

REVIEW

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Metal-free domino one-pot protocols for quinoline synthesis

Jaideep B. Bharate,^{ab} Ram A. Vishwakarma^{*ab} and Sandip B. Bharate^{*ab}

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

^aMedicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India. E-mail: sbharate@iim.ac.in; ram@iim.ac.in; Fax: +91-191-2586333; Tel: +91-191-2585006

^bAcademy of Scientific & Innovative Research (AcSIR), CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180001, India



Jaideep B. Bharate was born in 1985 in Beed district, Maharashtra, India. He obtained his B.Sc. degree from Dr B. R. Ambedkar Marathwada University Aurangabad in June 2007, and M.Sc. degree in Organic Chemistry from the University of Pune in 2009. Currently he is pursuing Ph.D. in Chemical Sciences, at Academy of Scientific and Innovative Research, CSIR-Indian Institute of Integrative Medicine, Jammu under the supervision of Dr Ram A. Vishwakarma. His current research interests are in the field of development of new tandem one-pot or multicomponent approaches for synthesis of medicinally important scaffolds and development of new metal catalyzed C-H functionalization reactions.



*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 B₁₂) 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, IGF1R), 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-naphthalene 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} anti-cancer,^{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



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 innovative awards in the area of new drug discovery.

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 isocryptolepine and neo-cryptolepine 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.

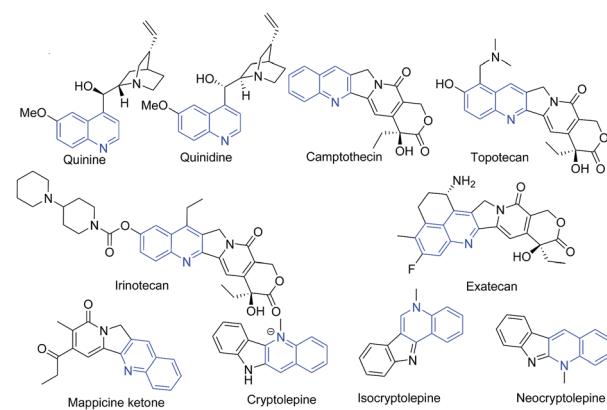


Fig. 1 Structures of quinoline ring containing natural products and their analogs.

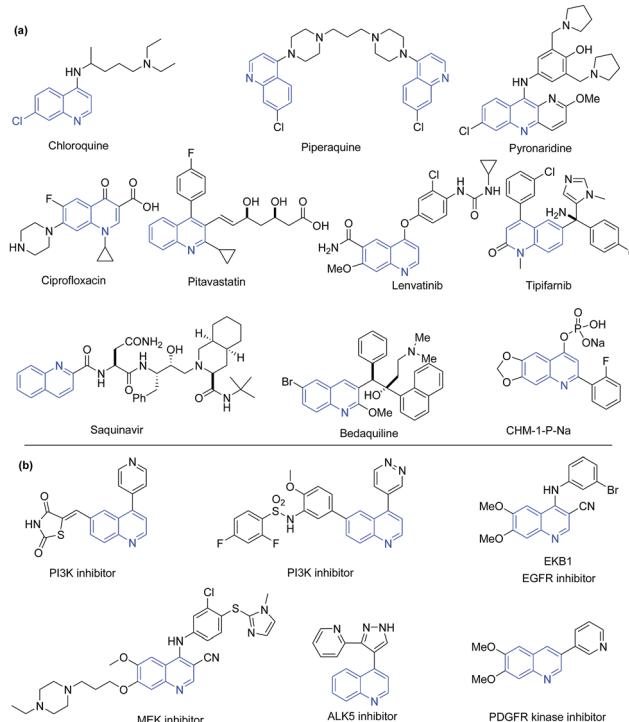


Fig. 2 Chemical structures of (a) quinoline containing drugs and clinical candidates; and (b) quinoline-based kinase inhibitors.

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)⁴³ 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)⁴⁵ reviewed recent developments in the chemistry of pyrazolo[4,3-*c*]quinolines. Barluenga *et al.* (2009)⁴⁶ 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 ethoxy-methylene 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) Nientowksi quinoline synthesis (from anthranilic acid and carbonyl compounds); (m) Meth–Cohn synthesis (from acylanilides and DMF/POCl₃); 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 pyridines⁶¹ 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

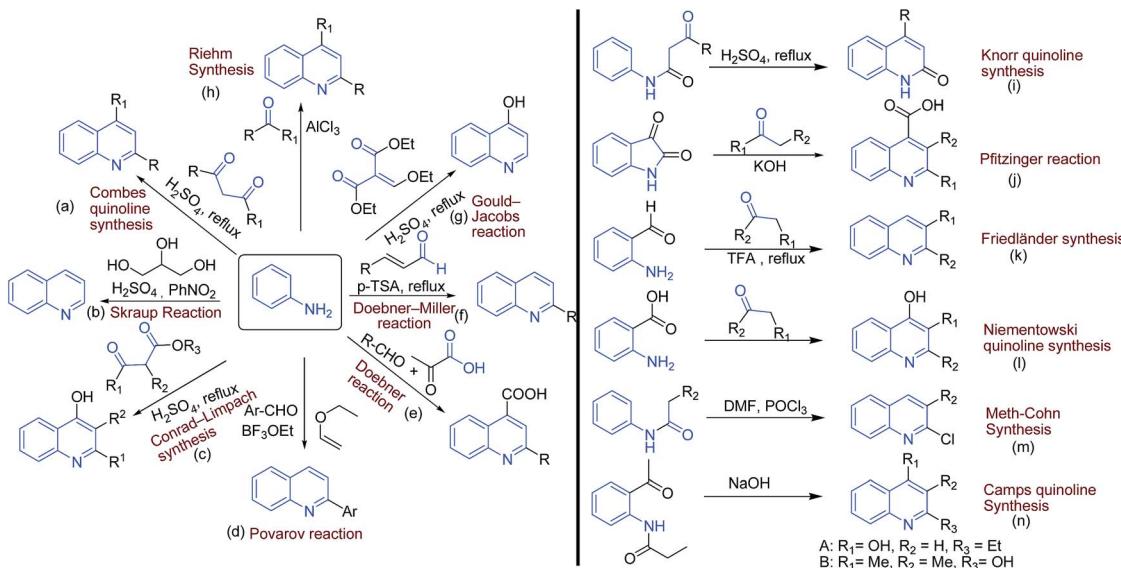


Fig. 3 Classical methods ("Name Reactions") for quinoline synthesis.

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.

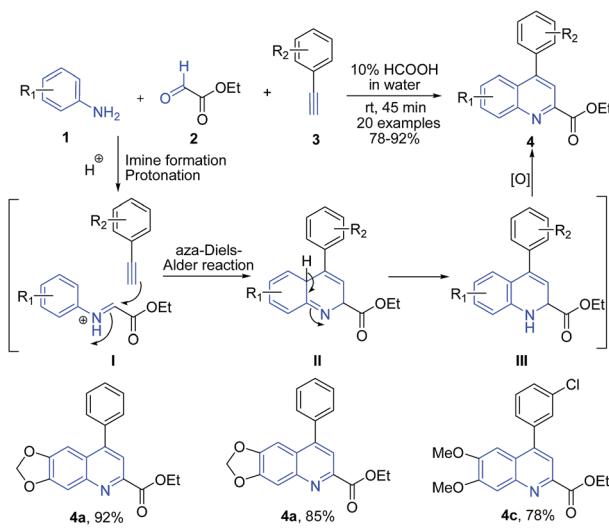
3.1. Acid catalyzed protocols

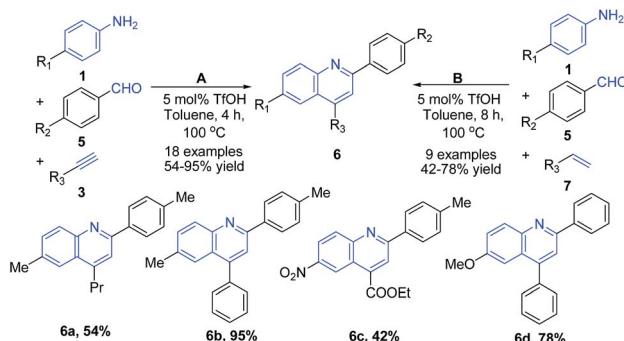
Acids have been widely used as simple and ecofriendly catalysts and promoters for various organic reactions. Acid catalysts which are routinely used in various organic transformations include trifluoroacetic acid (TFA), formic acid, acetic acid, triflic acid, and pTSA. Acetic acid and formic acid are 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 group⁶³ 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 $\text{BF}_3 \cdot \text{OEt}_2$, 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.

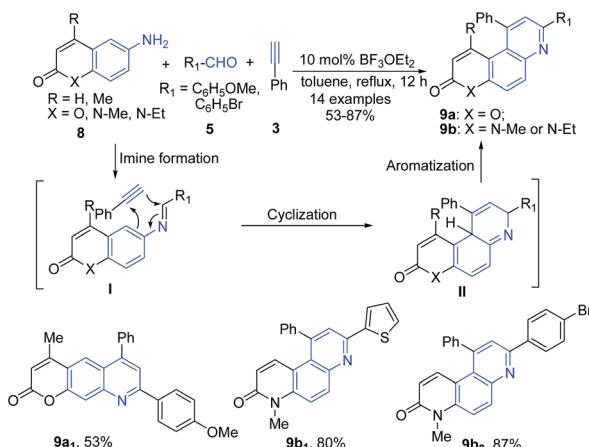


Scheme 2 TfOH-catalyzed synthesis of 2,4-disubstituted quinolines 6; some representative examples are shown.

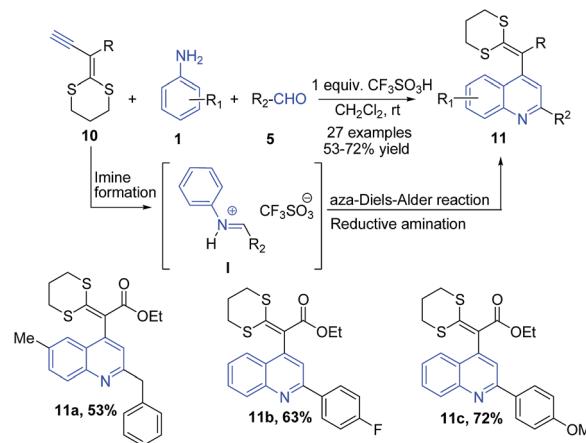
Ketene-dithioacetals have been used as important building blocks for construction of heterocycles.⁶⁶ Ethynyl-*S,S*-acetals **10** are highly reactive electron-rich dienophiles which undergo regiospecific aza-Diels–Alder (Povarov) reaction with arylimines to produce quinoline skeleton. A triflic acid 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**



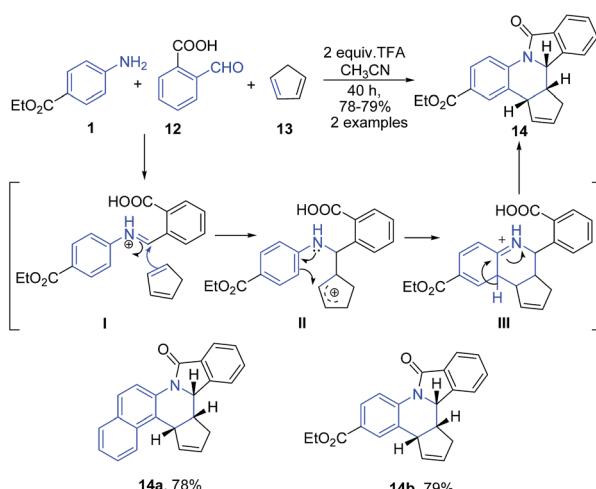
Scheme 3 $\text{BF}_3\text{-OEt}_2$ -catalyzed synthesis of pyrano[3,2-*f*]quinolines **9a** and phenanthrolines **9b**; some representative examples are shown.



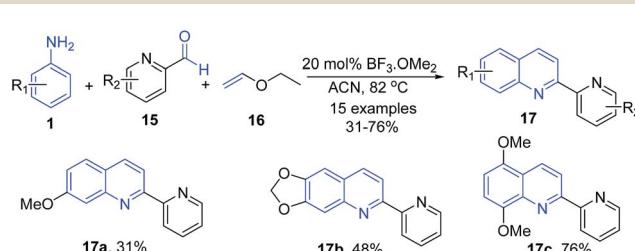
Scheme 4 Triflic acid-catalyzed synthesis of 2,4-disubstituted quinolines **11** via three-component aza Diels–Alder reaction; some representative examples are shown.

in presence of boron trifluoride methyl etherate producing 2-(2-pyridyl)quinolines **17** (Scheme 6).

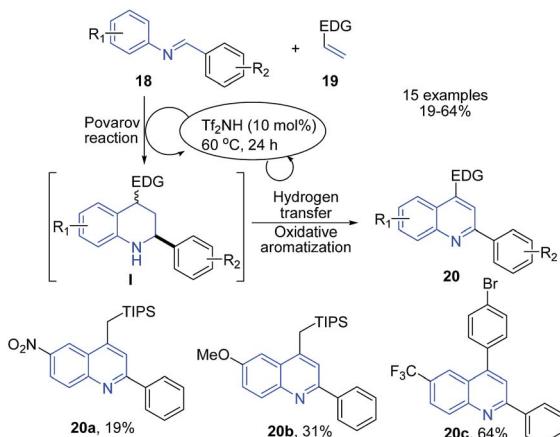
Shindoh *et al.*⁷⁰ reported triflic imide and triflic acid catalyzed Povarov-Hydrogen-Transfer cascade reaction to produce quinolines **20**. The reaction between electron-rich olefins **19** and excess amount of imines **18** in the presence of triflic imide



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



Scheme 6 $\text{BF}_3\text{-OMe}_2$ -catalyzed synthesis 2-(2-pyridyl)quinolines **17**; some representative examples are shown.

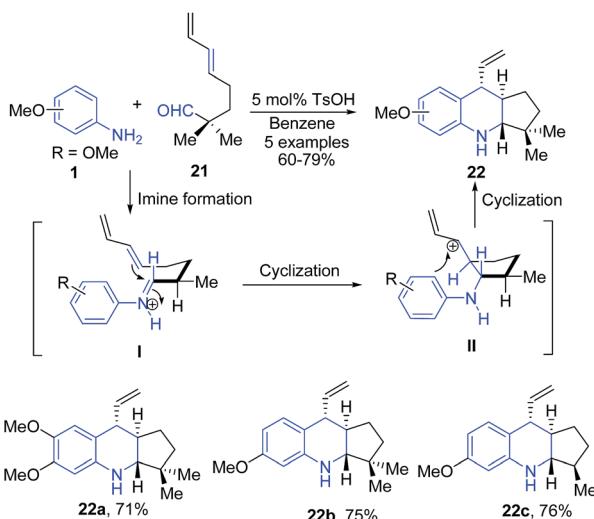


Scheme 7 Triflic imide-catalyzed synthesis of imidazopyrrolo-quinolines 20; some representative examples are shown.

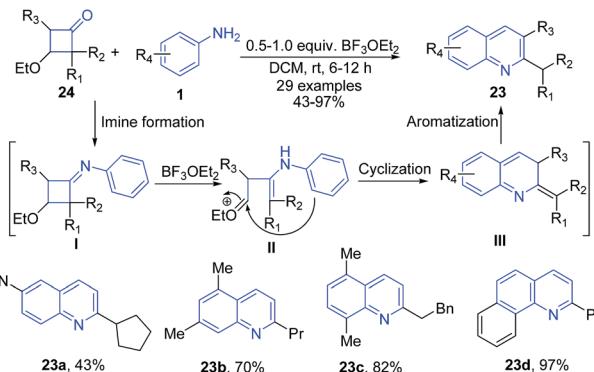
in DCM at 60 °C afforded substituted quinolines 20 in one-pot (Scheme 7).

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



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



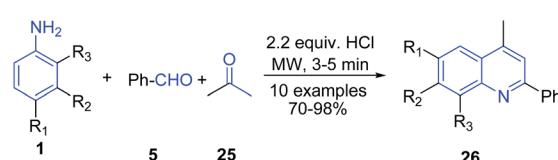
Scheme 9 BF_3OEt_2 -catalyzed synthesis of alkyl quinolines 23 from 3-ethoxycyclobutanones 24 and aromatic amines 1; some representative examples are shown.

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).

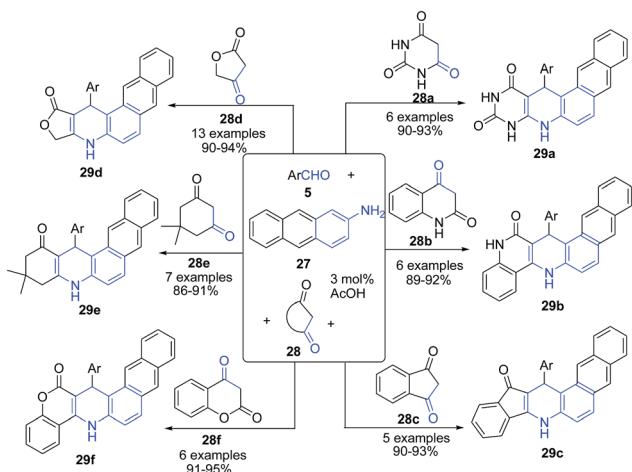
Apart from the Povarov reaction, arylamines are also one of the key precursors in several other protocols. There are several reports on the three-component reaction of arylamines, aryl aldehydes and active methylene compounds leading to formation of a quinoline skeleton. Mirza and Samiei⁷³ reported Doebner 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 group⁷⁴ established a sequential three-component reaction between 2-aminoanthracene 27, aromatic aldehyde 5 and cyclic 1,3-dicarbonyl compounds 28 (such as tetrone acid 28d, 5,5-dimethyl,3-cyclohexanone 28e, 1,3-indanone 28c, 3H-chromene-2,4-dione 28f, quinoline-2,4(1H, 3H)-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 Das⁷⁵ 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.



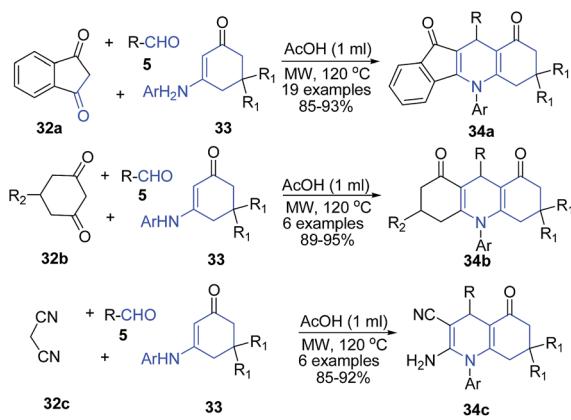
Scheme 10 HCl-catalyzed synthesis of 4-methyl quinolines 26.



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

Tu and coworkers⁷⁶ employed the use of enaminones 33 as the amine precursor and 1,3-indanodione 32a as an active methylene precursor for preparation of quinoline skeleton. The three component one-pot protocol involving treatment of aldehydes 5, 1,3-indanodione 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

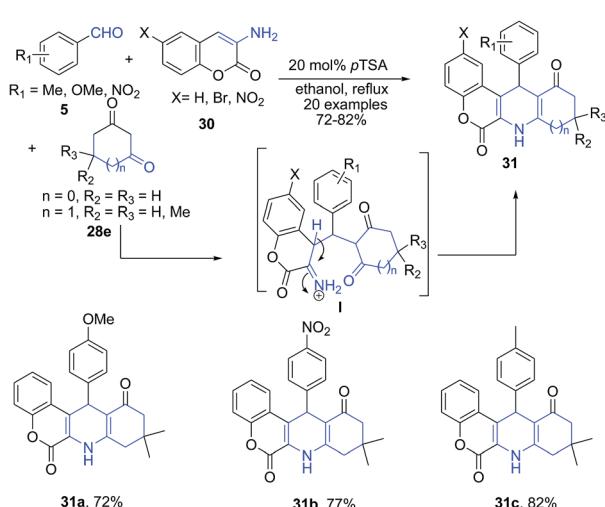


Scheme 13 AcOH-catalyzed synthesis of imidazopyrrolo-quinolines 34a-c.

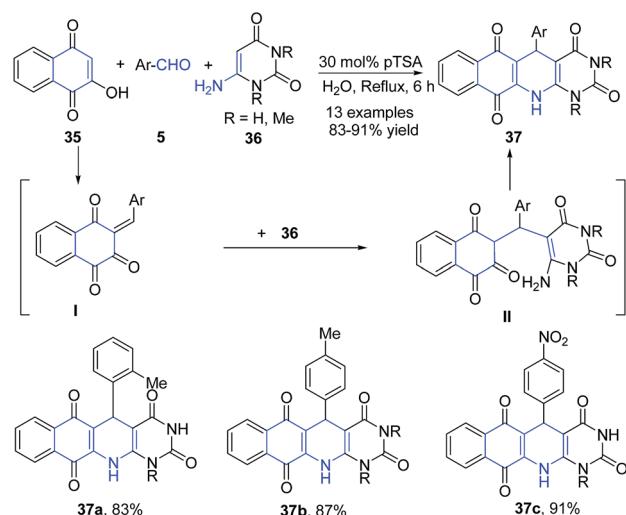
aromatic aldehydes 5 in presence of *p*TSA in aqueous media produced pyrimido[4,5-*b*]quinoline-tetraones 37. This reaction has been proposed to proceed by first condensation of 2-hydroxynaphthalene-1,4-dione 35 and aldehyde 5 followed by coupling with 6-amino-uracil 36 and then cyclization of II to 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

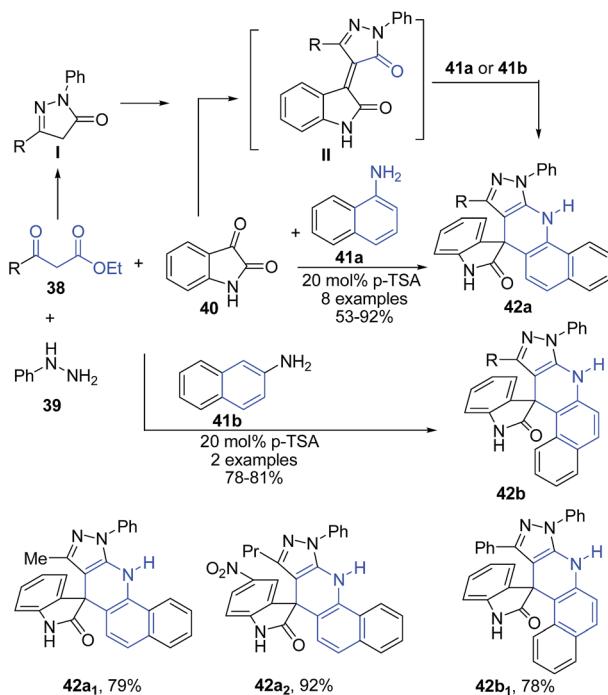
Yu *et al.*⁷⁹ reported acetic acid catalyzed three-component reaction between aryl aldehyde 5, *β*-naphthylamine 41b, and 2*H*-thiopyran-3,5(4*H*,6*H*)-dione 44 in the presence of acetic acid leading to formation of benzo[*f*]thiopyrano[3,4-*b*]quinolin-11(8*H*)-ones 43 (Scheme 16).



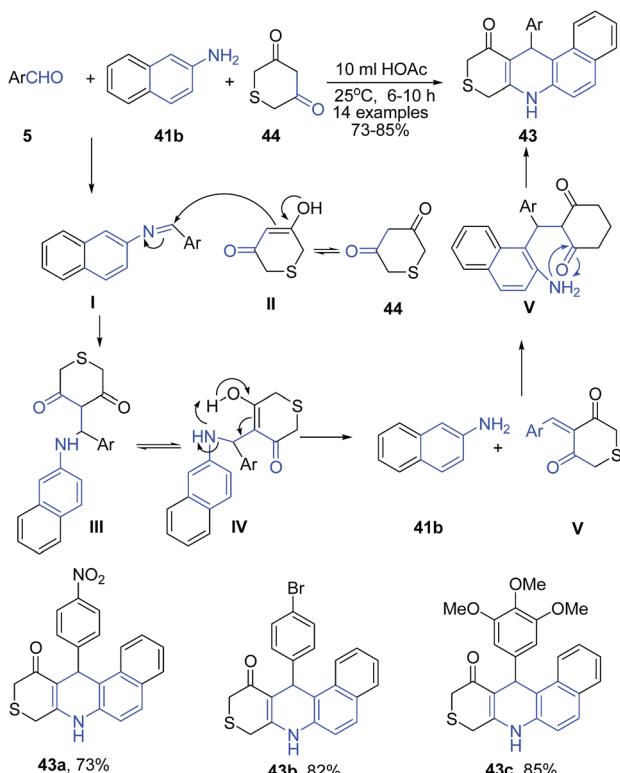
Scheme 12 *p*TSA-catalyzed synthesis of chromeno[3,4-*b*]quinolines 31; some representative examples are shown.



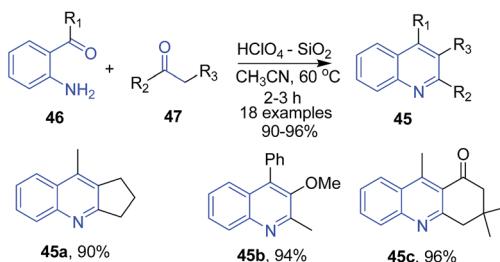
Scheme 14 *p*TSA-catalyzed synthesis of pyrimido[4,5-*b*]quinoline-tetraones 37; some representative examples are shown.



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.



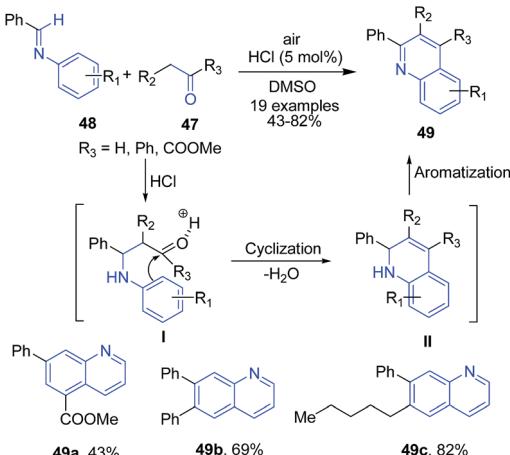
Scheme 17 Silica supported perchloric acid-catalyzed synthesis of poly-substituted quinolines 45; some representative examples are shown.

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).

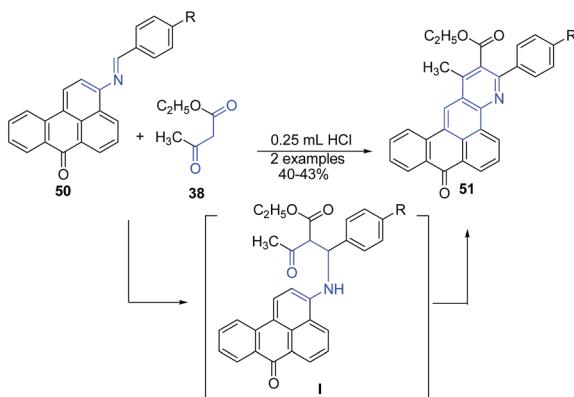
The quinoline synthesis through condensation of benzylideneanilines with active methylene compounds has been reported by two groups. Tanaka *et al.*⁸¹ reported the condensation of benzylideneanilines 48 with carbonyl compounds (aldehydes or ketones or diketones) 47 in presence of catalytic HCl leading 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 Grabchev⁸² 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



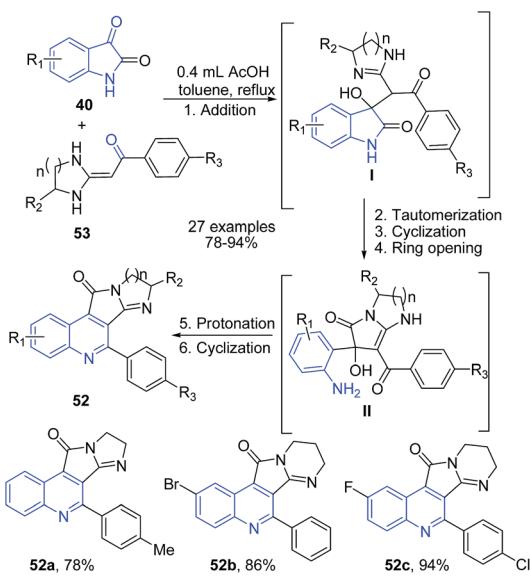
Scheme 18 HCl-catalyzed synthesis of substituted quinolines 49; some representative examples are shown.



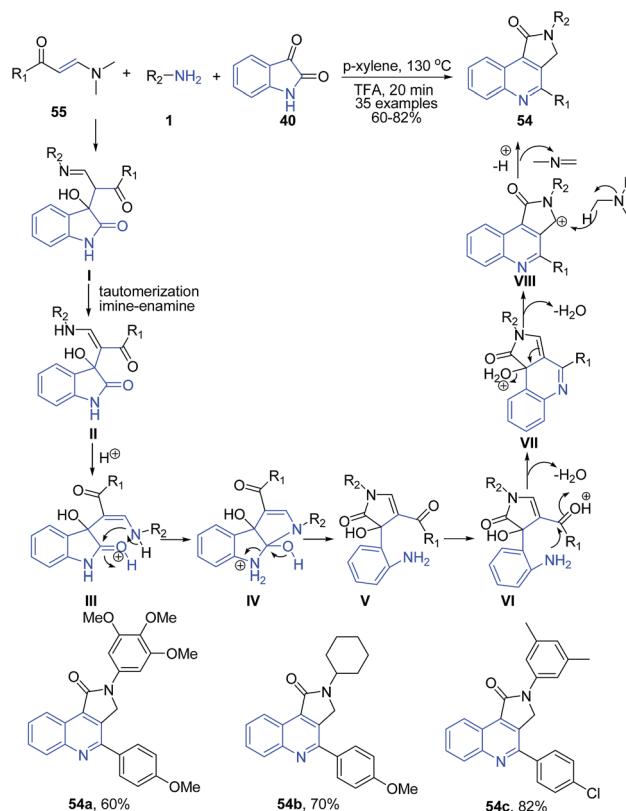
Scheme 19 HCl-catalyzed synthesis of anthra[9,1-*gh*]quinoline-2-carboxylates **51** by cyclization of 3-(arylidene-amino)-benzo[*de*]-anthracen-7-ones **50**.

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 enamones **55**, amines **1**, and isatin **40** under acidic condition. The reaction proceeds through an unusual hydride transfer from *in*



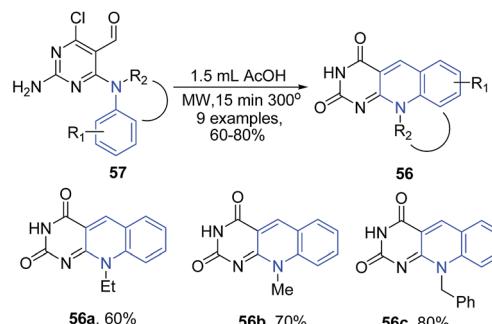
Scheme 20 AcOH-catalyzed synthesis of imidazopyrrolo-quinolines **52** via cascade of reactions; some representative examples are shown.



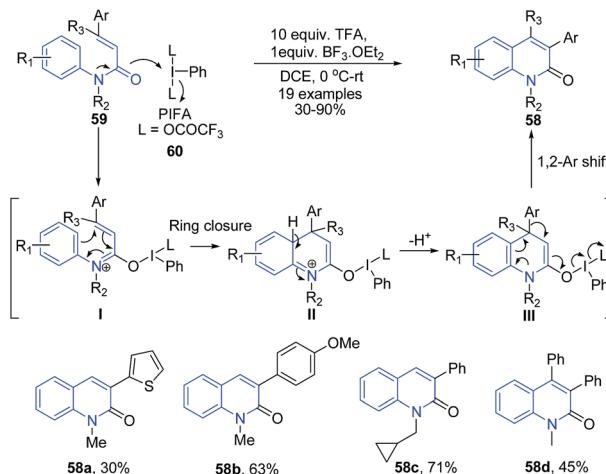
Scheme 21 TFA-catalyzed synthesis of pyrrolo[3,4-*c*]quinoline-1-ones **54**; some representative examples are shown.

situ formed dimethylamine to a carbocation intermediate **VIII** to produce structurally diverse pyrrolo[3,4-*c*]quinoline-1-ones **54** (Scheme 21).

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 NH₂ 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.

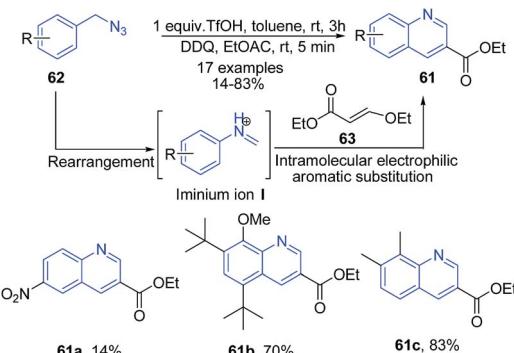


Scheme 23 TFA catalyzed synthesis of 3-arylquinolin-2-ones **58** from *N*-methyl-*N*-phenylcinnamamides **59**; some representative examples are shown.

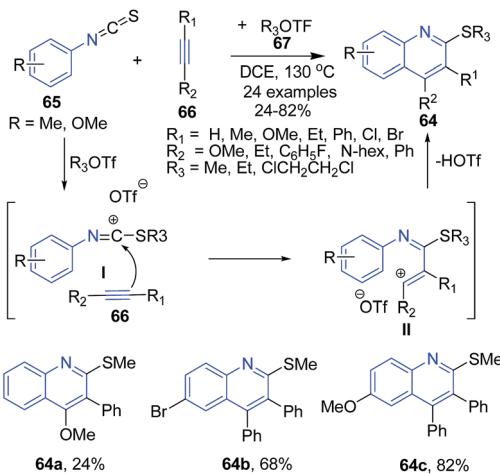
The reaction of *N*-methyl-*N*-phenylcinnamamides **59** with phenyliodine bis(trifluoroacetate) (PIFA) in the presence of TFA produced 3-arylquinolin-2-one compounds **58**. First, the nucleophilic attack on the iodine center by the carbonyl oxygen of the amide moiety in **59** affords 3-azatriene **I** 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



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

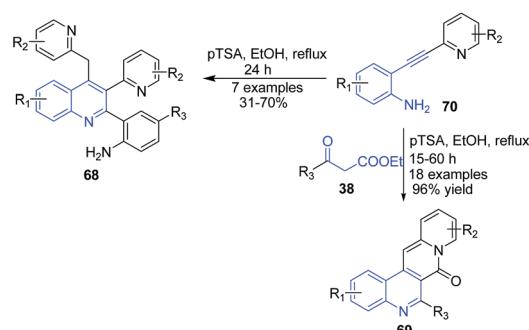


Scheme 25 Alkyl triflate triggered-synthesis of quinolines **64** from arylisothiocyanates **65**; some representative examples are shown.

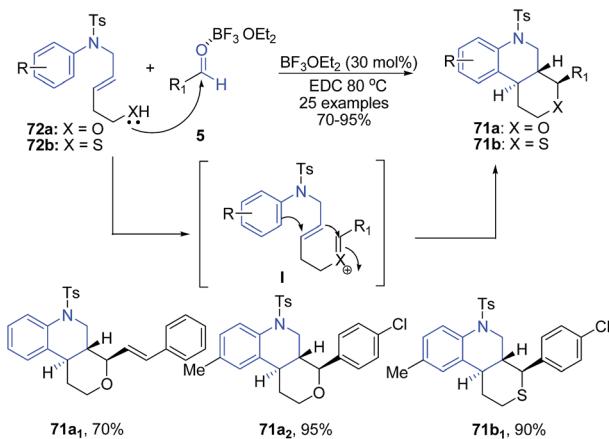
undergoes alkyltriflate triggered domino electrophilic activation and avoids the use of a transition-metal catalyst. This transformation consisted of a cascade reaction of the arylisothiocyanate **65** with alkyltriflate **67** to form alkylthiosubstituted carbenium ion **I**, which followed the reaction 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, multi-substituted 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% $\text{BF}_3\text{-OEt}_2$ in 1,2-dichloroethane at 80 $^{\circ}\text{C}$ 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 26 *p*TSA-catalyzed synthesis of quinoline-based tetracyclic scaffolds **69** and multisubstituted quinolines **68** from *o*-alkynylanilines.

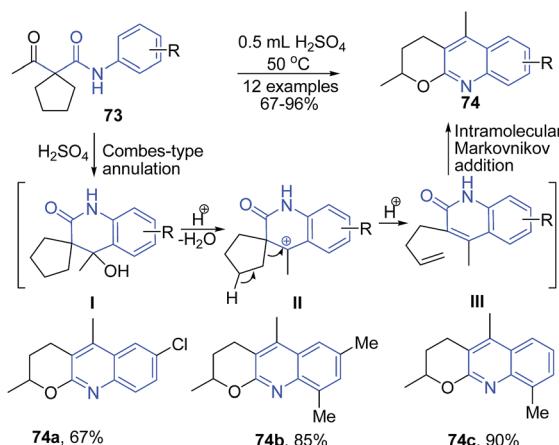


Scheme 27 $\text{BF}_3\text{-OEt}_2$ -catalyzed synthesis of hexahydro-1*H*-pyranos[3,4-*c*]quinolines 71a–b; some representative examples are shown.

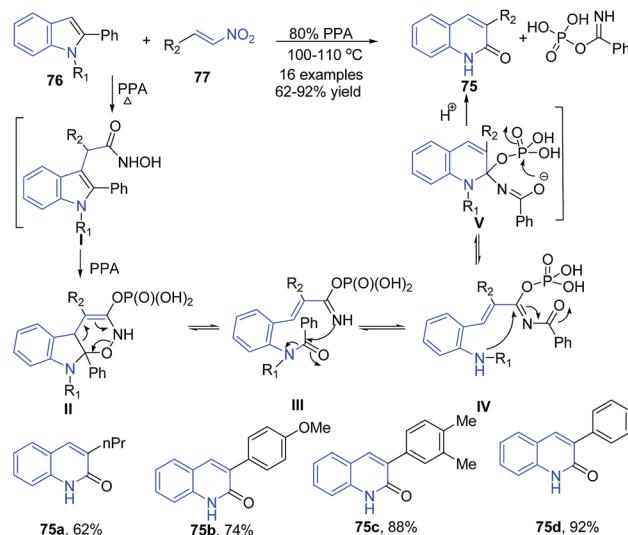
from the aldehyde and a homoallylic alcohol likely after activation with $\text{BF}_3\text{-OEt}_2$. The oxocarbenium ion is attacked by an internal olefin resulting in the formation of a carbocation that is simultaneously trapped by a tethered aryl group, leading to the formation of hexahydro-1*H*-pyranos[3,4-*c*]quinolines 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



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

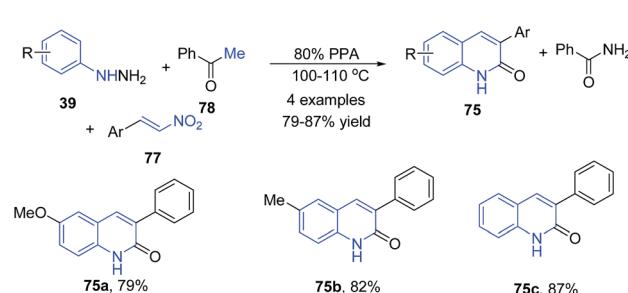


Scheme 29 PPA-catalyzed synthesis of 3-aryl-2-quinolones 75 from 2-substituted indoles 76 and nitroalkenes 77; some representative examples are shown.

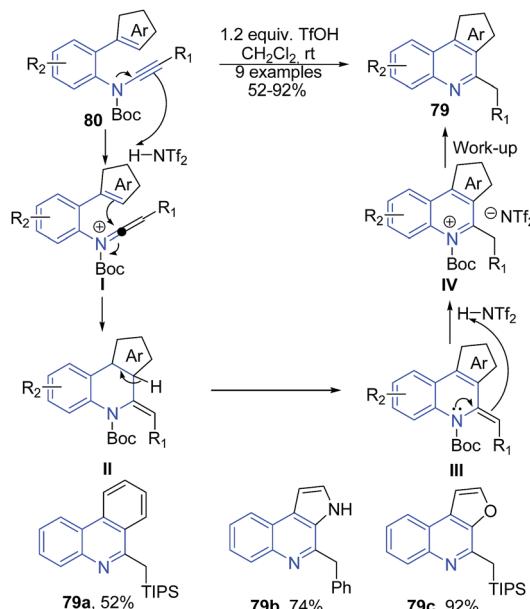
polyphosphoric acid. The conjugation of nitroalkene with indole in presence of PPA produces hydroxamic acid intermediate I. Next the intramolecular nucleophilic attack by the *N*-hydroxyl moiety at the C-2 of indole followed by tautomerization affords cyclized enamine II. Retro-Diels–Alder reaction followed 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 acyliuminium moiety in IV affords aminoquinoline V, which further on hydrolytic cleavage produces 3-aryl-2-quinolones 75 (Scheme 29).

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).



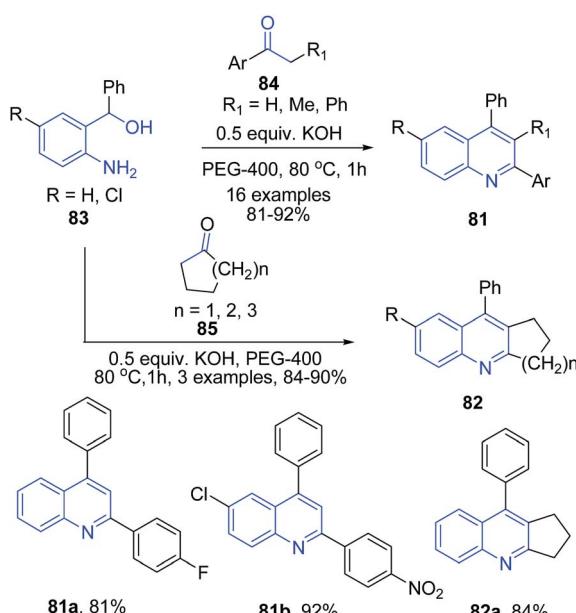
Scheme 30 PPA-catalyzed synthesis of 3-aryl-2-quinolones 75 from arylhydrazines 39; some representative examples are shown.



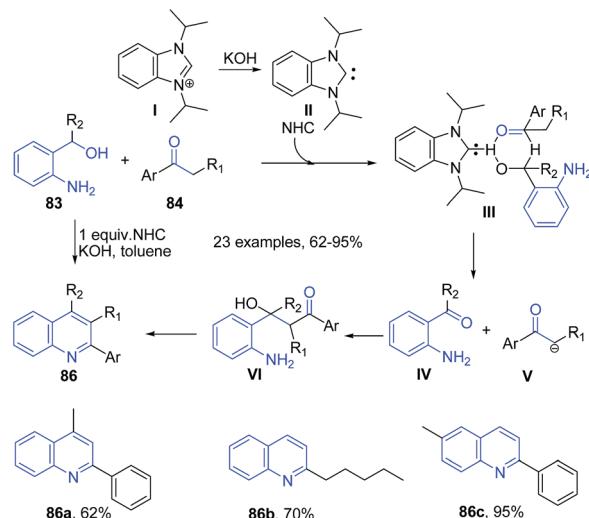
Scheme 31 TfOH catalyzed synthesis of 3*H*-pyrrolo[2,3-*c*]quinolines 79; some representative examples are shown.

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



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



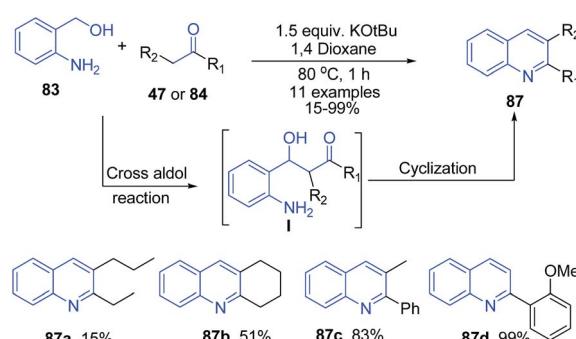
Scheme 33 N-heterocyclic carbene and KOH catalyzed synthesis of quinolines 86; some representative examples are shown.

85 such as cyclopentanone, cyclohexanone and cycloheptanone producing corresponding substituted quinolines 82.

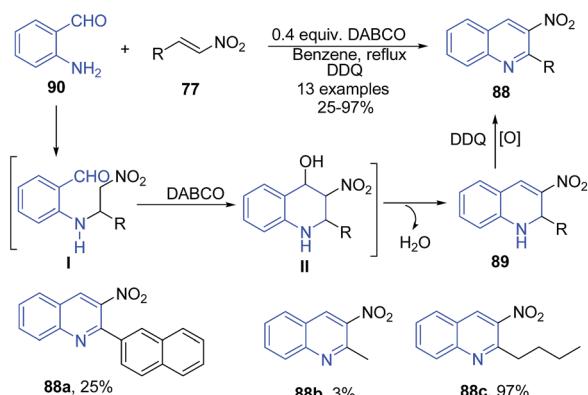
Zhu and Cai⁹⁶ reported similar protocol for synthesis of quinolines 86 using N-heterocyclic carbene as a catalyst. The reaction between 2-aminobenzyl alcohol 83 and ketones 84 proceeds *via* two tandem reactions – alpha-alkylation and indirect Friedländer annulation. The base deprotonates N-heterocyclic carbene salt I to generate a free carbene 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 coworkers⁹⁸ 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 KOtBu-catalyzed synthesis of quinolines 86 from amino benzyl alcohol 83; some representative examples are shown.

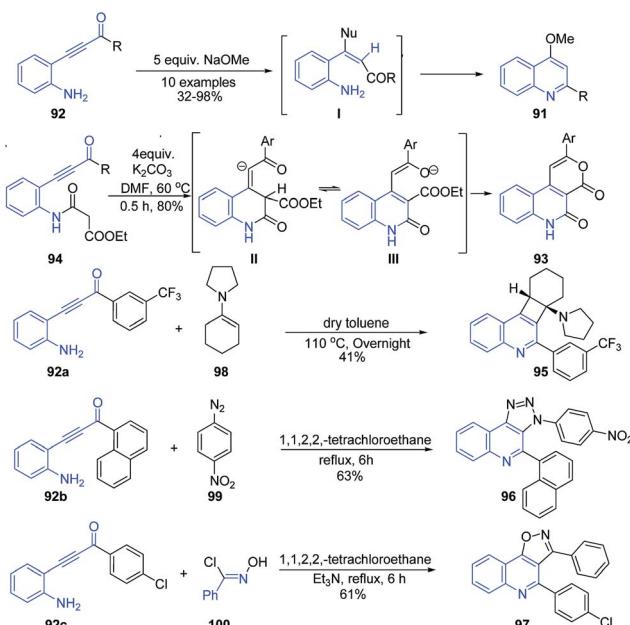


Scheme 35 DABCO-catalyzed synthesis of 3-nitro quinolines **88**; some representative examples are shown.

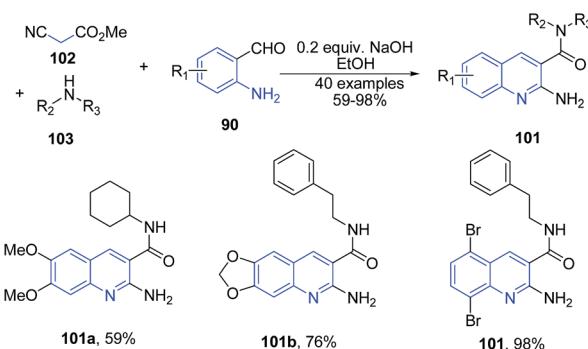
1,4-addition intermediate **I**, which on cyclization followed by dehydration gives product **88**. After oxidation with DDQ, high yields of 2-alkyl-3-nitroquinolines **88** were obtained (Scheme 35).

Base-catalysed cyclization of β -(2-aminophenyl)- α,β -ynones **92** led to formation of 2,4-disubstituted quinolines **91** through tandem nucleophilic 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.

Wang and coworkers¹⁰¹ reported a three-component reaction between cyanoacetic acid methyl ester **102**, substituted



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



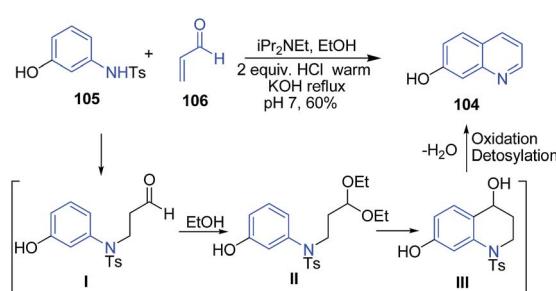
Scheme 37 Base catalyzed one-pot three-component synthesis of 2-aminoquinoline-3-carboxamides **101**; some representative examples are shown.

secondary amine **103** and 2-aminobenzaldehyde **90** in the presence of NaOH in ethanol as a solvent produced 2-aminoquinoline-3-carboxamides **101** in good yields (Scheme 37).

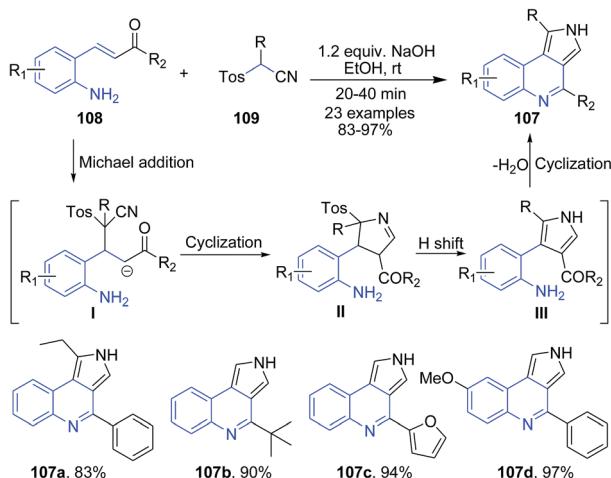
Cameron *et al.*¹⁰² described an efficient one-pot procedure for the four-step preparation of 7-hydroxyquinoline **104** from 3-N-tosylaminophenol **105** in presence of diisopropylethylamine in 60% isolated yield. This one-pot procedure has reduced the risk of exposure to acrolein. The 3-N-tosylaminophenol **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-Crafts 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



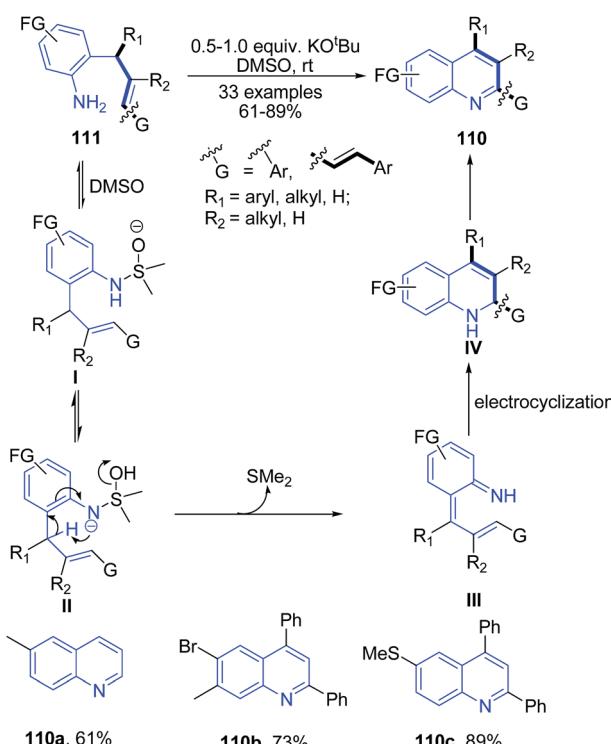
Scheme 38 Diisopropylethylamine catalyzed synthesis of 7-hydroxyquinoline **104** from 3-N-tosylaminophenol **105**.



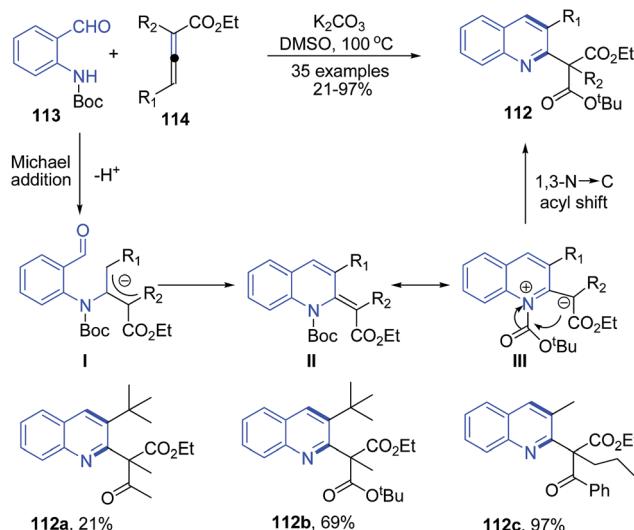
Scheme 39 Synthesis of pyrrolo[3,4-c]quinolines 107 in presence of base in ethanol; some representative examples are shown.

prepared from anilines and cinnamylalcohols). The reaction occurs *via* a regioselective 6-endo-trig intramolecular oxidative cyclization using KO^tBu 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 -dialkylallenotes 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 \rightarrow C rearrangement (Scheme 41).¹⁰⁵



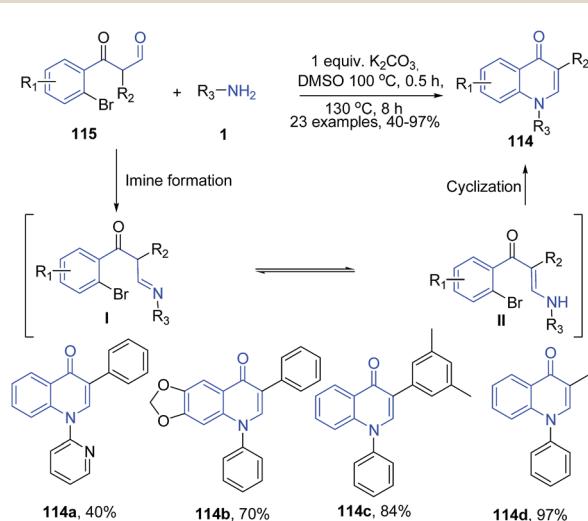
Scheme 40 Potassium *tert*-butoxide catalyzed synthesis of 2-aryl 4-substituted quinolines 110; some representative examples are shown.



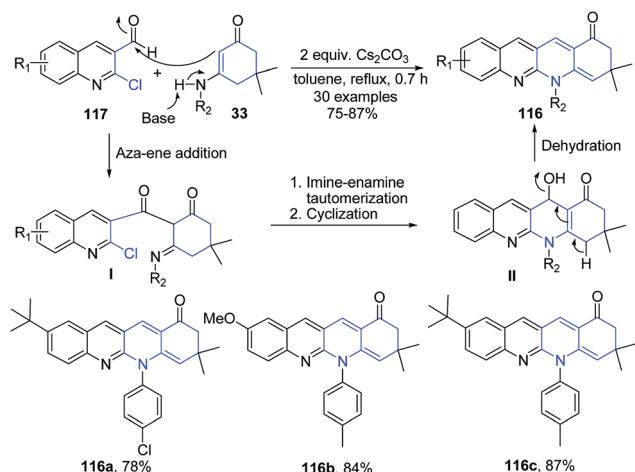
Scheme 41 K_2CO_3 catalyzed synthesis of 2,3-disubstituted quinolines 112; some representative examples are shown.

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.

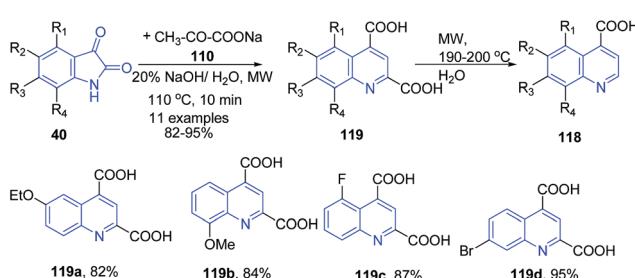
Fu *et al.*¹⁰⁷ have constructed another quinoline ring in the 2-chloroquinoline-3-carbaldehyde structure 117 by treatment with enaminones 33 in presence of Cs_2CO_3 catalyst, producing 1,8-naphthyridines 116. Initially, the aza-ene addition of enaminones 33 to 2-chloroquinoline-3-carbaldehyde 117 catalyzed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



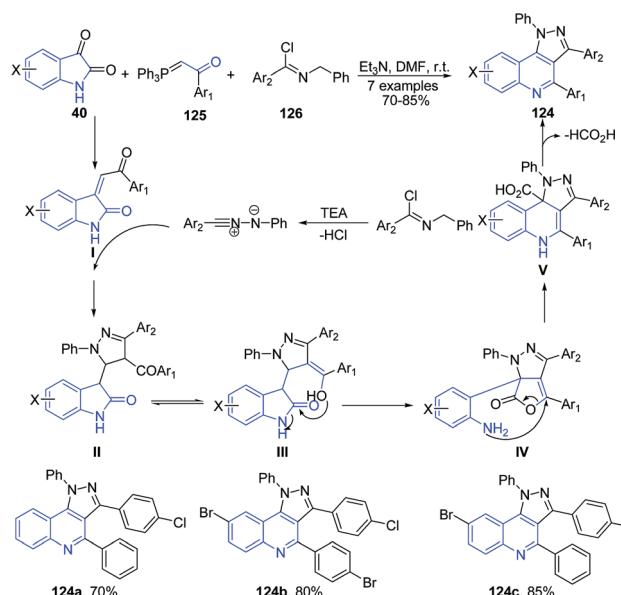
Scheme 42 K_2CO_3 -catalyzed synthesis of 3-substituted 4-quinolones 114 in DMSO; some representative examples are shown.



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

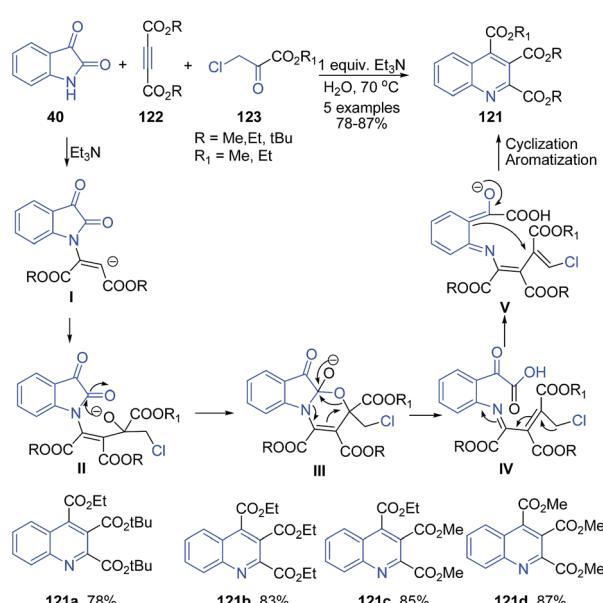
intermediate **I** then undergo an intramolecular cyclization to give intermediate **II**, which on elimination of water produces 1,8-naphthyridines **116** (Scheme 43).

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

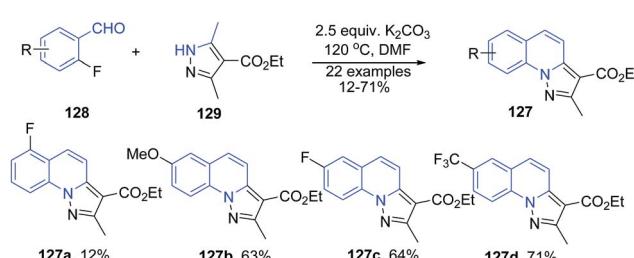
Rineh and coworkers¹⁰⁹ have established triethylamine mediated protocol for synthesis of quinolines **121** *via* reaction between ethyl chloropyruvate **123** and activated acetylenic compounds **122** in the presence of nucleophilic form of isatin in water as the solvent. Nucleophilic form of isatin 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- λ 5-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).

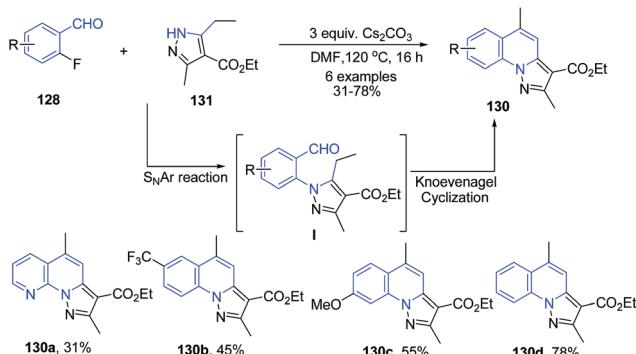
Kato *et al.*¹¹¹ developed a domino protocol for synthesis of pyrazolo[1,5-a]quinolines **127** starting from 2-fluorobenzaldehydes



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



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



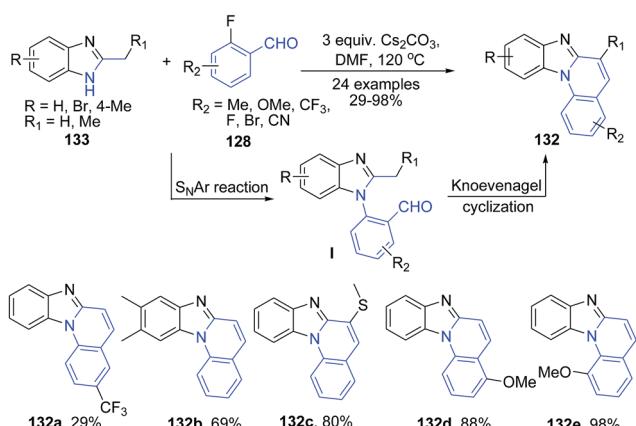
Scheme 48 Cs_2CO_3 -catalyzed cascade synthesis of pyrazolo[1,5-a]-quinolines 130; some representative examples are shown.

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).

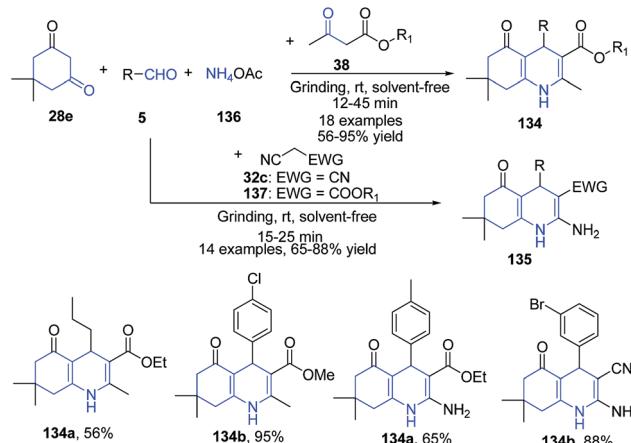
Kato *et al.*¹¹² reported another similar protocol for synthesis of pyrazolo[1,5-a]quinolines **130** from 2-fluoro aryl aldehydes **128** and pyrazole-3-carboxylic acid ester **131** using cesium carbonate base. This cascade reaction involves a sequential intermolecular aromatic nucleophilic substitution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

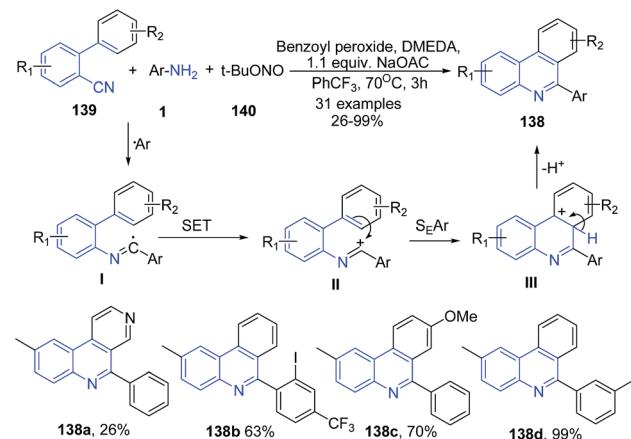
Kapoor and coworkers¹¹⁴ have reported synthesis of polyhydroquinolines **134**–**135** *via* a four-component one-pot reaction of aldehydes **5**, dimedone **28e**, active methylene compounds **38** and ammonium acetate **136** under solvent-free conditions at room temperature *via* grinding. The products of



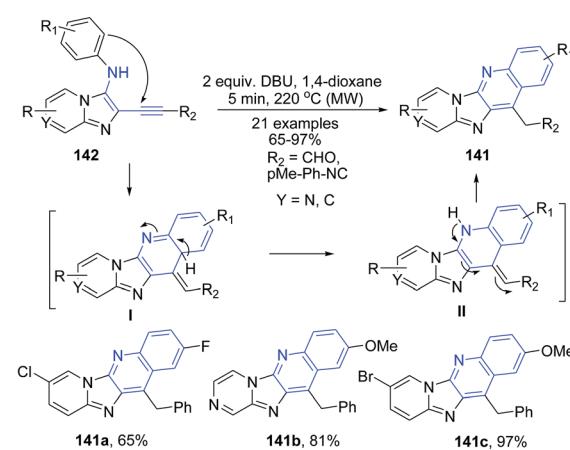
Scheme 49 Cs_2CO_3 catalyzed synthesis of benzimidazo[1,2-*a*]quinolines **132**; some representative examples are shown.



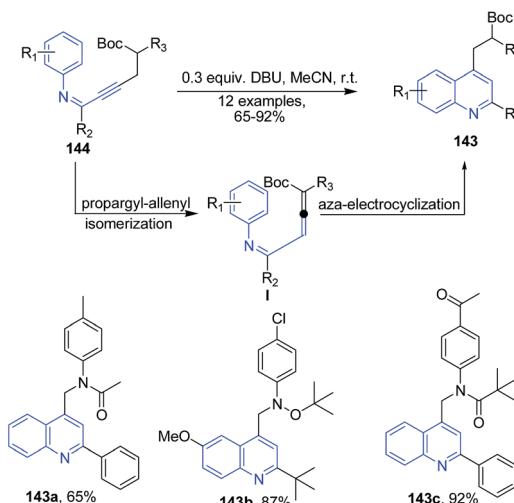
Scheme 50 Catalyst and solvent free synthesis of polyhydroquinolines **134**–**135** using a one pot four component reaction; some representative examples are shown.



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



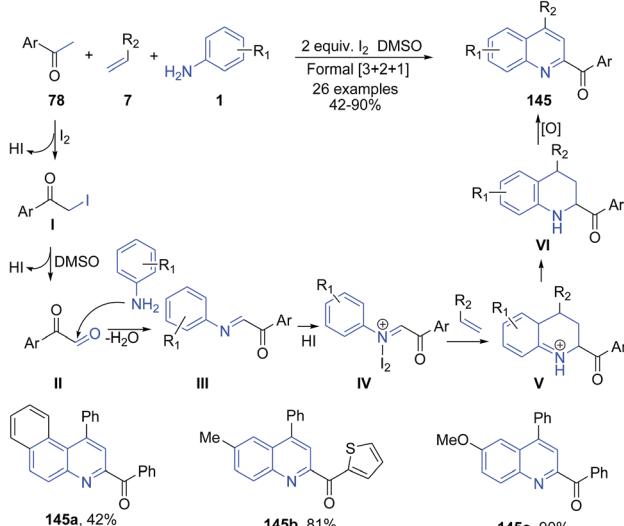
Scheme 52 DBU-catalyzed synthesis of pyrido[2',1':2,3]imido[4,5-b]quinolines **141**; some representative examples are shown.



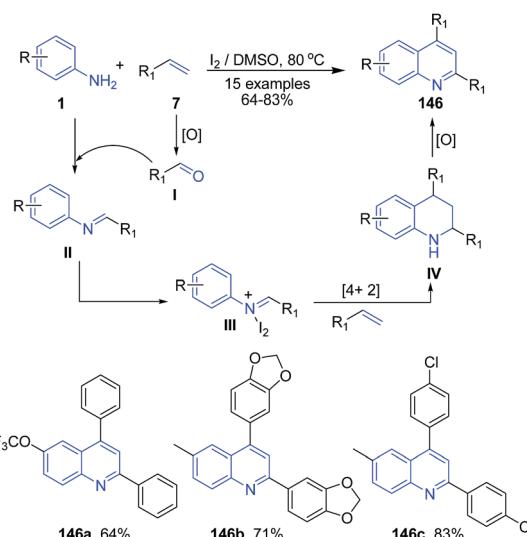
Scheme 53 DBU promoted synthesis of polyfunctionalized quinolines 143; some representative examples are shown.

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

Zhu and coworkers¹¹⁵ have developed a transition-metal-free method for the synthesis of C6 phenanthridine derivatives **138** by arylation cyclization of 2-isocyanobiphenyls **139** with aryl-amines **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 aryl diazonium ion which then gets decomposed (releasing N₂ 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



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

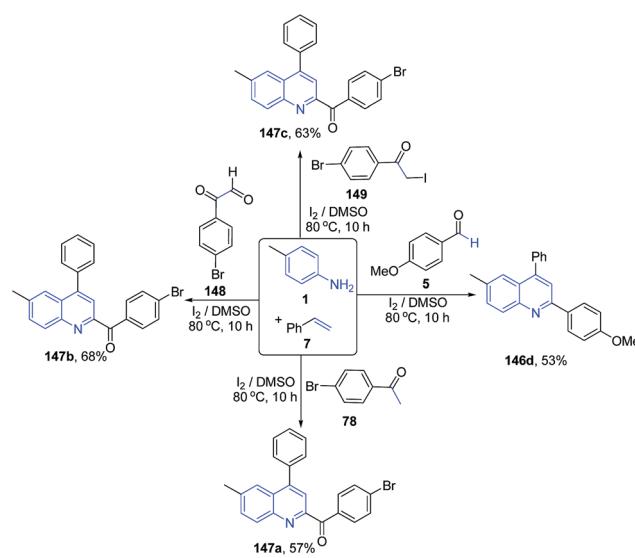


Scheme 55 Synthesis of 2,4-disubstituted quinolines **146**; some representative examples are shown.

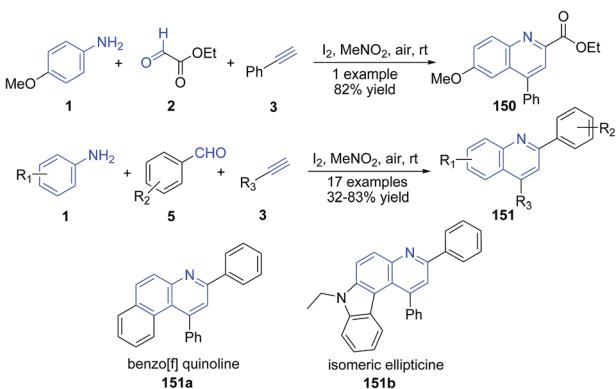
radical on the pending phenyl ring, forms the cyclohexadienyl radical intermediate **III**. Finally, deprotonation of the intermediate **III** produces **138**, as depicted in Scheme 51.

Berteina-Raboin and Guillaumet¹¹⁶ 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 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

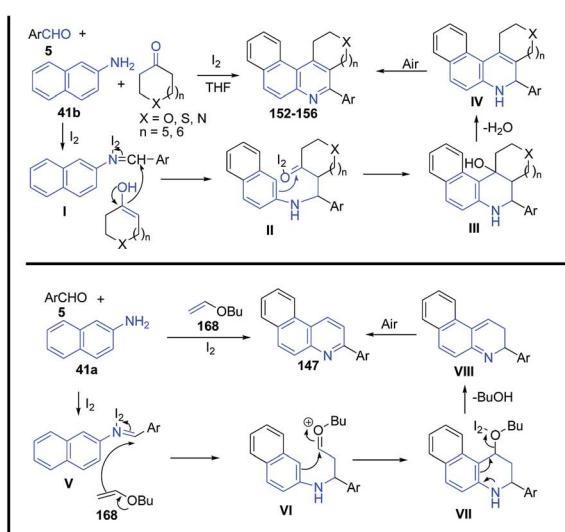
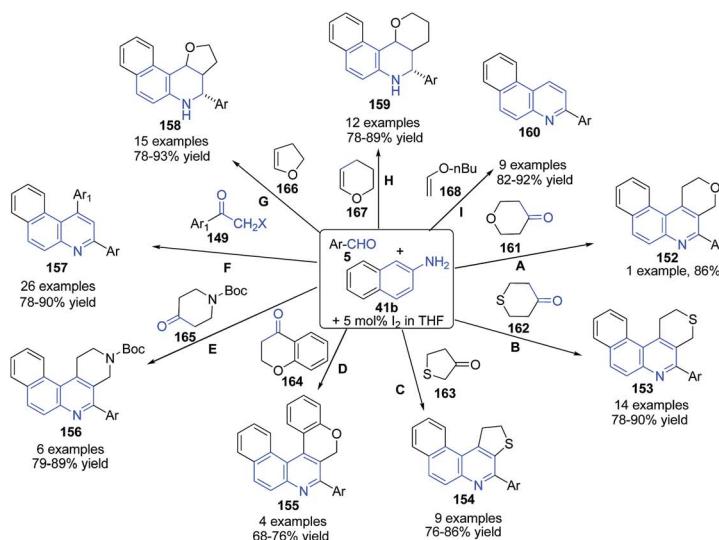
Iodine has been very extensively used in organic chemistry to catalyze diverse range of organic transformations including multicomponent reactions.¹¹⁸ Gao *et al.*¹¹⁹ developed a highly efficient molecular iodine mediated formal [3 + 2 + 1] cycloaddition reaction for the direct synthesis of substituted 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 cycloaddition 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).

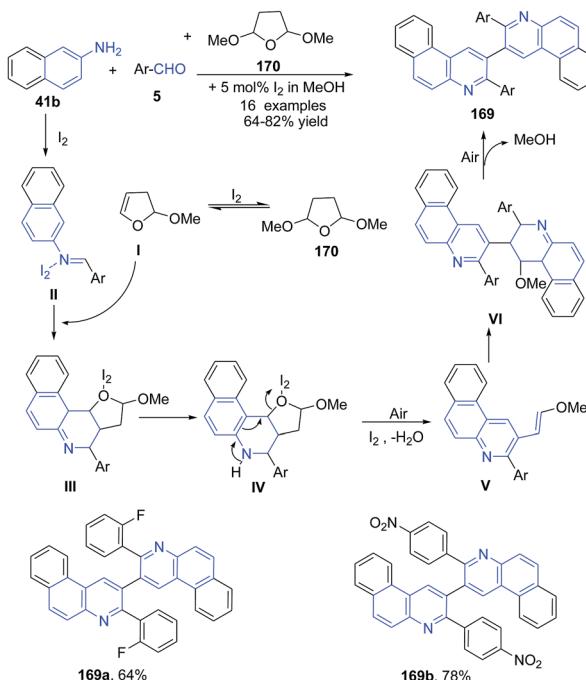
Deshidi *et al.*¹²⁰ also reported molecular iodine catalyzed three-component reaction between arylamines 1, styrenes 7 and carbonyl compound 5, 78, 148–149 leading to formation of substituted quinolines 146a, 1147a–c (Scheme 56).

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(2H)-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.



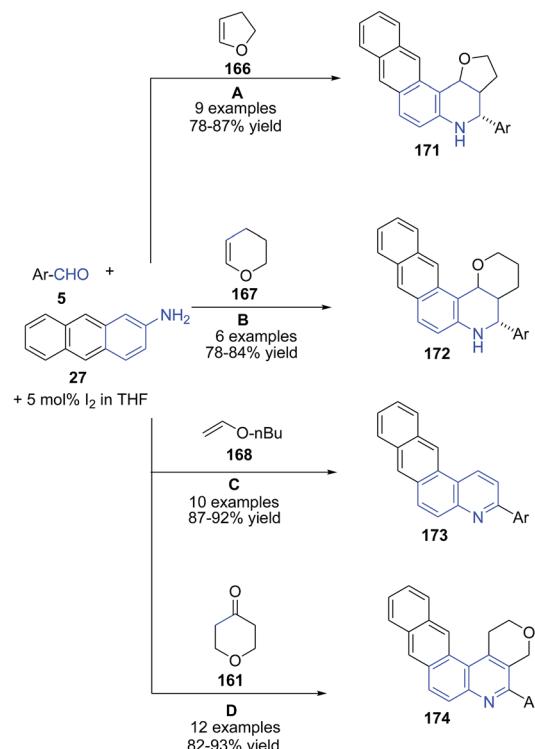
Scheme 59 Molecular iodine catalyzed synthesis of bis-benzoquinolines **169**; some representative examples are shown.

Wang's group¹²⁵ 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

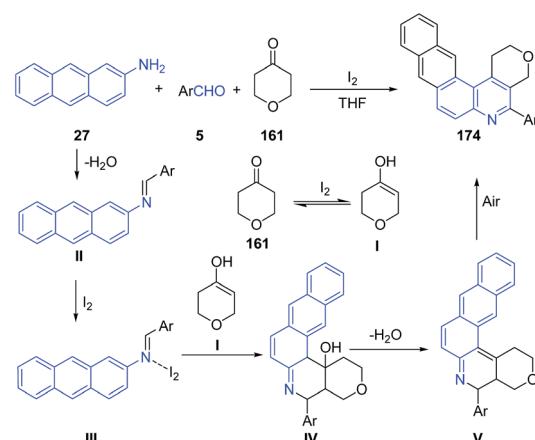
Anionic surfactant sodium dodecyl sulfate has also been employed in heterocycle synthesis.¹²⁸ Recently Ganguly and Chandra¹²⁹ have employed the use of molecular iodine and sodium dodecyl sulfate for the construction of quinoline skeleton using a three-component reaction. A three-component coupling of 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



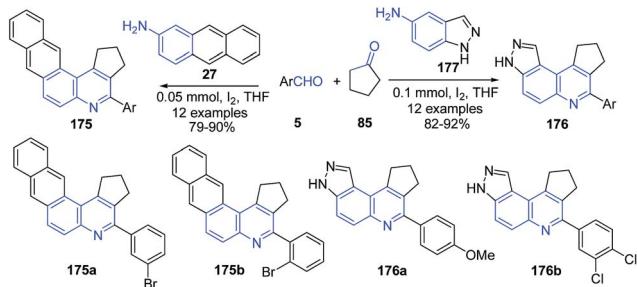
Scheme 60 Molecular iodine catalyzed synthesis of naphthoquinolines **171**–**174** from anthracenyl amines.

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).

Wu and coworkers¹³⁰ 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**.



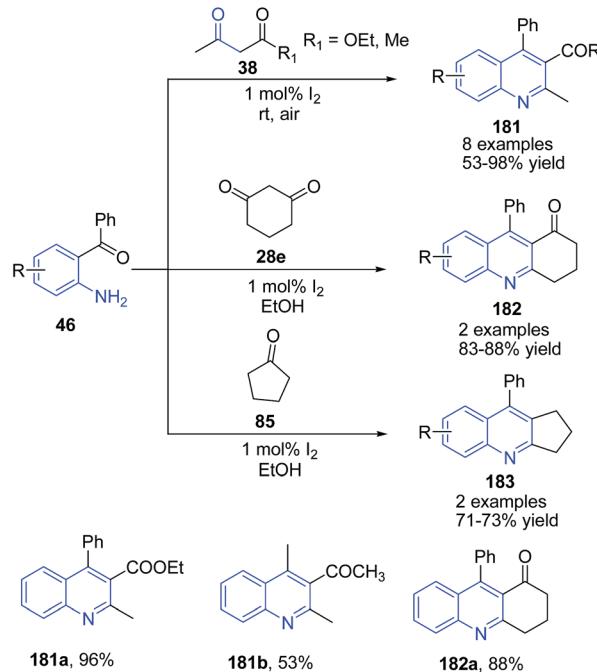
Scheme 62 Molecular iodine catalyzed synthesis of cyclopenta[c]naphtho[2,3-f]quinoline **175** and cyclopenta[c] pyrazolo[4,3-f]quinolines **176**.

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 bromide¹³¹ or cyanuric chloride¹³² as a catalyst.

Zeng and Cai¹³³ 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.

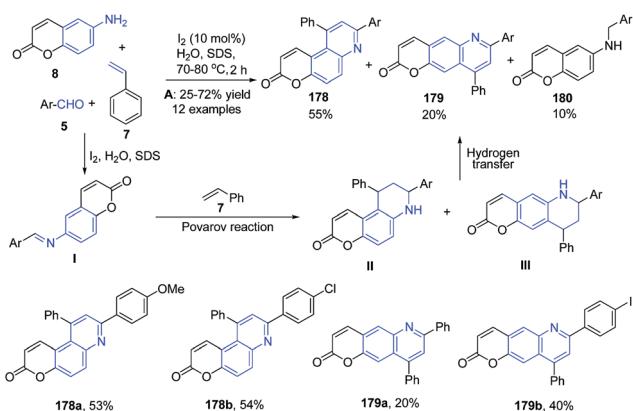
The oxidative cyclization of phenyl-*N*-(*o*-alkynylphenyl) imines **190** in presence of molecular iodine produced furanoquinolines **189** (Scheme 67).¹³⁵ The iodide cation on coupling with imine **190** generated iminium ion **I** which further



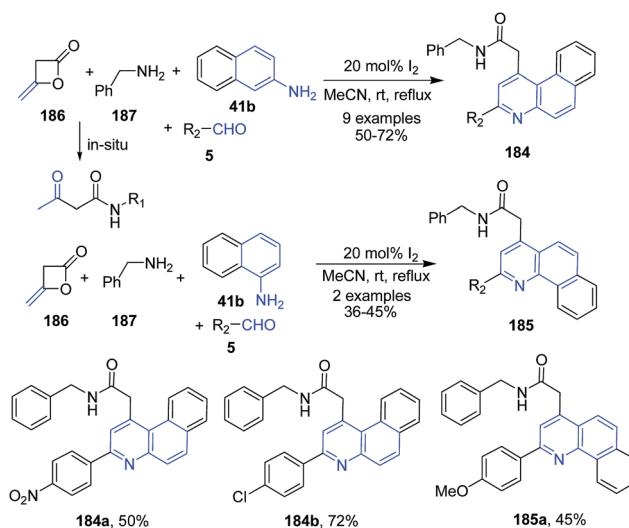
Scheme 64 Molecular iodine-catalyzed synthesis of 2,3,4-trisubstituted quinolines **181–183**; some representative examples are shown.

undergoes intramolecular cyclization to produce quinoline **II**, which in elimination of HI produces **189**.

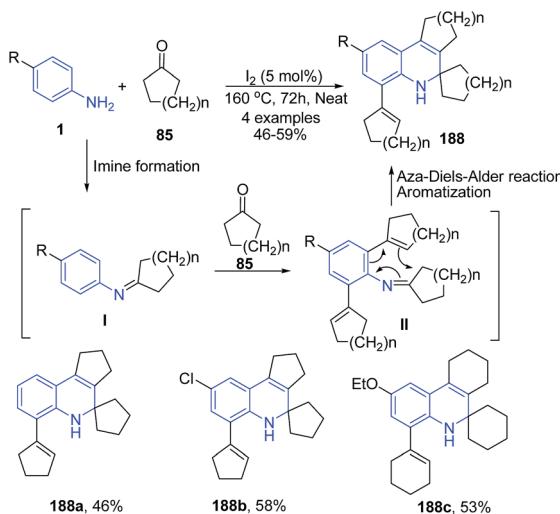
Batra's group¹³⁶ reported molecular iodine catalyzed synthesis of 2-substituted quinolines **191** from substituted primary allyl amines **192**. Iodine initially activates the carbonyl group, which is then followed by electrophilic cyclization to produce dihydroquinoline **II**. The intermediate **II** 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.



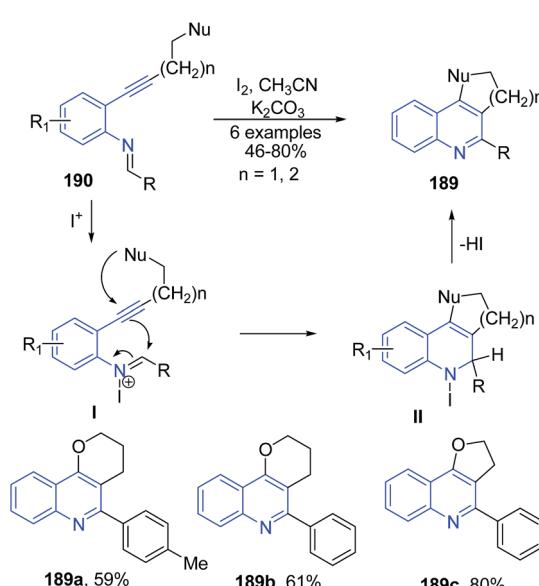
Scheme 65 Molecular iodine catalyzed synthesis of benzo[f]quinolinyl and benzo[h]quinolinyl acetamides **184–185**; some representative examples are shown.



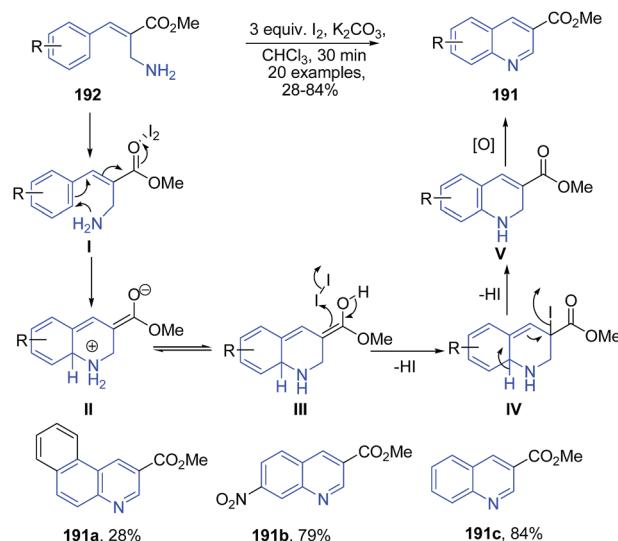
Scheme 66 I_2 -catalyzed synthesis of cyclopenta[c]quinolines **188**; some representative examples are shown.

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-tosylamino-phenyl)ketones **197** or 2-tosylaminobenzaldehyde afforded



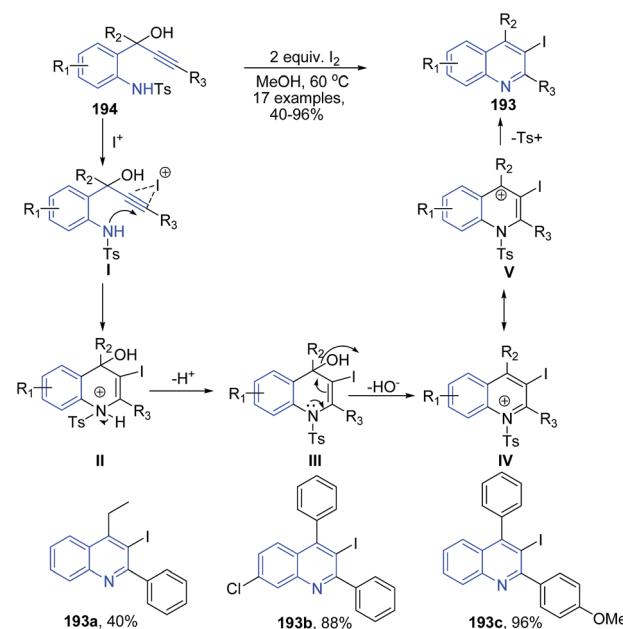
Scheme 67 I_2 -catalyzed synthesis of furanoquinolines **189**; some representative examples are shown.



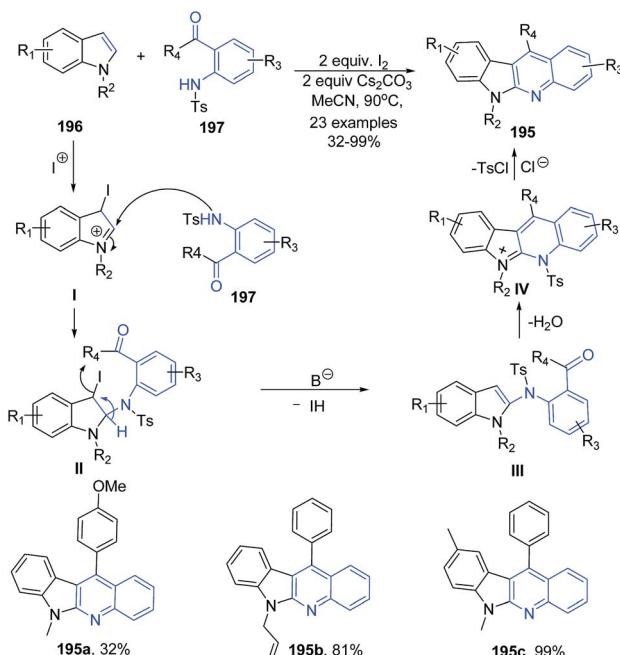
Scheme 68 Iodine-catalyzed synthesis of 2-substituted-quinolones **191** from allylamines **192**; some representative examples are shown.

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



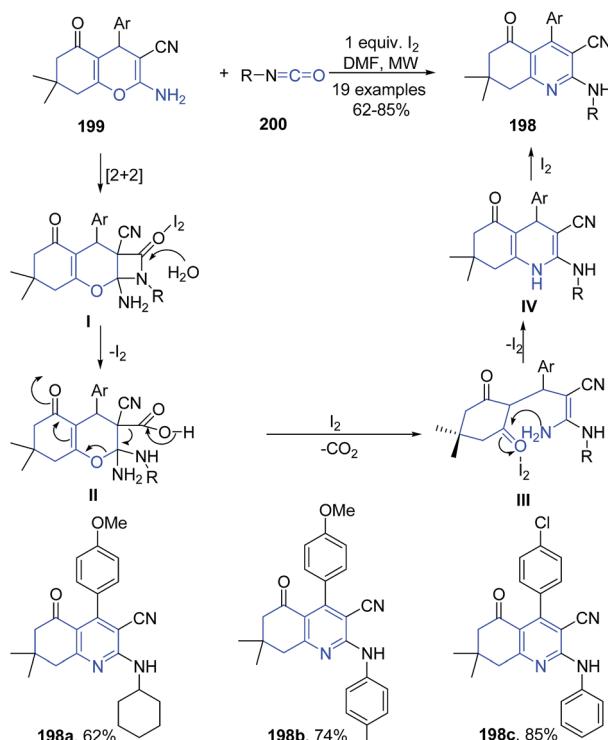
Scheme 70 I_2 -catalyzed synthesis of indolo(2,3-*b*)quinolines 195; some representative examples are shown.

quinolines.^{139–141} Tu and coworkers¹⁴² 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 aromatization of IV led to formation of 198 (Scheme 71).

Mitamura and Ogawa¹⁴³ 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 take 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 group¹⁴⁴ 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



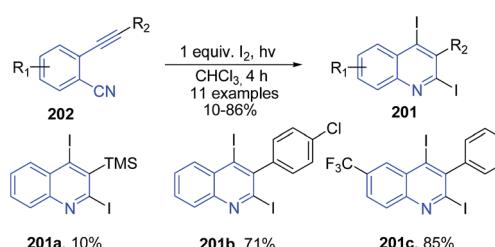
Scheme 71 I_2 -catalyzed synthesis of aminoquinoline-3-carbonitriles 198; some representative examples are shown.

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).

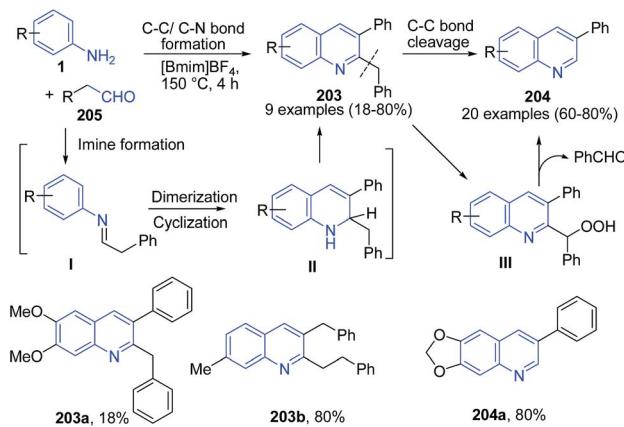
Another ionic liquid mediated synthesis of quinolines is reported, involving a four-component, one-pot reaction of aromatic aldehyde 5, cyclohexanone 85, malononitrile 33c, and amines 1 or 205 in basic ionic liquid [Bmim]OH to produce tetrahydroquinoline-3-carbonitriles 206 (Scheme 74).¹⁴⁵

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



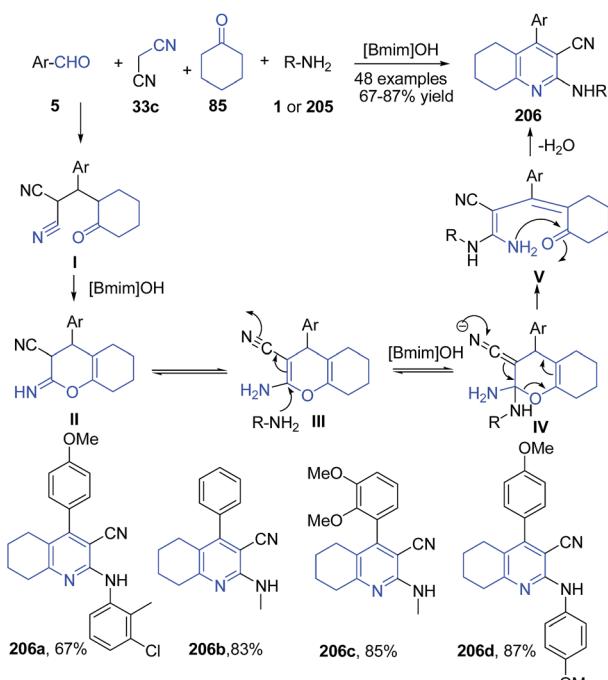
Scheme 72 Synthesis of 2,4-diiodoquinolines 201 via the photochemical cyclization of *O*-alkynylaryl isocyanides 202 with molecular iodine; some representative examples are shown.



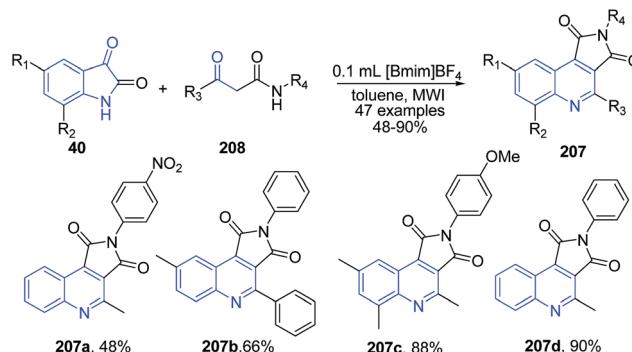
Scheme 73 Synthesis of 2,3-disubstituted **203** and 3-substituted quinolines **204** in ionic liquid; some representative examples are shown.

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 Mallakmohammadi¹⁴⁸ 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**



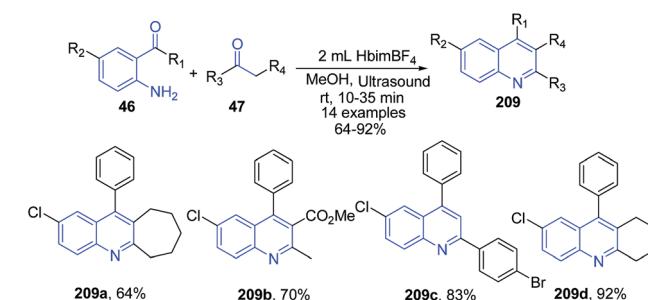
Scheme 74 Synthesis of tetrahydroquinoline-3-carbonitriles **206** in ionic liquid; some representative examples are shown.



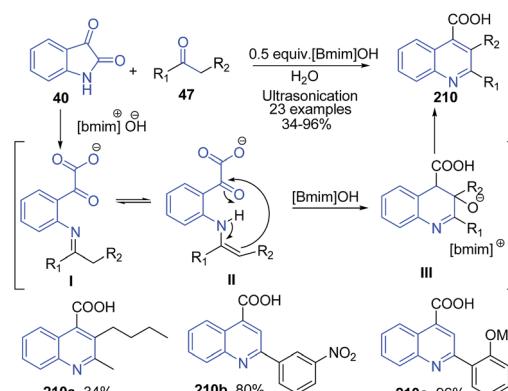
Scheme 75 Synthesis of pyrrolo[3,4-c]quinoline-1,3-diones **207** in ionic liquid; some representative examples are shown.

which finally on dehydration result in the formation of desired quinoline product **210**.

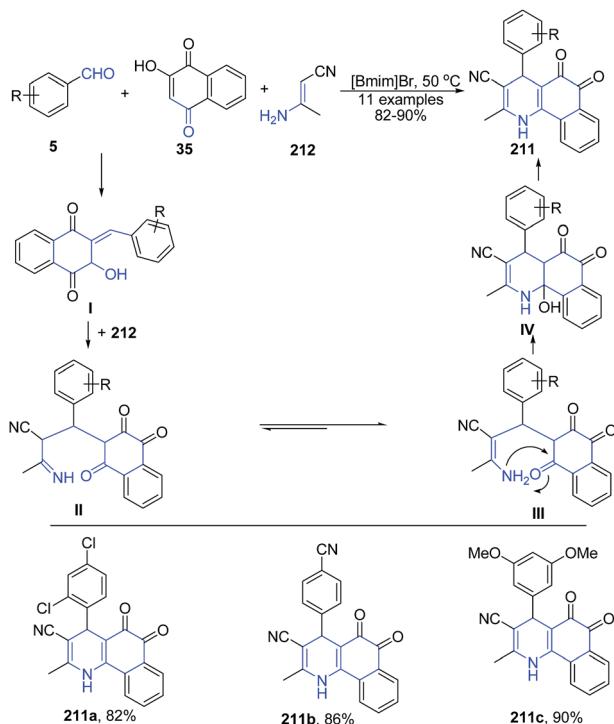
A three-component reaction of aryl aldehyde **5**, (*E*)-3-aminobut-2-enenitrile **212** and 2-hydroxynaphthalene-1,4-dione **35** in ionic liquid produced polysubstituted benzo[*h*]quinolines **211** (Scheme 78). Another three-component reaction involving condensation of aryl aldehyde **5**, (*E*)-3-aminobut-2-enenitrile **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



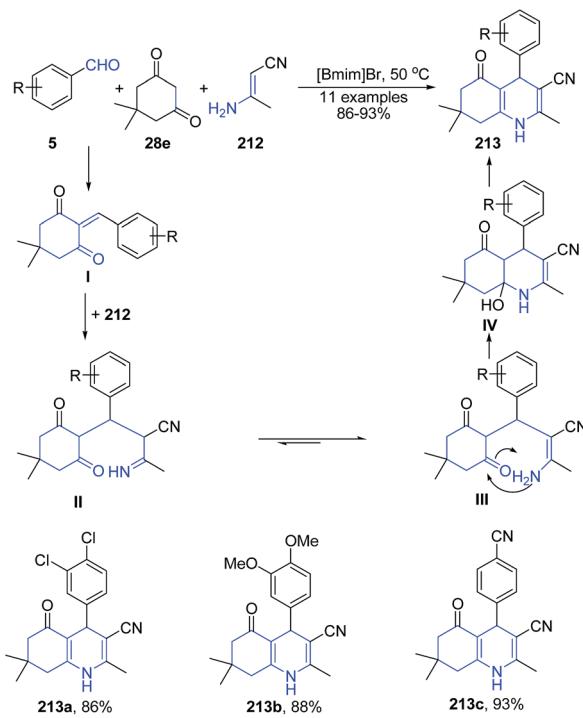
Scheme 76 Synthesis of substituted quinolines **209** in ionic liquid under ultra-sound irradiation; some representative examples are shown.



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

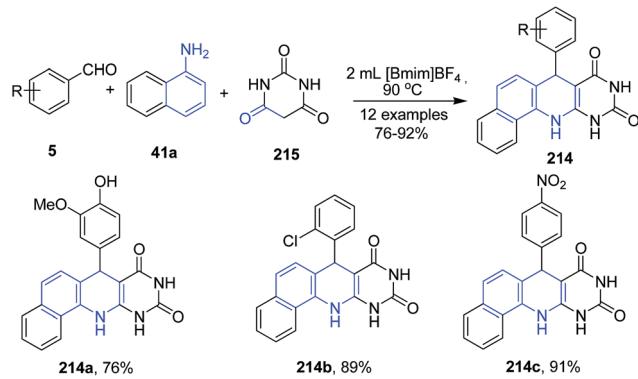
3.5. Organocatalysis for quinoline synthesis

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).

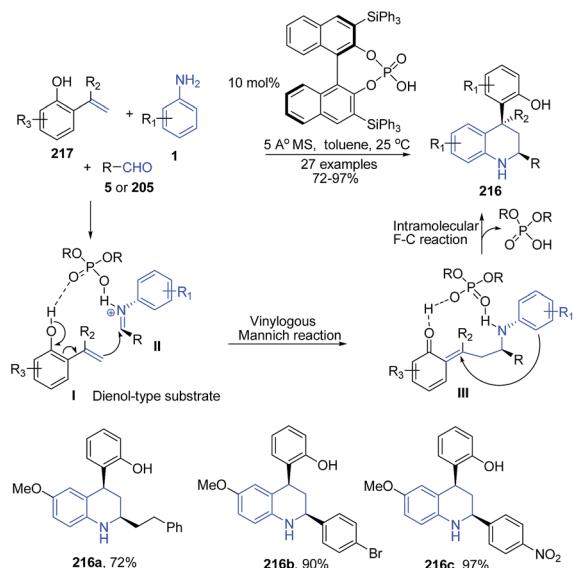
A series of 4-aza-podophyllotoxin derivatives **218** have been synthesized regioselectively *via* the three-component reaction of

aldehydes **5**, aromatic amines **1**, and tetrone acid **28d** catalyzed by L-proline.¹⁵⁵ L-Proline catalyzes the formation of iminium ion **II** in a reversible reaction with tetrone 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**.

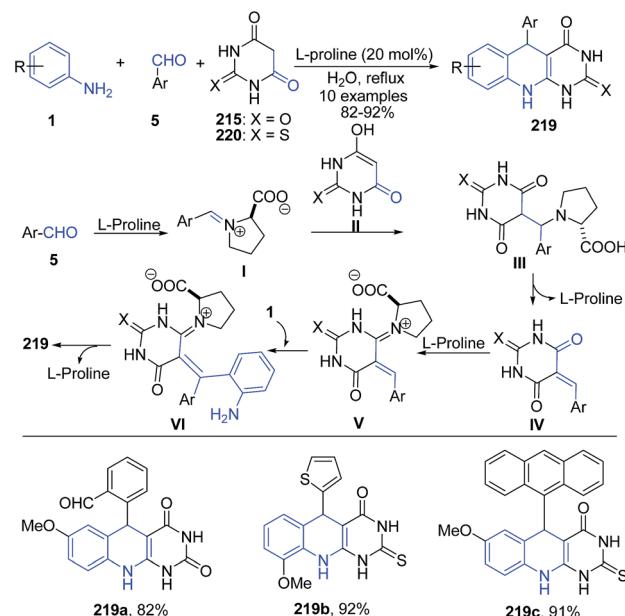


Scheme 80 Synthesis of pyrimido-[4,5-*b*]quinoline-8,10(7*H*,9*H*)-diones **214**; some representative examples are shown.

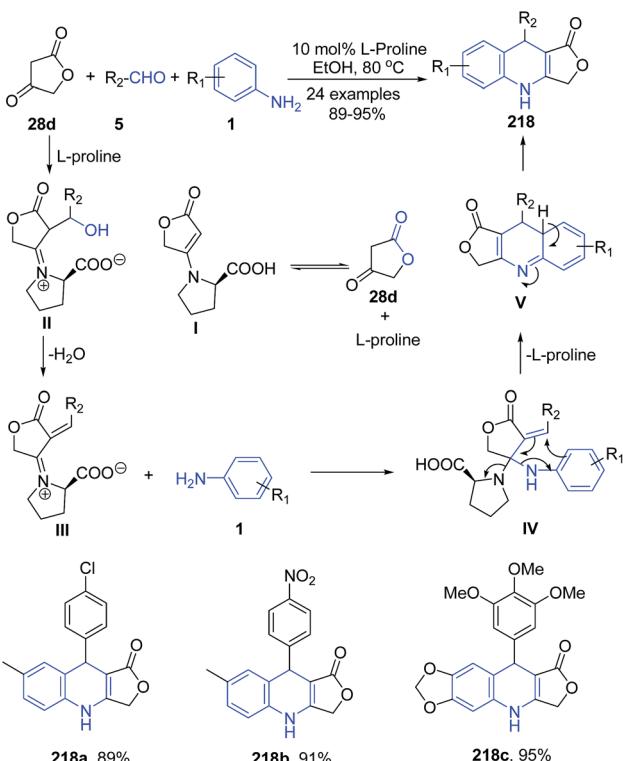


Scheme 81 Chiral phosphoric acid-catalyzed synthesis of *cis*-disubstituted tetrahydroquinolines **216**; some representative examples are shown.

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**



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



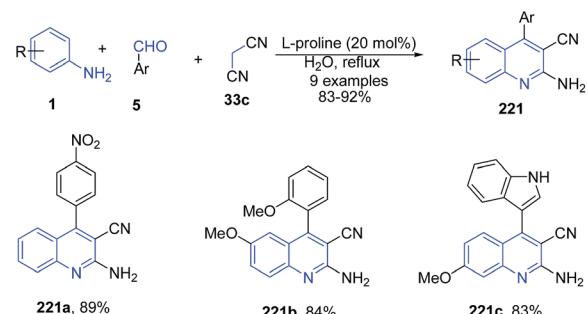
Scheme 82 *L*-Proline-catalyzed synthesis of dihydrofuro[3,4-b]quinolin-1(3H)-ones **218**; some representative examples are shown.

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

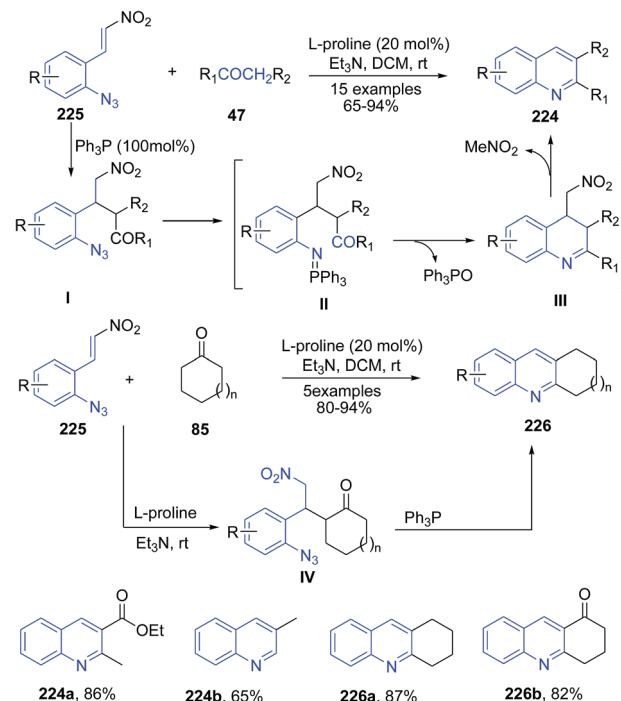
This iminophosphorane **II** undergoes the intramolecular ring-closure *via* the aza-Wittig reaction at room temperature to produce quinoline **III** which on elimination of nitromethane moiety produces **224**. The cyclic ketones **85** produced corresponding tricyclic products **226** *via* intermediate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

3.6. Catalyst-free quinoline synthesis

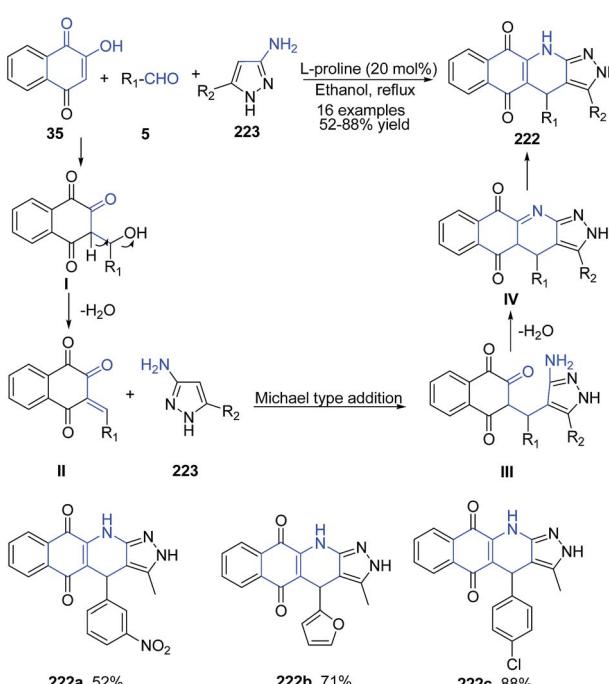
Apart from the use of above discussed simple non-metal catalysts, several reactions proceeds efficiently in suitable solvents without use of any catalyst. Reaction of 2-(aminomethyl)aniline **228** with ketones **47** in presence of oxygen atmosphere produced quinoline products **207**.¹⁵⁹ Reaction involved 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



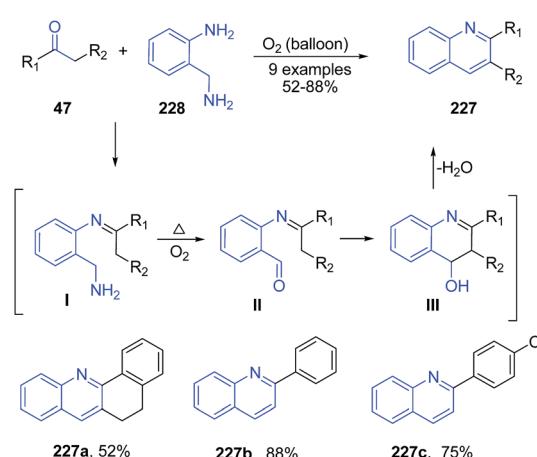
Scheme 86 L-Proline-catalyzed synthesis of 2,3-disubstituted quinolines **224**, **226**; some representative examples are shown.



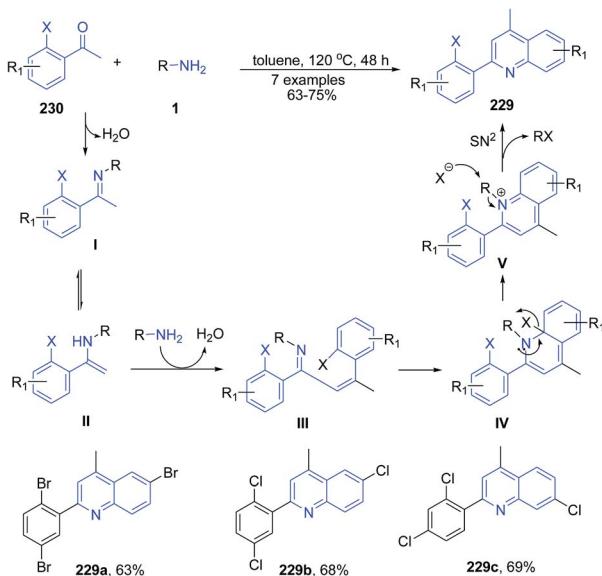
Scheme 85 L-Proline-catalyzed synthesis of benzo[g]pyrazolo[3,4-*b*]quinoline diones **222**; some representative examples are shown.

Fayol and Zhu¹⁶² 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 pre-disposed 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



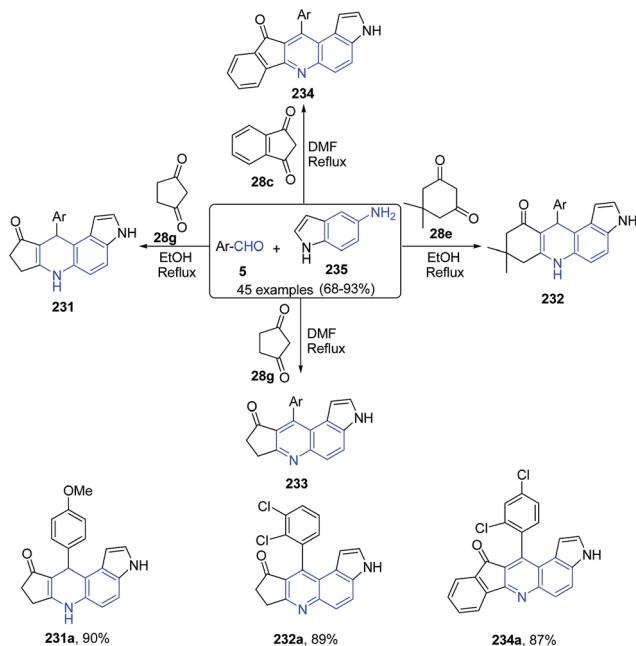
Scheme 87 Catalyst-free synthesis of 2-substituted quinolines **227** by treatment of 2-(aminomethyl)aniline **228** with ketones **47**; some representative examples are shown.



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 authors¹⁶³ 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.

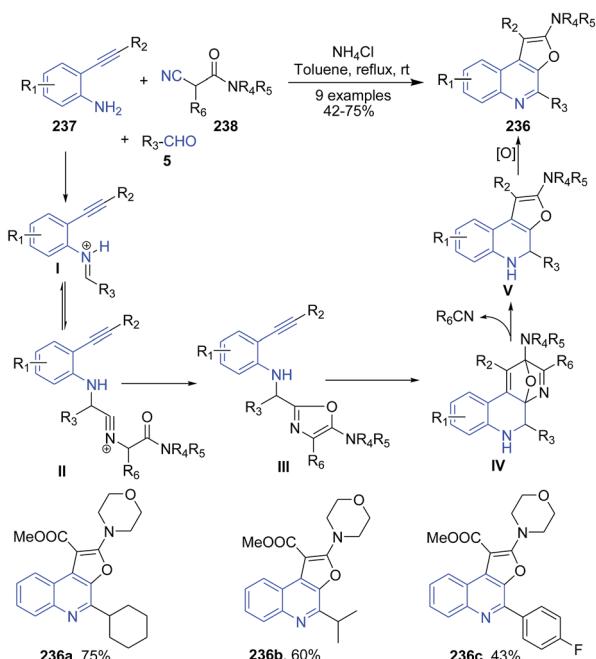


Scheme 89 Catalyst free synthesis of pyrrolo[3,2-f]quinoline 231–233 and pyrrolo[3,2-a]acridines 234; some representative examples are shown.

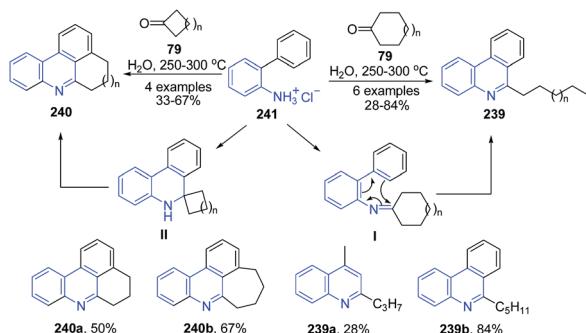
Yuvraj *et al.*¹⁶⁴ described a microwave-assisted, chemo-selective synthesis of oxazolo[5,4-*b*]quinoline – fused spirooxindoles 245 *via* three-component tandem Knoevenagel/Michael addition reaction of 5-amino-3-methylisoxazole 246, β -diketones 28e and isatins 40 in good to excellent yields under catalyst- 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 cyclocondensation 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

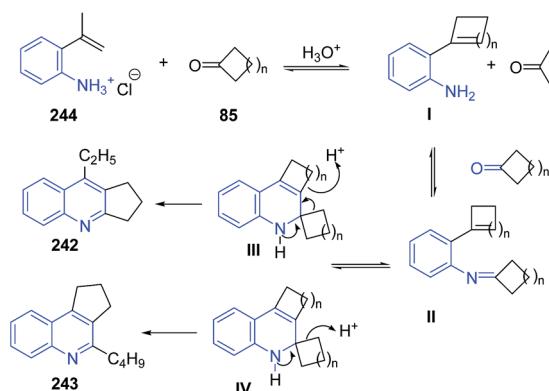
Alizadeh and Rezvaniyan¹⁶⁶ reported one-pot, catalyst-free, four-component synthesis of octahydro-imidazo[1,2-*a*]quinolin-6-ones 248 from aromatic aldehydes 5, cyclic 1,3-diones 28e, diamines 250, and nitro ketene dithioacetal 249 under catalyst and solvent free conditions. Mechanism involves first 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.



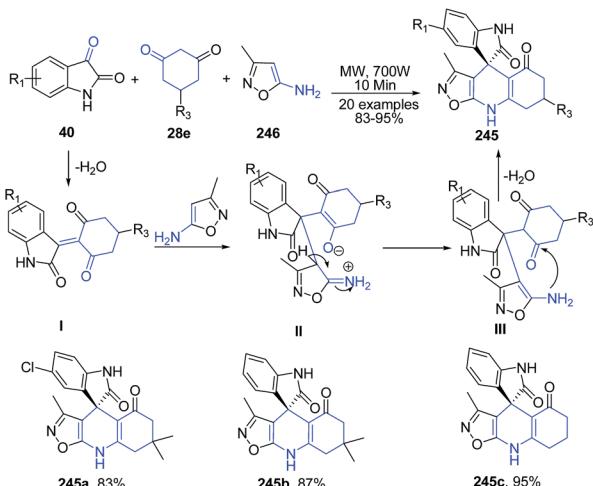
Scheme 91 Catalyst free synthesis of phenanthridines 239–240; some representative examples are shown.



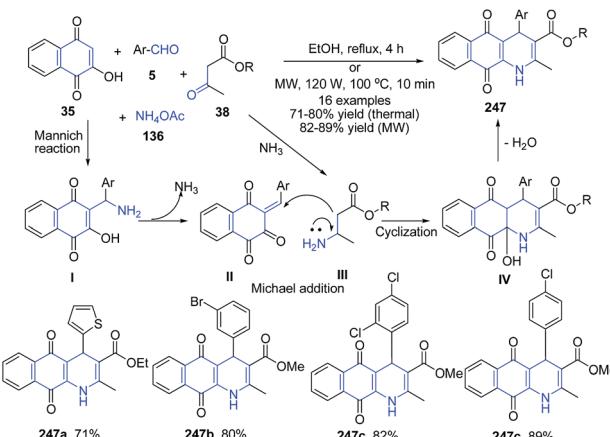
Scheme 92 Catalyst-free synthesis of quinolines 242–243.

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).

Chidurala *et al.*¹⁶⁷ reported one-pot multicomponent atom-efficient, catalyst-free reaction between resorcinol 252,



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



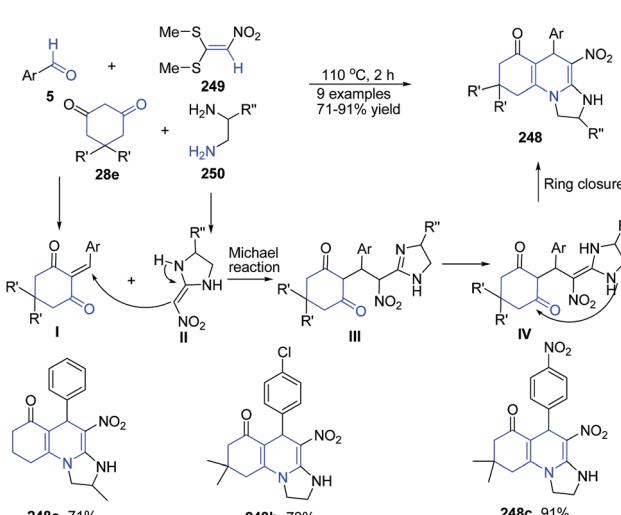
Scheme 94 Catalyst free synthesis of tetrahydrobenzo[g]quinolines 247; some representative examples are shown.

aromatic aldehyde 5, acetoacetanilide 253 and ammonium acetate 136 to produce substituted 1,4-dihydroquinolines 251 (Scheme 96).

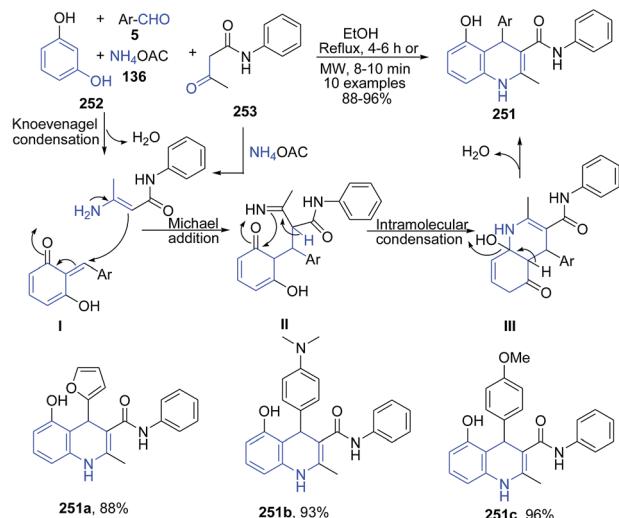
Findik *et al.*¹⁶⁸ reported one-pot four-component condensation of dimedon 28e, α -ionone 255, ammonium acetate 136 and benzaldehyde 5 under reflux condition to produce 7,8-dihydroquinolin-5-(1*H*,4*H*,6*H*)-ones 254 (Scheme 97).

3.7. Miscellaneous protocols

Ghorbani-Vaghei and Malaekahpoor¹⁶⁹ 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.



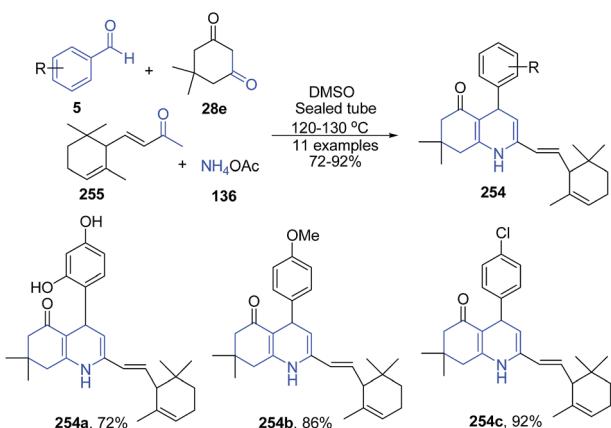
Scheme 95 Catalyst-free synthesis of octahydro-imidazo[1,2-a]quolin-6-ones 248; some representative examples are shown.



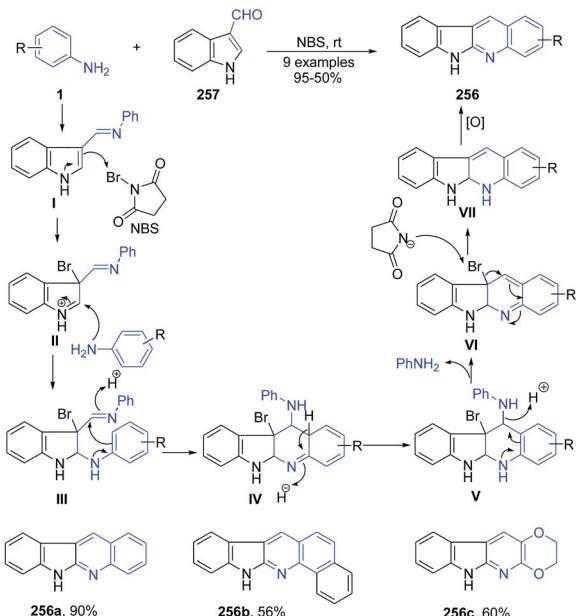
Scheme 96 Catalyst-free synthesis of substituted 1,4-dihydroquinolines 251; some representative examples are shown.

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 Kwon¹⁷¹ 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 PPh₃ produces anion intermediate IV. Nucleophilic addition of the free phosphine to the activated alkyne 262 generates 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 aromatization produces 260.

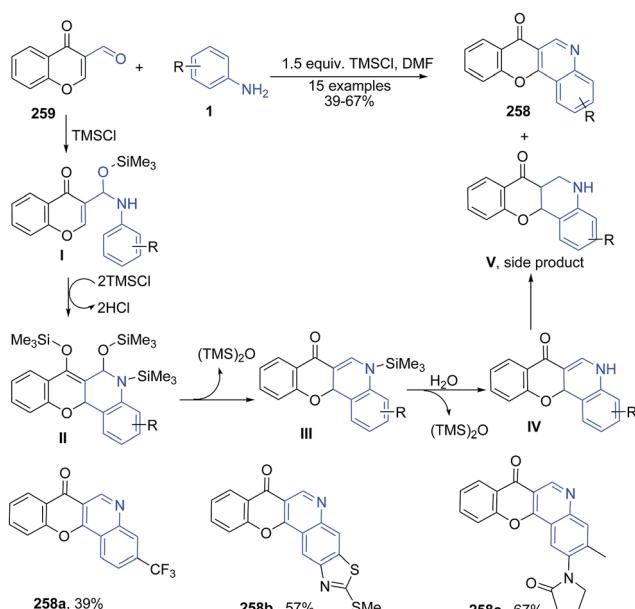


Scheme 97 Catalyst free synthesis of substituted 7,8-dihydroquinolin-5-(1*H*,4*H*,6*H*)-ones 254; some representative examples are shown.

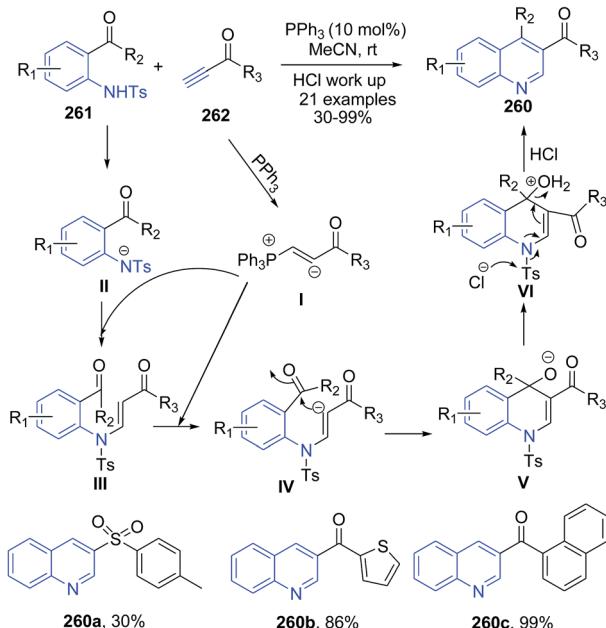


Scheme 98 NBS catalyzed synthesis of polycyclic indolo[2,3-*b*]quinolines 256; some representative examples are shown.

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

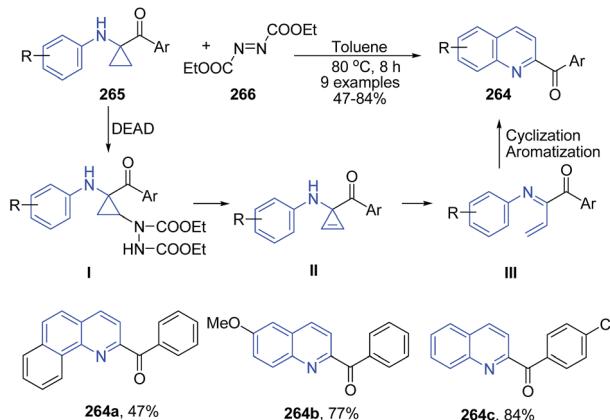


Scheme 99 TMSCl-mediated synthesis of quinolines 258 from 3-formyl chromones 259; some representative examples are shown.



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

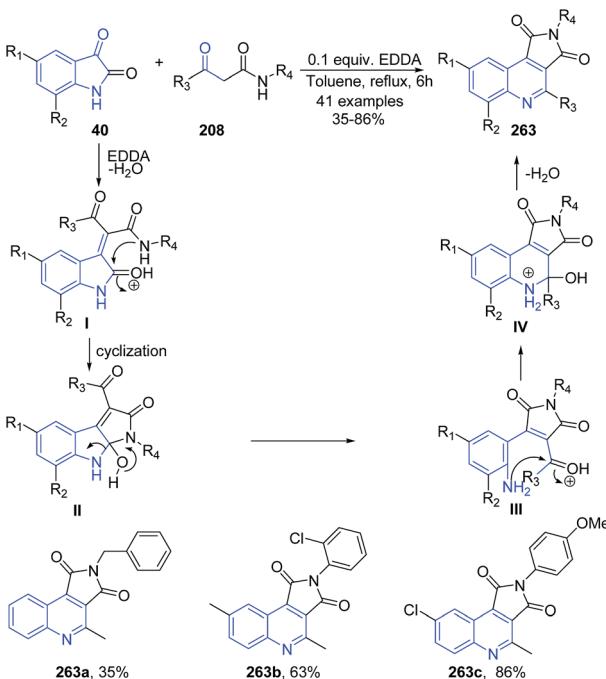
of the β -ketoamide group followed by proton transfer to form intermediate II. Ring opening of intermediate II followed by proton transfer gives the free aromatic amine III. Subsequently, the NH₂ group of III attacks a carbonyl group by intramolecular cyclization to form intermediate IV, which on elimination of



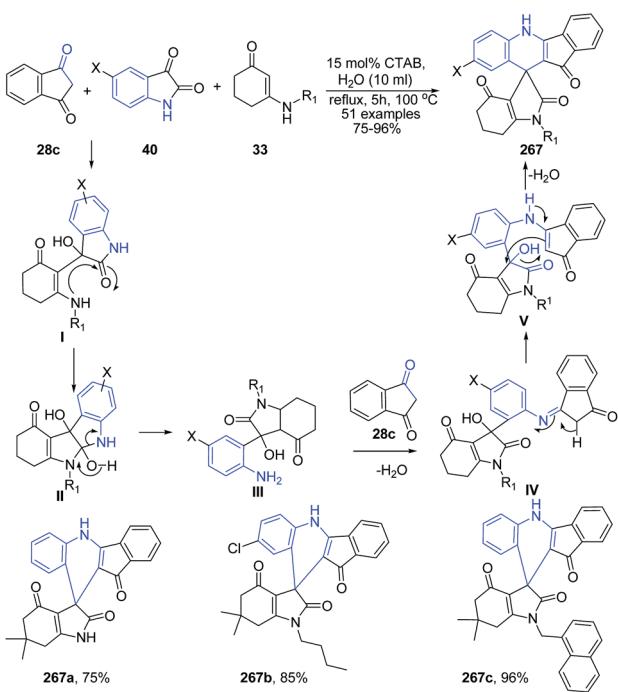
Scheme 102 Catalyst free synthesis of 2-benzoyl quinolines 264 from 1,1-cyclopropane aminoketones 265; some representative examples are shown.

water and deprotonation results in formation of 263 (Scheme 101).

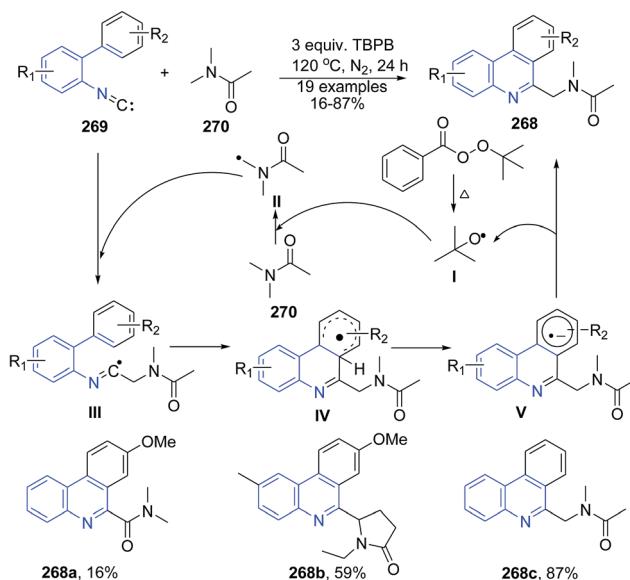
1,1-Cyclopropane aminoketones 265 on reaction with diethyl azodicarboxylate 266 (DEAD, 2.0 equiv.) in toluene at 80 °C for 8 h produced 2-benzoyl quinolines 264 *via* oxidation, ring-opening and cyclization.¹⁷³ The reaction is proposed to proceed *via* a cascade procedure. 1,1-Cyclopropane aminoketone 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/H₂O 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 (TBPPB) 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 and 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.

Acknowledgements

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