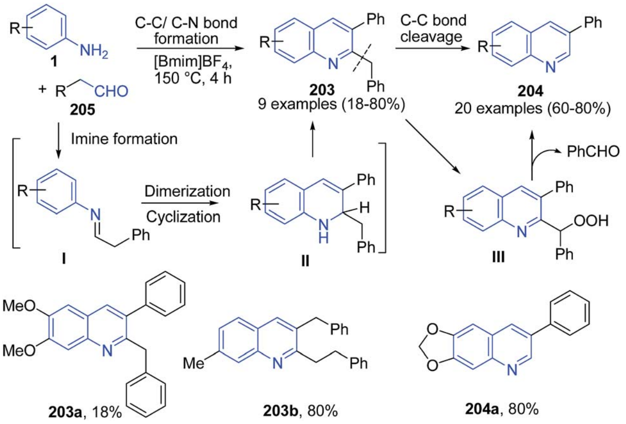
Another ionic liquid mediated synthesis of quinolines is reported, involving a four-component, one-pot reaction of aromatic aldehyde **5**, cyclohexanone **85**, malononitrile **33c**, and amines **1** or **205** in basic ionic liquid [Bmim]OH to produce tetrahydroquinoline-3-carbonitriles **206** (Scheme 74).[145]

A two-phase microwave-assisted cascade reaction between isatins **40** and β-ketoamides **208** in [Bmim]BF_4/toluene led to the formation of pyrrolo[3,4-*c*]quinoline-1,3-diones **207** (Scheme 75).[146] The recyclability of the ionic liquid for 6 cycles was shown. The prepared pyrrolo[3,4-*c*]quinoline-1,3-diones displayed antibacterial activity.

The condensation reaction involving an *O*-aminoaryl ketones **46** with α-methylene ketones **47** in ionic liquid [Hbim][BF_4] as a



Scheme 72 Synthesis of 2,4-diiodoquinolines **201** *via* the photochemical cyclization of *o*-alkynylaryl isocyanides **202** with molecular iodine; some representative examples are shown.

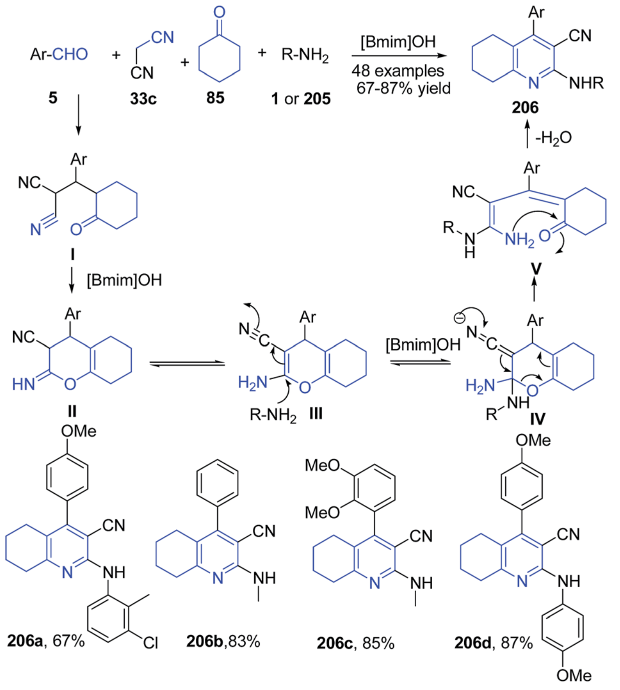


Scheme 73 Synthesis of 2,3-disubstituted **203** and 3-substituted quinolines **204** in ionic liquid; some representative examples are shown.

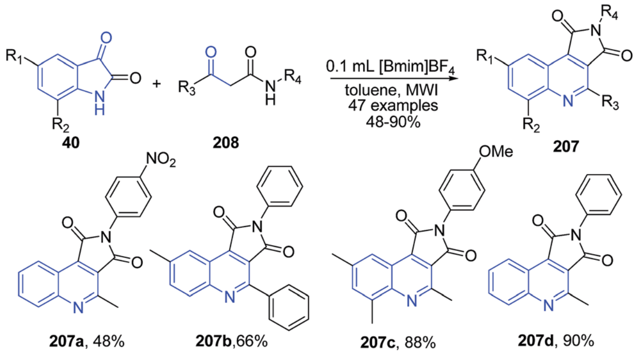
solvent with methanol as co-solvent at room temperature under ultrasound irradiation afforded the corresponding quinolines derivatives **209** in excellent yields, *via* tandem addition/annulation reactions.[147] The reaction was also applicable to cyclic ketones producing tricyclic compounds (Scheme 76).

Kowsari and Mallakmohammadi[148] described synthesis of quinoline-4-carboxylates **210** by condensation of isatins **40** α-methylene ketones **47** in presence of 0.5 equiv. [Bmim]OH ionic liquid and ultrasonication (Scheme 77). The mechanism of this reaction involves the reaction of isatin **40** with a [Bmim]OH that hydrolyses the amide bond to produce the keto-acid **I**. The enamine **II** form on cyclization produces quinoline **III** which finally on dehydration result in the formation of desired quinoline product **210**.

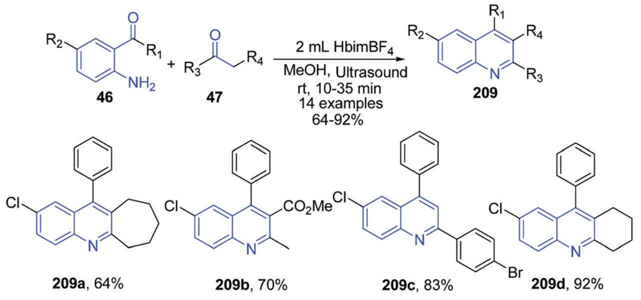
A three-component reaction of aryl aldehyde **5**, (*E*)-3-aminobut-2-enenitrile **212** and 2-hydroxynaphthalene-1,4-dione **35** in ionic liquid produced polysubstituted benzo[*h*]quinolines **211** (Scheme 78). Another three-component reaction involving condensation of aryl aldehyde **5**, (*E*)-3-aminobut-2-enenitrile **212** and dimedone **28e** in ionic liquid produced 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-arylquinoline-3-carbonitriles **213** (Scheme 79).[149] The reaction mechanism involves



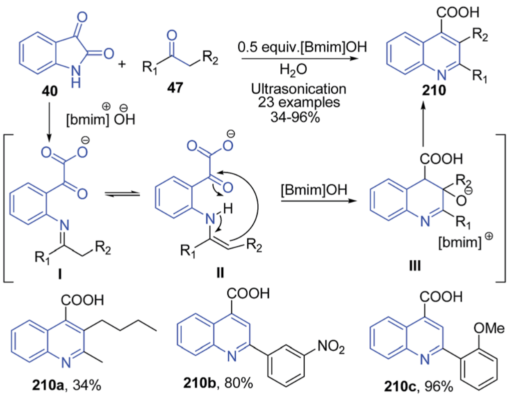
Scheme 74 Synthesis of tetrahydroquinoline-3-carbonitriles **206** in ionic liquid; some representative examples are shown.



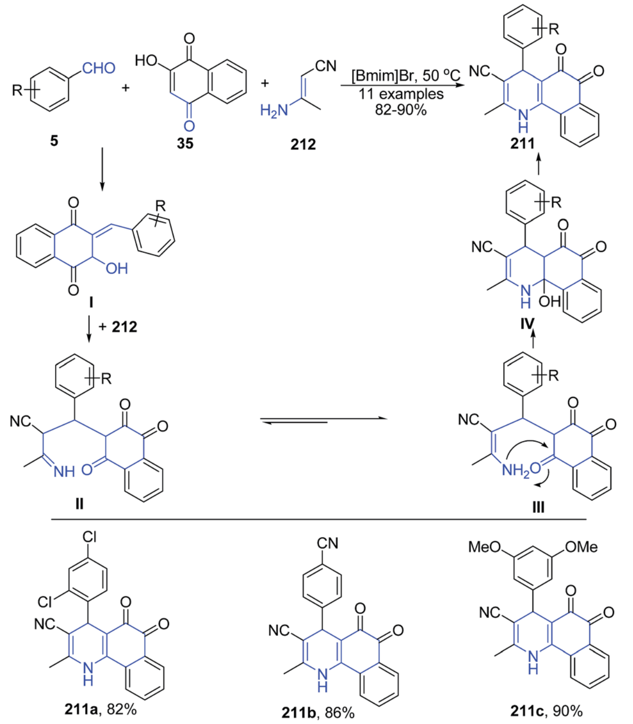
Scheme 75 Synthesis of pyrrolo[3,4-*c*]quinoline-1,3-diones **207** in ionic liquid; some representative examples are shown.



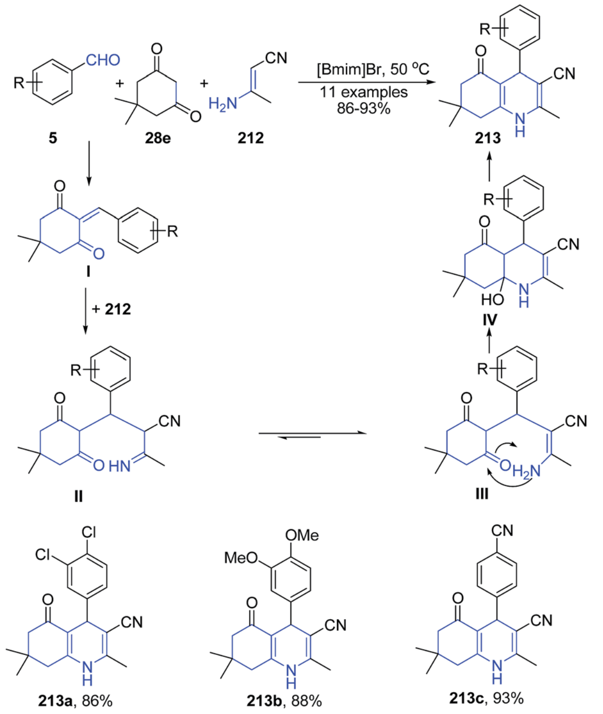
Scheme 76 Synthesis of substituted quinolines **209** in ionic liquid under ultra-sound irradiation; some representative examples are shown.



Scheme 77 Synthesis of quinoline-4-carboxylates **210** in ionic liquid; some representative examples are shown.



Scheme 78 Synthesis of polysubstituted benzo[*h*]quinolines **211** in ionic liquid; some representative examples are shown.



Scheme 79 Synthesis of 2,7,7-trimethyl-5-oxo-4-arylquinoline-3-carbonitriles **213** in ionic liquid; some representative examples are shown.

subsequent Knoevenagel condensation, Michael addition, intra-molecular cyclization, and dehydration reaction.

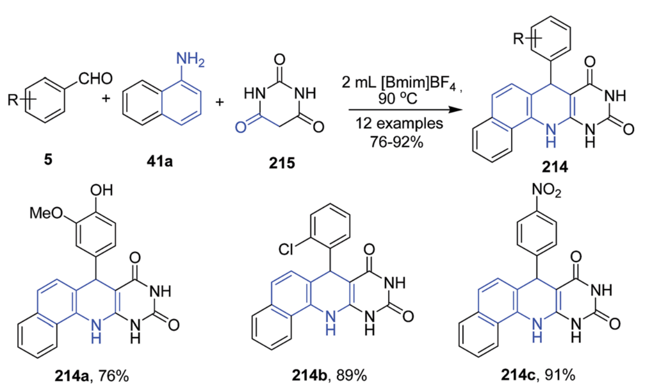
A series of 7-aryl-11,12-dihydrobenzo[*h*]pyrimido-[4,5-*b*]-quinoline-8,10(7*H*,9*H*)-diones **214** were synthesized *via* three-component reaction of aryl aldehydes **5**, 1-naphthylamine **41a** and barbituric acid **215** in ionic liquid (Scheme 80).[150]

3.5. Organocatalysis for quinoline synthesis

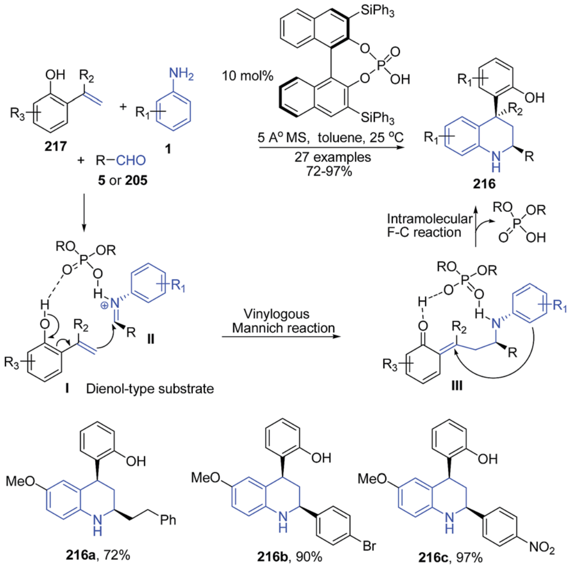
The use of small chiral organic molecules as catalysts, has proven to be a valuable and attractive tool for synthesis of enantiomerically enriched molecules and thus it finds wide applications in drug discovery.[151] Furthermore, organocatalysis finds tremendous utility in asymmetric C–C bond formation reactions.[152,153] The utility of these catalysts in quinoline synthesis has also been well reported. An organocatalytic asymmetric three-component Povarov reaction involving 2-hydroxystyrenes produced structurally diverse *cis*-disubstituted tetrahydroquinolines **216** in high stereoselectivities of up to >99 : 1 dr and 97% ee.[154] The 2-hydroxystyrene **217** is structurally similar to an dienol species, which participate in a vinylogous Mannich reaction with an aldimine **II** generated from an aryl aldehyde **5** or aliphatic aldehyde **205** and aniline **1** under the catalysis of a chiral phosphoric acid, forming a transient intermediate **III,** which principally undergoes an intramolecular Friedel–Crafts reaction (the 1,4-addition of aniline to the enone functionality) to afford enantio-enriched multiply substituted tetrahydroquinolines **216** (Scheme 81).

A series of 4-aza-podophyllotoxin derivatives **218** have been synthesized regioselectively *via* the three-component reaction of aldehydes **5**, aromatic amines **1**, and tetronic acid **28d** catalyzed by L-proline.[155] L-Proline catalyzes the formation of iminium ion **II** in a reversible reaction with tetronic acid **28d.** The higher reactivity of the iminium ion **II** compared with the carbonyl species facilitates the addition of aniline **1,** *via* intermediate **III,** producing intermediate **IV.** The intermediate **IV** on elimination of L-proline produces **V.** The product **218** was then formed by tautomerization of intermediate **V** (Scheme 82).

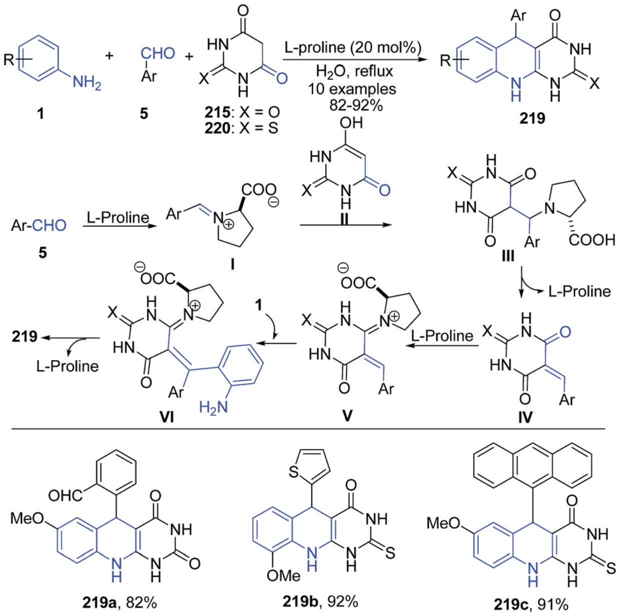
Khalafi-Nezhad *et al.*[156] have described a L-proline mediated synthesis of 5-arylpyrimido-[4,5-*b*]quinoline-diones **219** *via* a three-component reaction between anilines **1**, aldehydes **5** and barbituric acids **215** (or **220**) under aqueous conditions. L-Proline activates the aldehyde to produce intermediate **I.**



Scheme 80 Synthesis of pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*)-diones **214**; some representative examples are shown.



Scheme 81 Chiral phosphoric acid-catalyzed synthesis of *cis*-disubstituted tetrahydroquinolines **216**; some representative examples are shown.



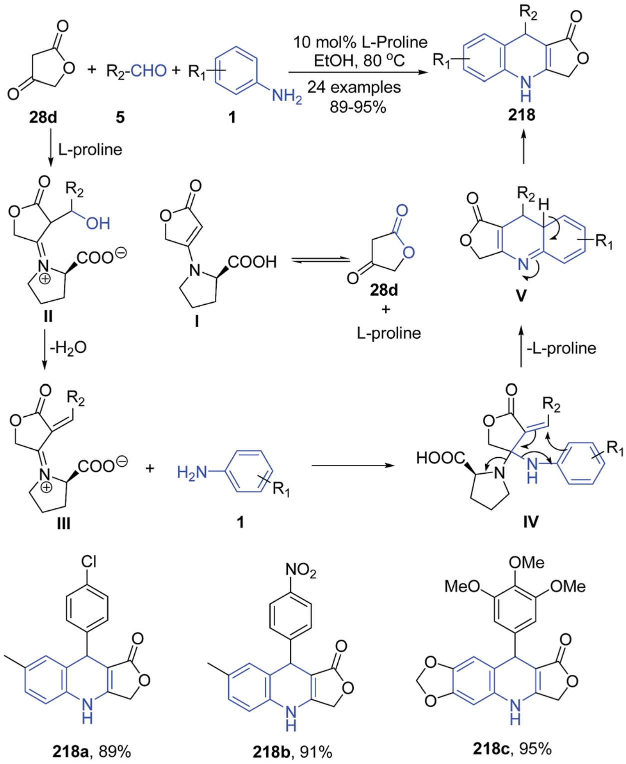
Scheme 83 L-Proline-catalyzed synthesis of aryl-pyrimido[4,5-*b*]quinoline-diones **219**; some representative examples are shown.

Similarly, L-proline assists in enolization of the barbituric acid **215** (or **220**) to produce **II**. Coupling of **I** and **II** produces adduct **III**, which further loses a L-proline molecule to generate *ortho*-quinone methide **IV**. L-Proline further activates this adduct **IV**, followed by coupling of aniline produces **VI**. Intermediate **VI** subsequently undergoes an intramolecular reaction to give the desired product **219** (Scheme 83).

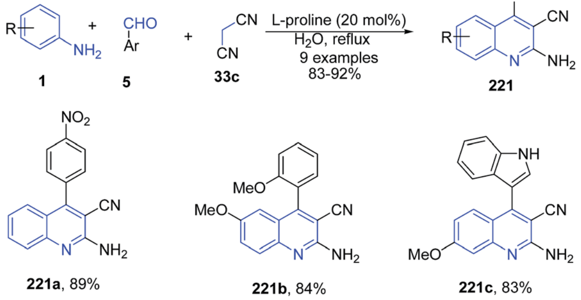
Khalafi-Nezhad *et al.*[156] also described a L-proline mediated synthesis of 2-amino-4-arylquinoline-3-carbonitriles **221** using a similar three-component reaction between anilines **1**, aldehydes **5** and malanonitrile **33c** under aqueous conditions (Scheme 84).

A series of 2*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10(4*H*,11*H*)-diones **222** were synthesized using three component reaction of 2-hydroxy-1,4-naphthoquinone **35**, aldehydes **5**, and aminopyrazoles **223** in the presence of a catalytic amount of L-proline.[157] Reaction proceeds *via* domino Aldol reaction–Michael addition–*N*-cyclization–tautomerism sequence to give fused quinoline product regioselectively (Scheme 85).

A cascade reaction of *ortho*-azido-β-nitro-styrenes **225** with various carbonyl compounds **45** furnished substituted quinolines **224** (Scheme 86).[158] The Michael reaction of ketone **47** to β-nitroolefins **225** followed by coupling of PPh_3 led to formation of iminophosphorane intermediate **II** *via* Staudinger reaction.



Scheme 82 L-Proline-catalyzed synthesis of dihydrofuro[3,4-*b*]quinolin-1(3*H*)-ones **218**; some representative examples are shown.



Scheme 84 L-Proline-catalyzed synthesis of 2-amino-4-arylquinoline-3-carbonitriles **221**; some representative examples are shown.

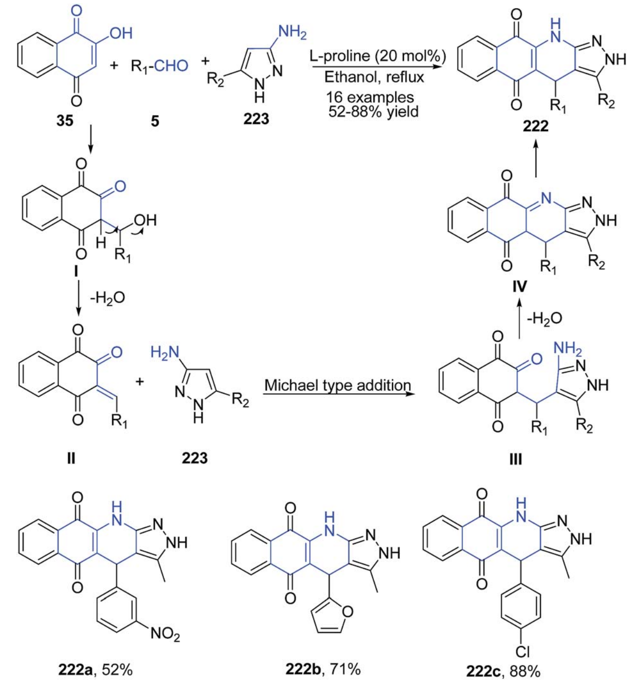
This iminophosphorane **II** undergoes the intramolecular ring-closure *via* the aza-Wittig reaction at room temperature to produce quinoline **III** which on elimination of nitromethane moiety produces **224.** The cyclic ketones **85** produced corresponding tricyclic products **226** *via* intermediate **IV.**

3.6. Catalyst-free quinoline synthesis

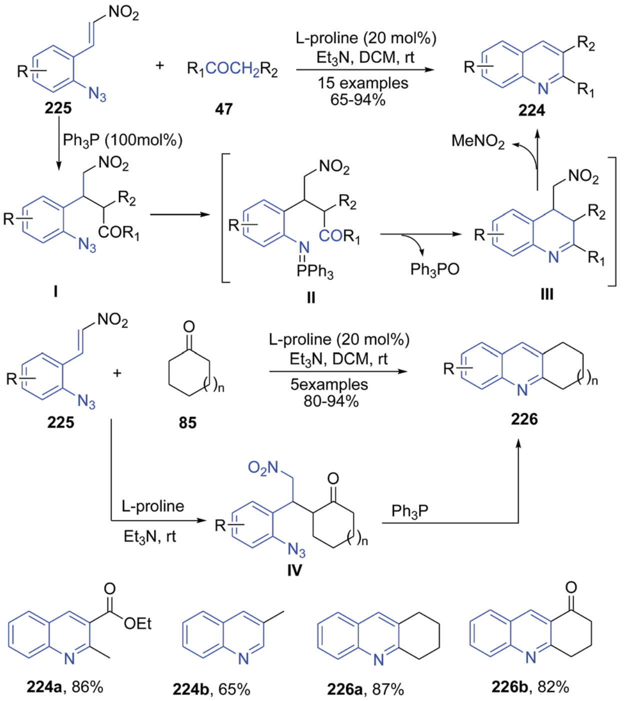
Apart from the use of above discussed simple non-metal catalysts, several reactions proceeds efficiently in suitable solvents without use of any catalyst. Reaction of 2-(aminomethyl)aniline **228** with ketones **47** in presence of oxygen atmosphere produced quinoline products **207.**[159] Reaction involved condensation of aniline **211** with ketone **47** to form imine **I** which gets oxidized to aldehyde **II** by oxygen and high temperature. This was followed by cyclization and dehydration to produce quinolines **227** (Scheme 87).

The condensation and cyclization of two molecules of *ortho*-haloacetophenones **230** with primary amines **1** produced halogen-substituted 2-aryl quinolines **229.**[160] The mechanism involves first the formation of ketimine **I** by dehydration of **230** with amine **1.** This was then followed by the intermolecular nucleophilic attack of **1** by enamine carbon of **II** followed by dehydration to give α,β-unsaturated imine **III.** Next the electrocyclic reaction of **III** leads to formation of the intermediate **IV.** Finally the elimination and subsequent SN_2 reaction of **IV** produces **229** (Scheme 88).

A three-component reaction of aromatic aldehyde **5**, 1*H*-indol-5-amine **235**, and 1,3-dicarbonyl compounds **28c**, **28e**, **28g** produced pyrrolo[3,2-*f*]quinoline **231–233** and pyrrolo[3,2-*a*]acridine **234** derivatives under catalyst-free conditions (Scheme 89).[161]



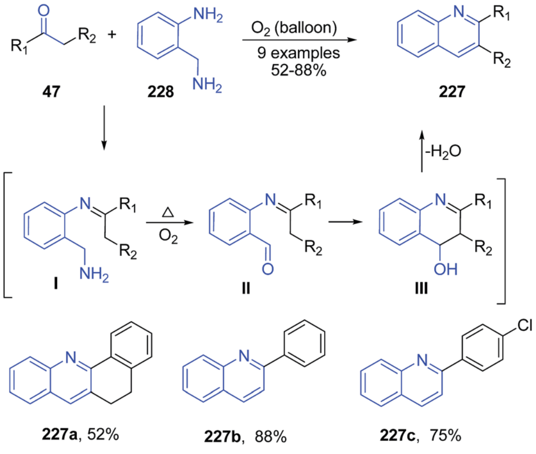
Scheme 85 L-Proline-catalyzed synthesis of benzo[*g*]pyrazolo[3,4-*b*]quinoline diones **222**; some representative examples are shown.



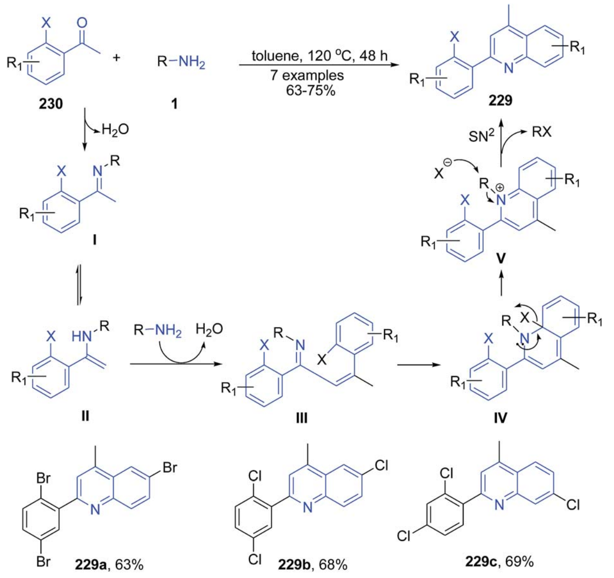
Scheme 86 L-Proline-catalyzed synthesis of 2,3-disubstituted quinolines **224**, **226**; some representative examples are shown.

Fayol and Zhu[162] have reported synthesis of polysubstituted furo[2,3-*c*]quinoline **236**, simply by mixing an *ortho*-alkynyl aniline **237**, an aldehyde **5**, and ammonium chloride in toluene at room temperature, followed by addition of an isocyanoacetamide **238** under heating condition (Scheme 90). The proposed reaction mechanism involves the formation of oxazole **III** as a key intermediate. Next the intramolecular cycloaddition reaction of an oxazole **III** as an aza-diene with the properly predisposed triple bond produce an furo[2,3-*c*]quinolines **236.**

The condensation of *O*-phenylaniline **241** and its homologues with cyclic ketones **85** under hydrothermal conditions



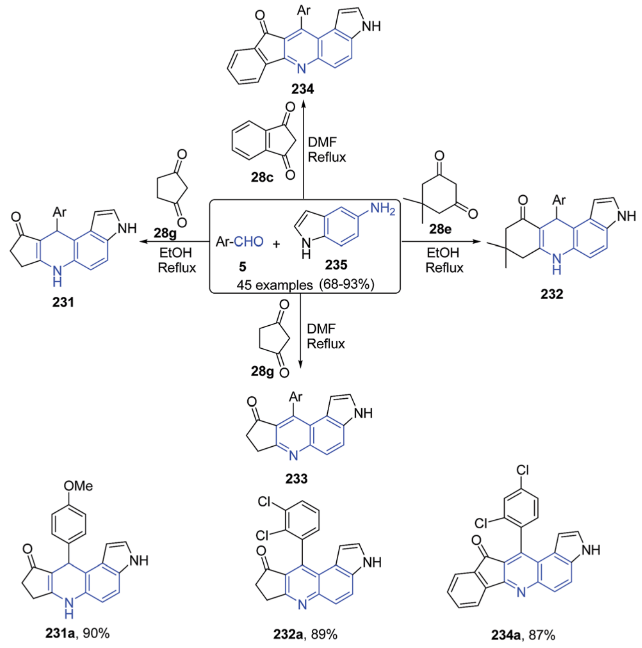
Scheme 87 Catalyst-free synthesis of 2-substituted quinolines **227** by treatment of 2-(aminomethyl)aniline **228** with ketones **47**; some representative examples are shown.



Scheme 88 Catalyst-free synthesis of 2-aryl quinolines **229**; some representative examples are shown.

led to formation of phenanthridines **239–240**.[163] The mechanism proposed for this transformation involves aza-triene-type electrocyclization, followed by irreversible cycloalkane ring-fission as crucial steps (Scheme 91).

These authors[163] further extended this protocol to the reaction of 2-isopropenylanilines HCl **244** to obtain quinoline derivatives **242–243**. The reaction pathway has been depicted in Scheme 92.

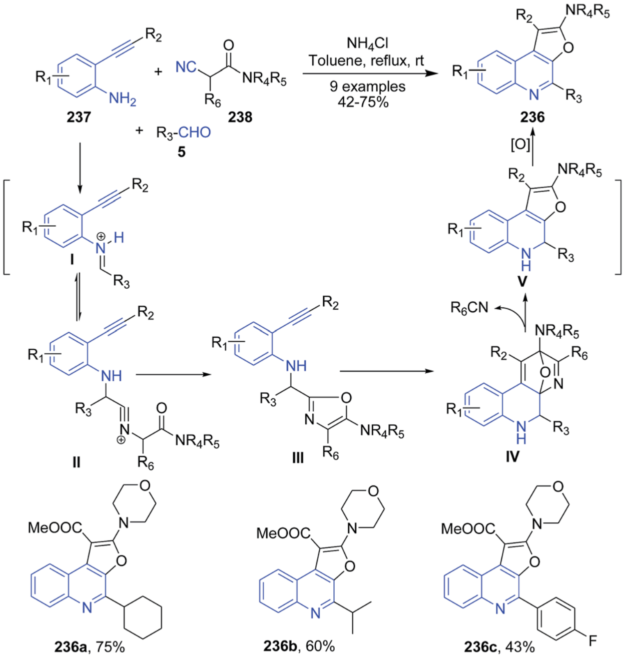


Scheme 89 Catalyst free synthesis of pyrrolo[3,2-*f*]quinoline **231–233** and pyrrolo[3,2-*a*]acridines **234**; some representative examples are shown.

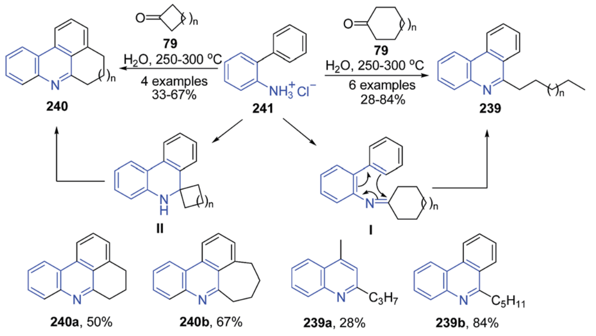
Yuvaraj *et al.*[164] described a microwave-assisted, chemoselective synthesis of oxazolo[5,4-*b*]quinoline – fused spirooxindoles **245** *via* three-component tandem Knoevenagel/Michael addition reaction of 5-amino-3-methylisoxazole **246**, β-diketones **28e** and isatins **40** in good to excellent yields under catalyst- and solvent- free conditions. A possible mechanism for the established 3CC reaction indicated that the β-diketone **28e** initially reacts with isatin **40** to give the Knoevenagel condensation product **I** which undergoes a Michael-type addition with 5-amino-3-methylisoxazole **246** followed by the cyclo-condensation of the intermediate adduct **II** to give corresponding quinolines **245** (Scheme 93).

The four-component domino reaction of 2-hydroxy-1,4-naphthaquinone **35**, aromatic aldehydes **5**, methyl/ethyl acetoacetate **38** and ammonium acetate in ethanol under microwave irradiation at 100 °C afforded tetrahydrobenzo[*g*]-quinoline-5,10-diones **247** regioselectively in good yields. The mechanism involved first the Mannich reaction between 2-hydroxy-1,4-naphthaquinone **35** with aromatic aldehydes **5** to produce intermediate **I** which further on release of ammonia produces **II.** The condensation of **II** with amine intermediate **III** leads to formation of a cyclized intermediate **IV,** which finally on dehydration generated product **247** (Scheme 94).[165]

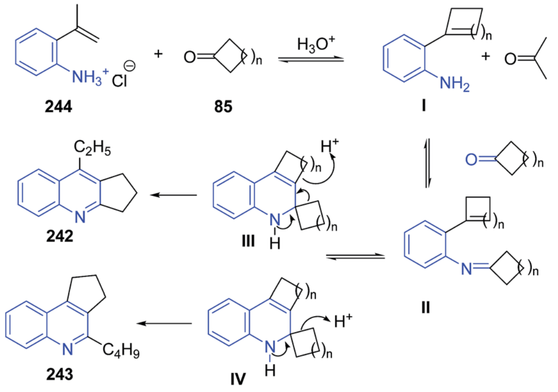
Alizadeh and Rezvanian[166] reported one-pot, catalyst-free, four-component synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-ones **248** from aromatic aldehydes **5**, cyclic 1,3-diones **28e**, diamines **250**, and nitro ketene dithioacetal **249** under catalyst and solvent free conditions. Mechanism involves first Knoevenagel condensation between the aldehyde **5** and the cyclic 1,3-dione **28e**, resulting in the adduct **I.** Then the reaction between intermediate **I** and the ketene aminal **II** (which is derived from the addition of diamine **250** to nitro ketene



Scheme 90 Catalyst-free synthesis of furo[2,3-*c*]quinolines **236**; some representative examples are shown.

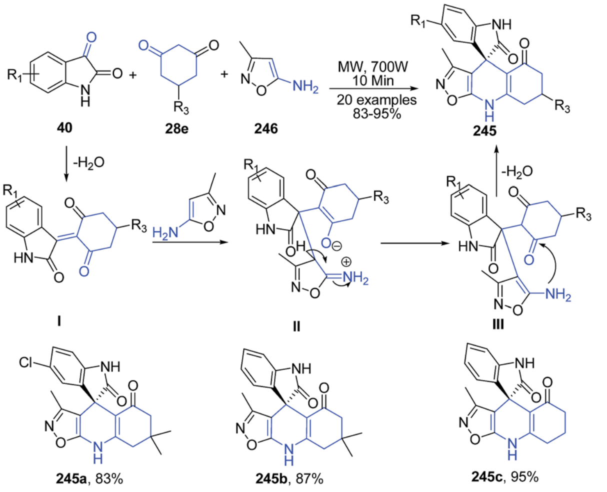


Scheme 91 Catalyst free synthesis of phenanthridines **239–240**; some representative examples are shown.

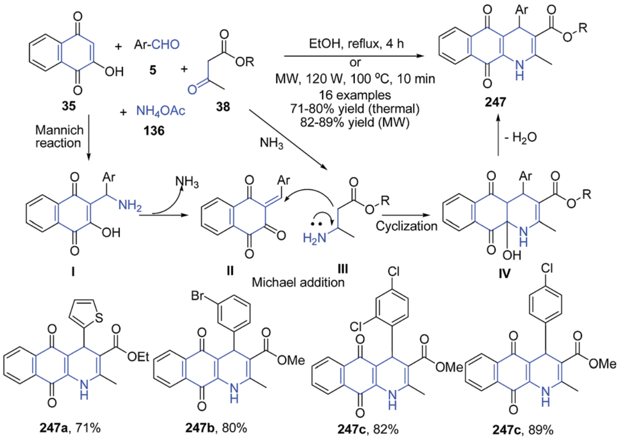


Scheme 92 Catalyst-free synthesis of quinolines **242–243**.

dithioacetal **249**) gives the Michael adduct **III**. The Michael adduct **III** undergoes a cyclocondensation reaction through amino and carbonyl to afford compound **248** (Scheme 95).



Scheme 93 Catalyst free MW assisted synthesis of oxazolo[5,4-*b*]quinoline-fused spirooxindoles **245**; some representative examples are shown.



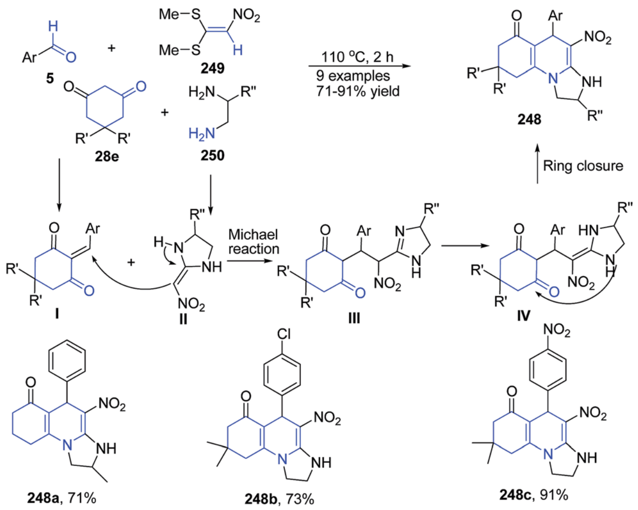
Scheme 94 Catalyst free synthesis of tetrahydrobenzo[*g*]quinolines **247**; some representative examples are shown.

Chidurala *et al.*[167] reported one-pot multicomponent atom-efficient, catalyst-free reaction between resorcinol **252**, aromatic aldehyde **5**, acetoacetanilide **253** and ammonium acetate **136** to produce substituted 1,4-dihydroquinolines **251** (Scheme 96).

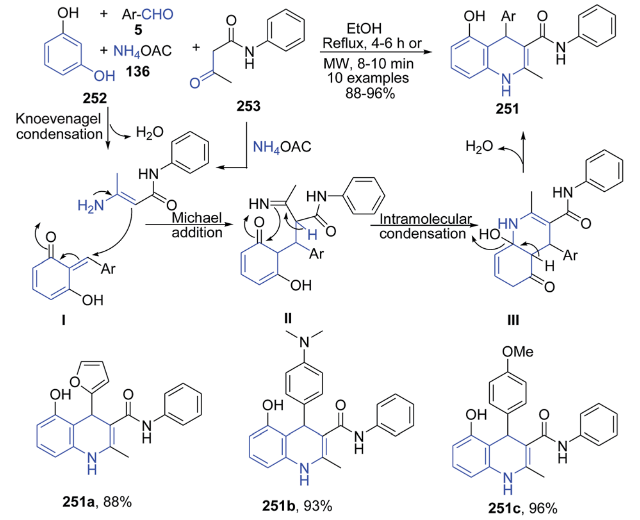
Fındık *et al.*[168] reported one-pot four-component condensation of dimedon **28e**, α-ionone **255**, ammonium acetate **136** and benzaldehyde **5** under reflux condition to produce 7,8-dihydroquinolin-5-(1*H*,4*H*,6*H*)-ones **254** (Scheme 97).

3.7. Miscellaneous protocols

Ghorbani-Vaghei and Malaekehpoor[169] reported the use of *N*-bromosuccinimide as a catalyst for synthesis of polycyclic indolo[2,3-*b*]quinolines **256** from aryl amines **1** with indole-3-carbaldehyde **257** at room temperature. Initially, *N*-bromosuccinimide catalyzed the formation of an imine **I** and then a 3-bromo-indolinium cation as intermediate **II**. After nucleophilic attack by a second mole of aniline, intramolecular cyclization and oxidation lead to indoloquinolines **256**. Reaction is shown in Scheme 98.



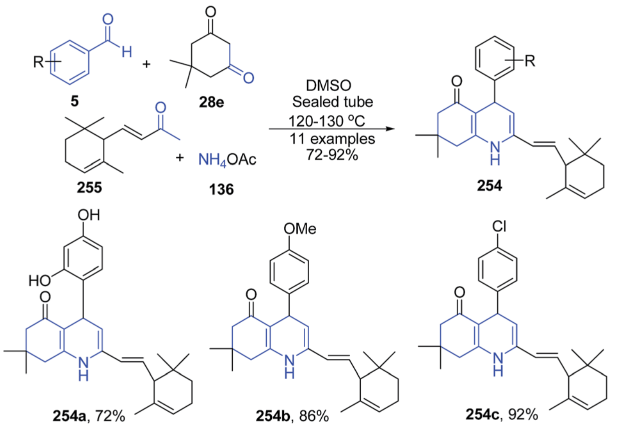
Scheme 95 Catalyst-free synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-ones **248**; some representative examples are shown.



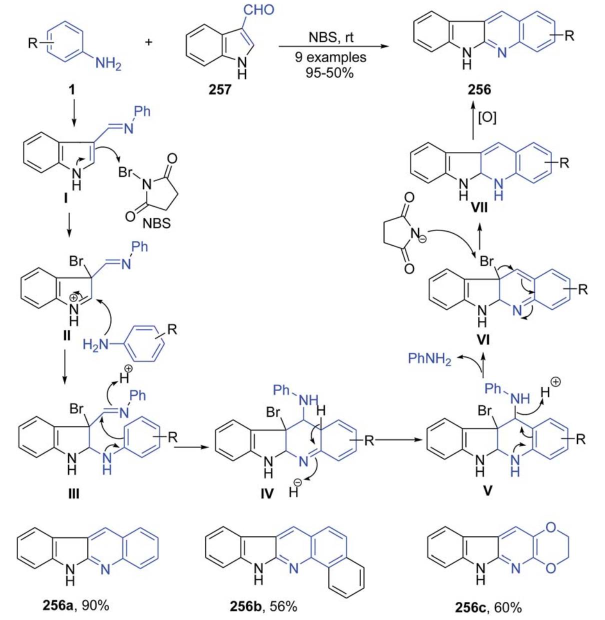
Scheme 96 Catalyst-free synthesis of substituted 1,4-dihydroquinolines **251**; some representative examples are shown.

Plaskon *et al.*[170] described synthesis of 7*H*-chromeno[3,2-*c*]quinolin-7-ones **258** using TMSCl-mediated recyclization of 3-formylchromone **259** with various anilines **1** (Scheme 99).

Khong and Kwon[171] reported phosphine-catalyzed efficient one-pot procedure for preparation of 3-substituted and 3,4-disubstituted quinolines **260** from stable starting materials (activated acetylenes **262** and *O*-tosylamidobenzaldehydes/*O*-tosylamidophenones **261**, respectively) under mild conditions. Mechanism involves a general base catalysis. Coupling of **261** and **262** in presence of PPh_3 produces anion intermediate **IV**. Nucleophilic addition of the free phosphine to the activated alkyne **262** generated phosphonium allenolate **I,** which acts as a base to activate the pro-nucleophile **IV** through deprotonation, resulting in a subsequent general base-catalyzed Michael/aldol reaction to produce **V** (Scheme 100). Intermediate **V** on aromatozation produces **260.**

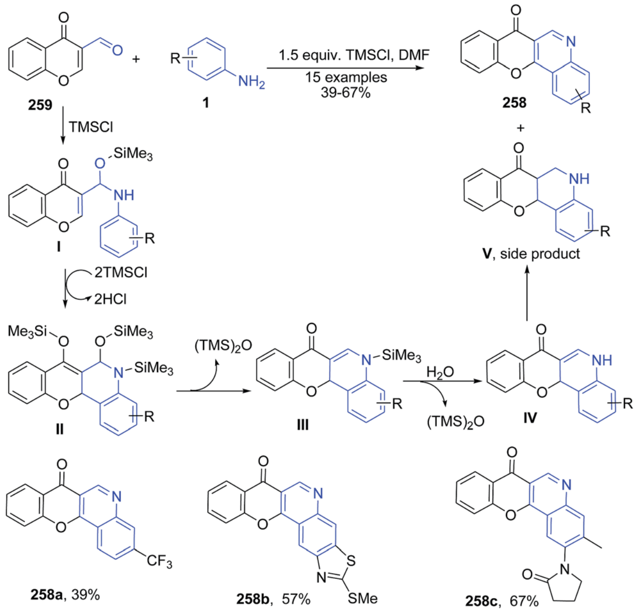


Scheme 97 Catalyst free synthesis of substituted 7,8-dihydroquinolin-5-(1*H*,4*H*,6*H*)-ones **254**; some representative examples are shown.

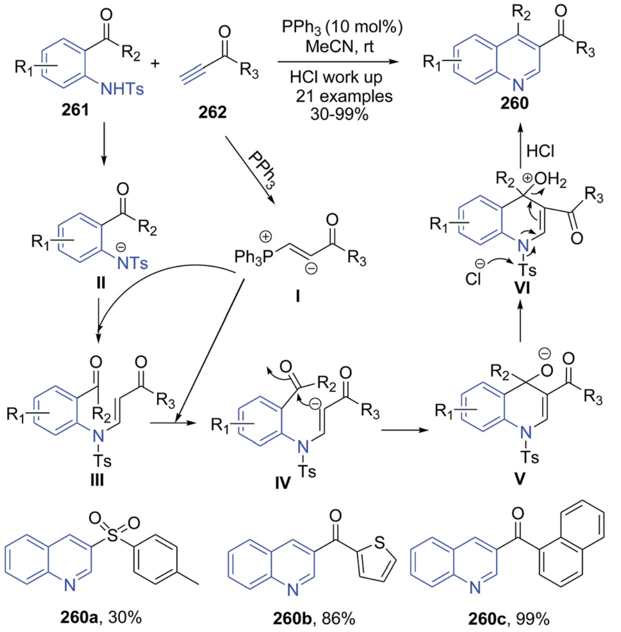


Scheme 98 NBS catalyzed synthesis of polycyclic indolo[2,3-*b*]quinolines **256**; some representative examples are shown.

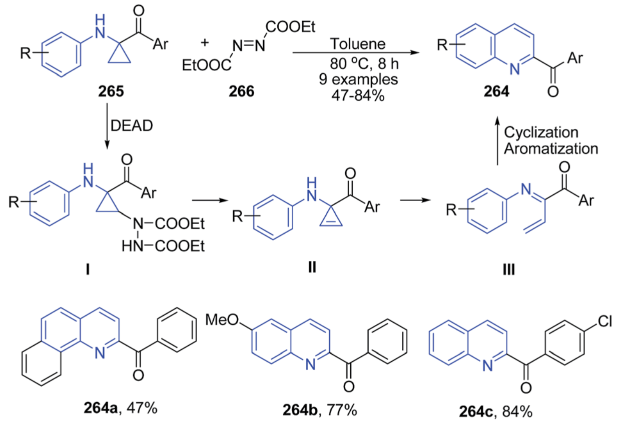
An efficient and facile one-step synthesis of pyrrolo[3,4-*c*]quinolinedione derivatives **263** has been developed using ethylenediamine diacetate (EDDA)-catalyzed cascade reactions of isatins **40** and β-ketoamides **208.**[172] The carbonyl group of isatin **40** gets protonated by EDDA, which facilitates a nucleophilic attack of the enol form of β-ketoamide **208** followed by dehydration and proton transfer to give **I.** Intermediate **I** then undergoes intramolecular cyclization by N1 nucleophilic attack



Scheme 99 TMSCl-mediated synthesis of quinolines **258** from 3-formyl chromones **259**; some representative examples are shown.



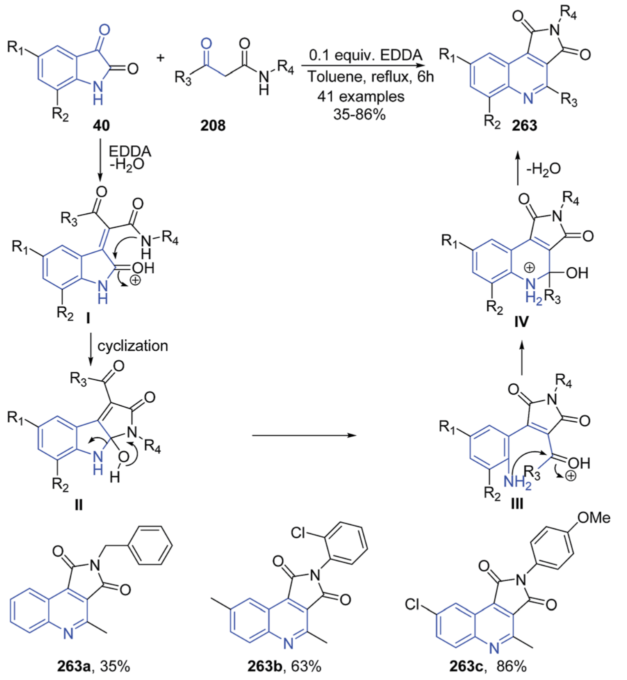
Scheme 100 Phosphine-catalyzed synthesis of dihydroquinolines **260**; some representative examples are shown.



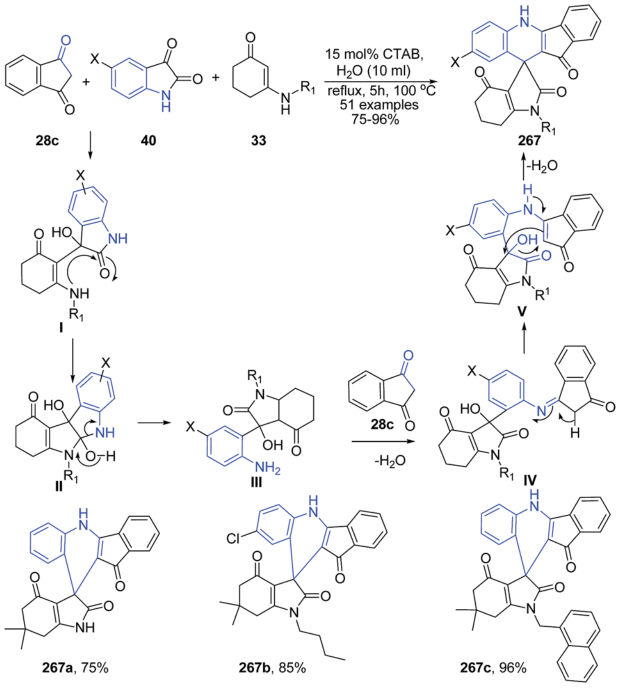
Scheme 102 Catalyst free synthesis of 2-benzoyl quinolines **264** from 1,1-cyclopropane aminoketones **265**; some representative examples are shown.

of the β-ketoamide group followed by proton transfer to form intermediate **II**. Ring opening of intermediate **II** followed by proton transfer gives the free aromatic amine **III**. Subsequently, the NH$_2$ group of **III** attacks a carbonyl group by intramolecular cyclization to form intermediate **IV**, which on elimination of water and deprotonation results in formation of **263** (Scheme 101).

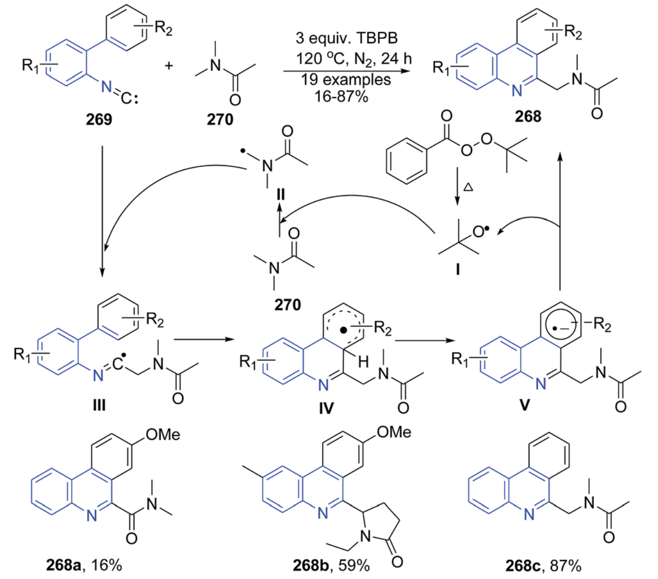
1,1-Cyclopropane aminoketones **265** on reaction with diethyl azodicarboxylate **266** (DEAD, 2.0 equiv.) in toluene at 80 °C for 8 h produced 2-benzoyl quinolines **264** *via* oxidation, ring-opening and cyclization.[173] The reaction is proposed to proceed *via* a cascade procedure. 1,1-Cyclopropane aminoketone **265** is first oxidized with DEAD to give cyclopropene intermediate **II**. Then, ring-opening of **II** gives *N*-aza-diene intermediate **III**, which undergoes an intramolecular [4 + 2]



Scheme 101 Ethylenediamine diacetate-catalyzed synthesis of pyrrolo[3,4-c]quinolinediones **263**; some representative examples are shown.



Scheme 103 Cetyltrimethyl ammonium bromide (CTAB)-catalyzed synthesis of spiro[indolo-3,100-indeno[1,2-*b*]quinolin]-2,4,11′-triones **267**; some representative examples are shown.



Scheme 104 Synthesis of 6-amidophenanthridines **268**; some representative examples are shown.

reaction, followed by dehydrogenation to form **264** (Scheme 102).

The synthesis of highly substituted spiro[indolo-3,10′-indeno[1,2-*b*]quinolin]-2,4,11′-triones **267** has been developed under CTAB/H_2O system to provide spiro-products with excellent yields.[174] At first, the nucleophilic addition reaction occurs between the enaminone **33** with the more electrophilic carbonyl centre of isatin **40** in ecofriendly water medium to give an imine species that tautomerizes to yield **I** (Scheme 103). This intermediate **I** undergoes intramolecular cyclization to form the intermediate **II**, which is immediately converted to a more reactive and unstable intermediate **III** *via* ring-opening of indoline-2,3-dione. After that, due to the high reactivity, intermediate **III** instantly undergoes further nucleophilic addition with the other molecule of indane-1,3-dione **28c** to produce another imine intermediate **IV**, which tautomerizes to yield **V**. Finally, the intramolecular cyclisation of **V** results in the ultimate spiro compound **267**.

Fang *et al.*[175] reported metal-free cyclization reaction of 2-isocyanobiphenyls **269** with amides **270** by using *tert*-butyl peroxybenzoate (TBPB) as oxidant, which provided an access to 6-amidophenanthridine **268.** The reactions proceeds through a sequence of functionalization of the C(sp3)–H bond adjacent to the nitrogen atom and intramolecular radical aromatic cyclization with good yields (Scheme 104).

4. Summary and future prospects

As illustrated through the comprehensive compilation of role of metal-free domino one-pot reactions for quinoline synthesis, it is clear that these protocols has numerous advantages such as high yields, shorter reaction times, environmentally benign milder reactions and safe operations.

Many metal-free domino one-pot protocols have been developed by using inorganic/organic acids, bases, organocatalysts, ionic liquids or molecular iodine. Use of these non-metal reagents certainly makes these protocols an environmentally friendly. Thus, these reagents and solvents have an indispensable role in the development of many new domino one-pot protocols for several other heterocycles. An appropriate use of solvent or reagents as catalysts in such protocols avoids the use of metal-catalyst and allows development of new metal-free methodologies for the efficient synthesis of quinolines. With the great importance of quinoline scaffold in drug discovery, these protocols will have great impact in rapid development of molecular libraries and structure–activity relationship generation.

In summary, metal-free domino one-pot strategies toward quinoline synthesis encompass the vast majority of green chemistry criteria and represent a solid, efficient, experimentally simple, and somehow elegant alternative to other methods. Based on the progress summarized in this review, we feel certain that combined strategy of domino one-pot protocols and metal-free capability of the reaction will find broad applications and will continue to attract much attention in organic synthesis applications.

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