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Advances in the syntheses of quinoline and quinoline-annulated ring systems

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Abstract- Quinoline is a heterocyclic scaffold of paramount importance to human race. The utility of quinoline derivatives in the areas of medicine, food, catalyst, dye, materials, refineries and electronics is well established. As a result, the synthesis of quinoline core and its derivatives have been an attractive goal for the synthetic organic chemist. In the recent past there have been several new developments in the chemistry associated with quinolines. In pursuit to develop easy and practical approaches to a variety of quinoline derivatives decorated with useful pharmacophores different research workers have made use of new catalysts, medium or physical conditions in several well established synthetic methodologies. Besides an array of new and innovative strategies from novel substrates have been developed which has rendered the synthesis of quinoline core a much simpler process as compared earlier. An assimilation of the literature related to the advances in the syntheses of quinolines and quinoline-annulated ring systems since 2005 is being presented here.

Contents

1.0 **Introduction**

Quinoline is a heterocyclic scaffold of paramount importance to human race. Several quinoline derivatives isolated from natural resources or prepared synthetically are significant with respect to medicinal chemistry and biomedical use. Indeed quinoline derivatives are some of the oldest compounds which have been utilized for the treatment of a variety of diseases. The bark of Cinchona plant (also known as Jesuit's or Cardinal's bark) containing quinine was utilized to treat palpitations, [1] fevers and tertians since more than 200 years ago. Quinidine, a diastereoisomer of quinine was in the early 20th century acknowledged as the most potent of the antiarrhythmic compounds isolated from the Cinchona plant. [2] Compounds containing quinoline motif are most widely used as antimalarials, [3] antibacterials, [4] antifungals [5] and anticancer agents. [6] Additionally, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids, rubber chemicals and flavoring agents. [7] They are also used as polymers, catalysts, corrosion inhibitors, preservatives, and as solvent for resins and terpenes. Furthermore, these compounds find applications in chemistry of transition-metal catalyst for uniform polymerization and luminescence chemistry. [8] Quinoline derivatives also act as antifoaming agent in refineries. [9] Owing to such significance, the synthesis of substituted quinolines has been a subject of great focus in organic chemistry. The first formal synthesis was reported by Skraup over a century ago. [10] It involved treatment of aniline with acrolein under heated sulfuric acid but later several variations to the original Skraup synthesis have been reported. [11] Alternatively, several new methods were unfolded which eventually became conventional for synthesizing the structural core of quinoline. These are (a) *Combes synthesis* using anilines and β-diketones; (b) *Conrad-Limpach synthesis* employing anilines and β-ketoesters; (c) *Doebner-Miller reaction* involving anilines and α,β-unsaturated carbonyl compounds; (d) *Friedlander synthesis* using 2-aminobenzaldehyde and acetaldehyde; (e) *Povarov reaction* which involves reaction of an aniline, a benzaldehyde and an activated alkene also known as Aza-Diels-Alder reaction; (f) *Camps quinoline synthesis* utilizing an 2-acylaminoacetophenone and hydroxide ion and (g) *Niementowski quinoline synthesis*

which is the reaction of anthranilic acids and ketones (or aldehydes) to form γ-hydroxyquinoline derivatives.

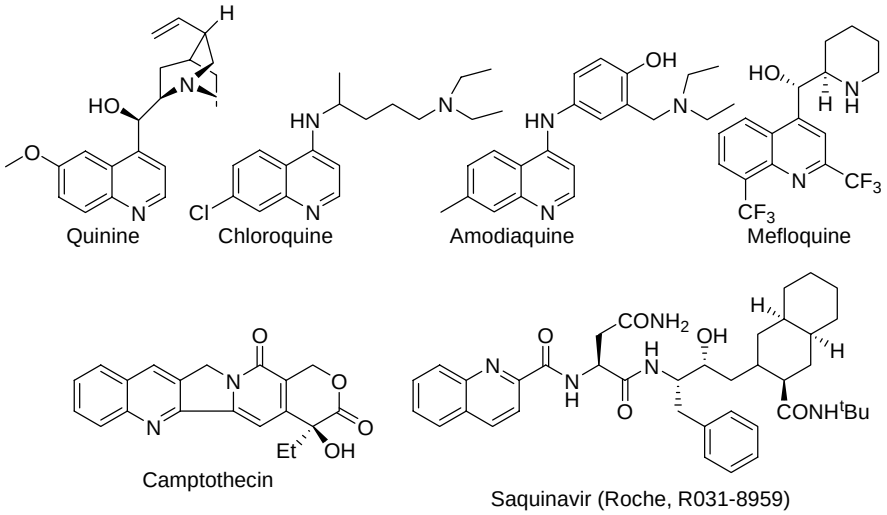


Fig. 1 A few quinoline derivatives in clinical use

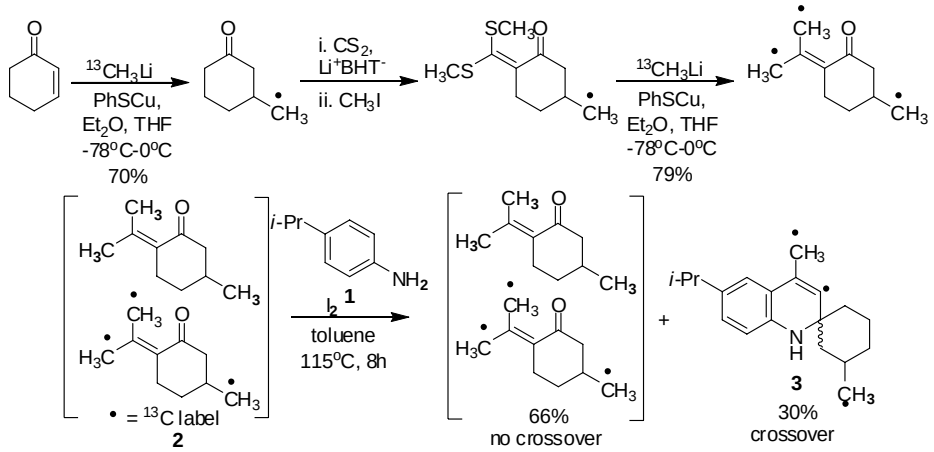
Although there has been tremendous development for obtaining several quinoline derivatives, different synthetic routes have been highlighted to suffer from various problems *viz*. (1) harsh conditions, [12] (2) multistep, [13] and (3) a large amount of promoters such as a base, [14] expensive and/or harmful metals, [15] the oxidants for the aromatization, [16] and other additives. [17] Kouznetsov *et al.* reviewed some of the recent progress made in the synthesis of quinolines in 2005. [18] They rightly mentioned that there are conceptually only two approaches towards the construction of quinoline. The first one relates to the use of the aromatic primary amine as the nucleophilic component providing nitrogen as the C-C-N unit whereas the second one employs the ortho-substituted anilines as the C-C-C-N unit. Strikingly, since 2005 there has been unusual increment in the number of publications describing the construction of quinolines decorated with a variety of functional groups at different positions. Although the basic two approaches described by Kouznetsov are universally relevant, the advancement generally concerns with the use of new catalysts, medium or physical conditions for already known reactions. As a result it was deemed suitable to make an effort to assimilate the literature pertaining to the synthesis of quinoline derivatives. The literature for the present review was obtained from the Sci-finder search using the keyword "Quinoline" from the period 2005-2007. In addition, other web resources available to us were also utilized to conduct searches related to the synthesis of quinoline derivatives.

The scope of this review article is limited to the references describing the synthesis of quinoline core including dihydroquinolines and quinoline annulated ring system. The referral to the bioactivity if described in the original report has been included herein. However no discussion has been provided for several reports describing methodologies towards quinoline synthesis which are well established and robust. For the sake of convenience we have classified all reports on the basis participating carbon skeletons for the construction of quinoline. Further subdivisions have been provided if the strategy concerns with the name reactions or certain specific reactant. Reports relating to the construction of quinoline in total synthesis of a natural product have been provided at the end of the article.

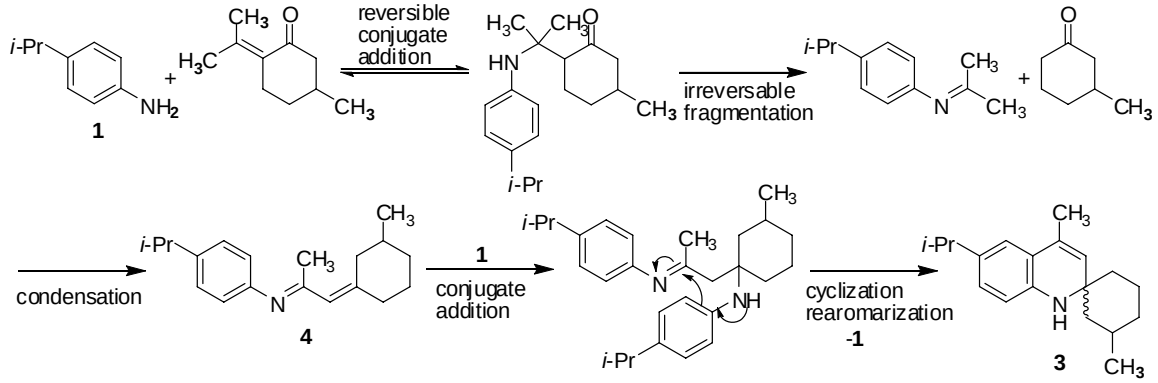
2.0 3+3 Unit approach- From N-C-C+ C-C-C Units

2.1 Skraup-Doebner-Von Miller reaction-

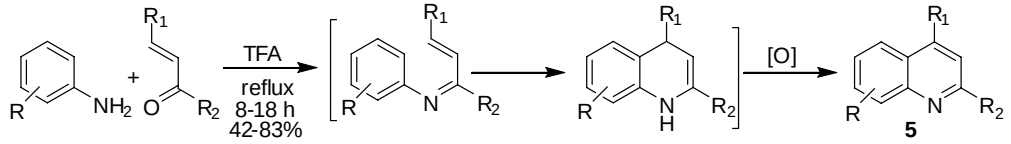
Skraup [11] and Doebner-Miller [19] synthesis of quinolines adopt similar reaction sequence which involve the reaction of aniline (C-C-N) with the α,β-unsaturated carbonyl (C-C-C) compounds. Although Yamashkin and Oreshkina have explicity discussed the progress for these two methods of quinoline synthesis including the traditional and modern approaches [20] recently, some of the very recent reports are only discussed here. Denmark and Venkatraman [21] studied the formation of substituted quinolines **(3)** (Skraup-Doebner-Von Miller) from anilines and α,β-unsaturated ketones mechanistically by the use of ^{13}C-labeled ketones in cross-over experiment (scheme 1). On the basis of their studies Skraup quinoline synthesis was proposed to involve a fragmentation-recombination mechanism. The aniline moiety **(1)** condenses with the α,β-unsaturated ketones **(2)** initially in a conjugate fashion, followed by a fragmentation to the corresponding imine and the ketone itself. These fragments reunite to form an anil **(4)** which furnishes the quinoline **(3)** by conjugate addition of a second molecule of aniline **(1)** followed by cyclization (scheme 2). Later Chen and co-workers [22] discovered a reversal of the standard regiochemistry of the Skraup-Doebner-Von Miller quinoline synthesis when anilines were condensed with γ-aryl-β,γ-unsaturated α-ketoesters in refluxing TFA. These workers postulated that the reaction involve 1,2-addition of anilines to γ-aryl-β,γ-unsaturated α-ketoesters to form Schiff's base followed by cyclization and oxidation to yield the final product **(5)** (scheme 3).



Scheme 1



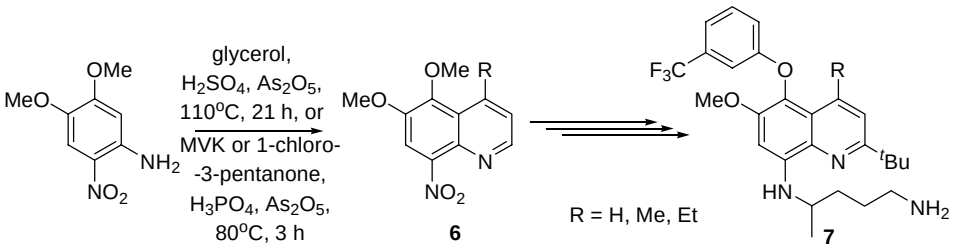
Scheme 2



R = H, Cl, F, OH, Me, OMe, NO_2; R^1 = C_6H_5, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4
R^2 = CO_2Me, CO_2Et; R^3 = C_6H_5, 4-Cl-C_6H_4, 4-Me-C_6H_4, 4-OMe-C_6H_4

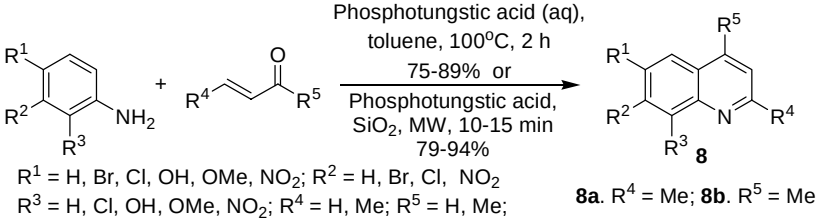
Scheme 3

Jain and co-workers [23] reported the synthesis of 4-alkyl-5,6-dimethoxy-8-nitro quinoline **(6)** from 4,5-dimethoxy-2-nitroaniline in the presence of As_2O_5. Resulting nitroquinolines were transformed to N^8-(4-amino-1-methylbutyl)-4-alkyl-2-tert-butyl-6-methoxy-5-(3-trifluoromethylphenoxy)-8-quinolinamines **(7)** (scheme 4). These 8-quinolinamine analogs exhibited promising antimalarial, antileishmanial, and antimicrobial activities.

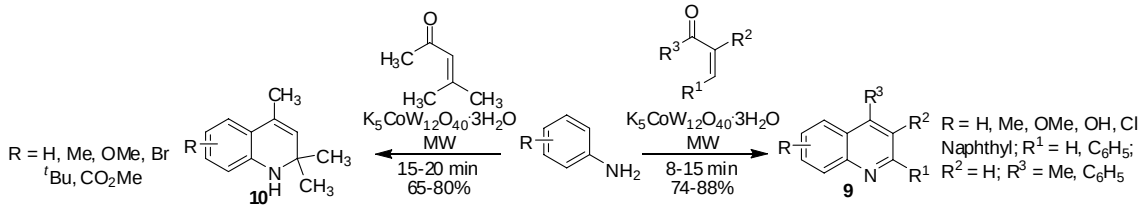


Scheme 4

Phosphotungstic acid was demonstrated to be a new catalyst for the Doebner-Miller quinaldine **(8a)** and lepidine **(8b)** synthesis by Perumal and co-workers. [24] Reactions of aromatic amines with α,β-unsaturated carbonyl compounds via Michael addition, cyclization and aromatization by conventional heating or microwave irradiation were described to afford the corresponding quinolines **(8)** in high yields as shown in scheme 5. Bose and Kumar [25] were also able to successfully achieve the microwave-assisted synthesis of quinoline **(9)** and dihydroquinoline **(10)** derivative under solvent free condition via Skraup synthesis. They demonstrated that 25 mol% of $K_5CoW_{12}O_{40}$ (PDTC) was effective for one-pot reaction of aniline with alkyl vinyl ketones as shown in scheme 6. This reagent was also demonstrated to be an effective catalyst for the Friedlander synthesis.



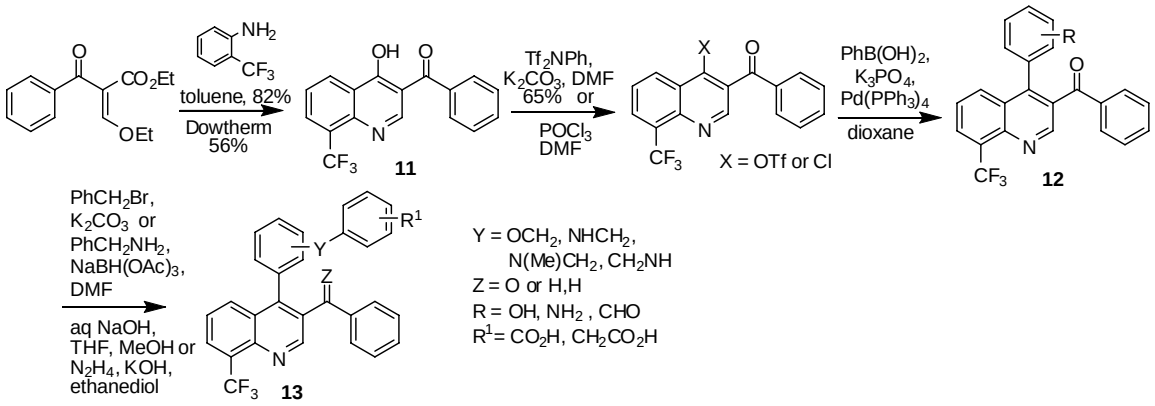
Scheme 5



Scheme 6

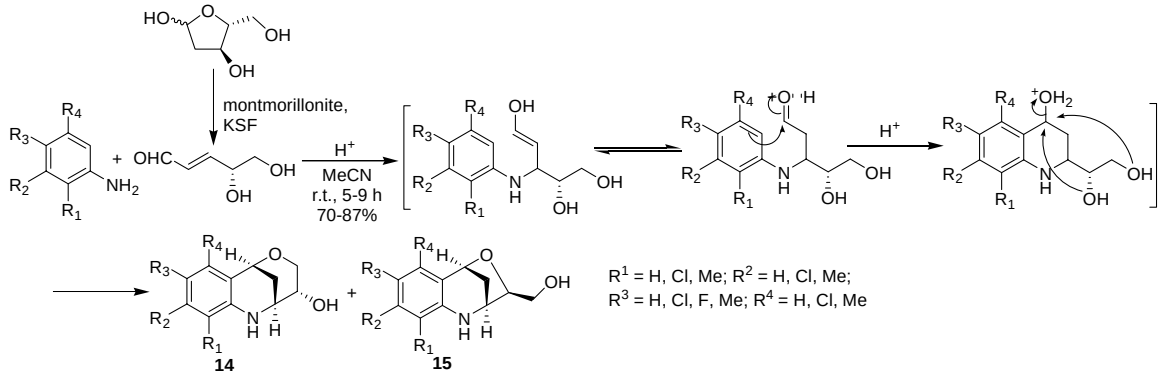
Quinolines carrying phenyl acetic acid as substitution at 4-position were generated from 2-benzoyl-3-ethoxyacrylate by Hu and co-workers. [26] Treatment of 2-benzoyl-3-ethoxyacrylate with 2-trifluoromethyl aniline followed by cyclization afforded the 3-benzoyl-4-hydroxyquinoline **(11)**, which on treatment with Tf_2NPh or $POCl_3$ gave the

corresponding triflate or chloride. The resulting triflates or chlorides were reacted with phenyl boronic acid in the presence of Pd-catalyst to furnish the 4-phenyl quinolines **(12)**. On alkylation with benzylbromide or reductive amination with benzaldehydes followed by hydrolysis, product **12** resulted in the carboxylic acids **13**. The reduction of benzoyl carbonyl was achieved with hydrazine (scheme 7). A few of the analogs were discovered to be potent liver X receptor (member of the nuclear hormone receptor super family which are involved in the regulation of cholesterol and lipid metabolism) agonists useful for the treatment of atherosclerosis.



Scheme 7

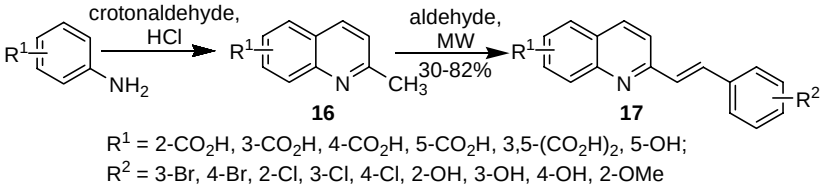
Yadav *et al*. [27] reported the synthesis of sugar-derived chiral tetrahydroquinolines **(14 & 15)** in high yields with moderate diastereoselectivity from the reaction of arylamines with 2-deoxy-*D*-ribose in the presence montmorillonite KSF clay in MeCN at ambient temperature (scheme 8).



Scheme 8

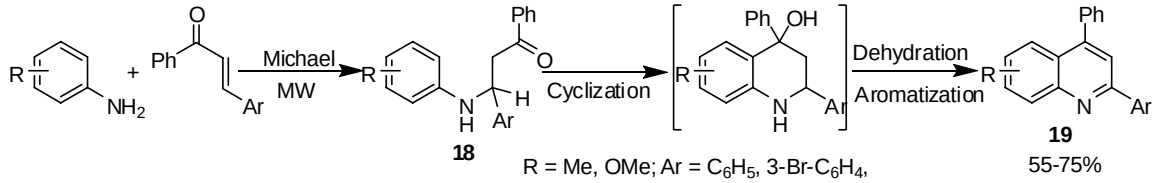
Polanski and co-workers [28] carried out the synthesis of styryl quinolines **(17)** via condensation of anilines with crotonaldehyde in the presence of HCl, followed by

microwave irradiation of the resulting quinaldine **(16)** with aldehydes (scheme 9). Some of the synthesized compounds exhibited the photosynthesis inhibiting activity.



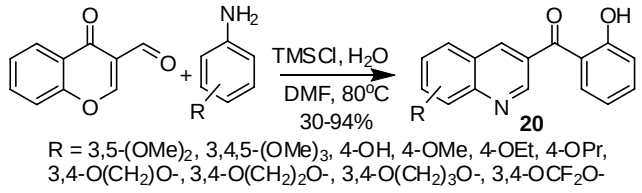
Scheme 9

Goswami and co-workers [29] reported one-pot catalyst-free synthesis of functionalized quinolines **(19)** by microwave assisted reaction. Indeed the synthesis of quinoline carried out by these workers was in order to provide support for the formation of 1,8-naphthyridines prepared under identical conditions. Though they claimed that such quinoline synthesis had precedence, their methodology involved irradiation of aniline and β-aryl vinyl ketone to produce a Michael adduct **(18)** by subsequent cyclization and aromatization (scheme 10).



Scheme 10

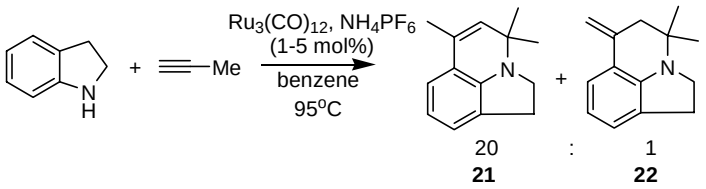
Volochnyuk *et al.* [30] demonstrated that the reaction of 3-formylchromone with electron rich anilines in the presence of TMSCl ensued the corresponding quinolines **(20)** in good yields (scheme 11).



Scheme 11

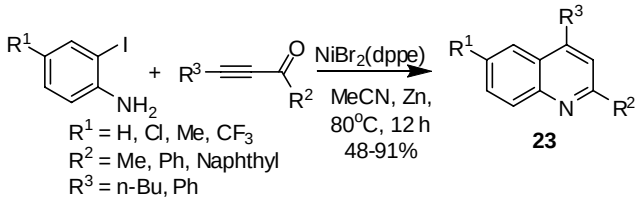
2.2 From Alkynes-

Yi *et al.* [31] developed an efficient C-H bond activation/hydroamination strategy for the synthesis of tricyclic quinoline derivatives. Coupling reaction of indoline with excess of alkyne (10-20 eq) in the presence of $Ru_3(CO)_{12}/NH_4PF_6$ in benzene at 95°C, afforded the tricyclic quinolines **(21 & 22)** in excellent yields as shown in scheme 12.



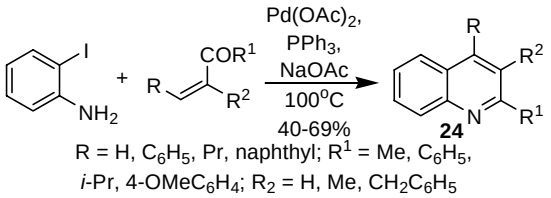
Scheme 12

Korivi and Cheng [32] developed an efficient and convenient Ni-catalyzed cyclization of 2-iodoanilines with alkynyl aryl ketones to give 2,4-disubstituted quinolines **(23)** (scheme 13). They proposed that the reaction proceeded via formation of 2-amino chalcone on the basis of the regiochemistry of the product isolated.



Scheme 13

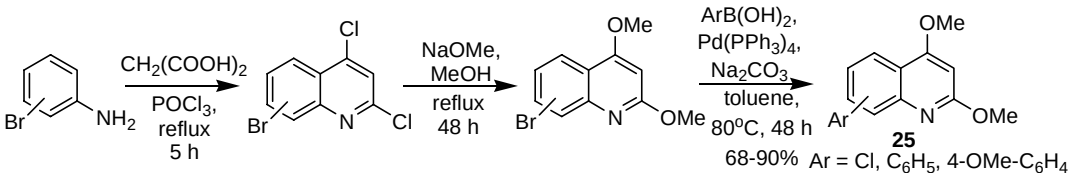
Recently a Pd-catalyzed approach to quinolines from 2-iodoanilines was also described by Cho and Kim. [33] The reaction of 2-iodoaniline with α,β-unsaturated carbonyl compounds catalyzed by $Pd(OAc)_2$, and NaOAc in DMF afforded the substituted quinolines **(24)** via Heck coupling and subsequent cyclization as depicted in scheme 14.



Scheme 14

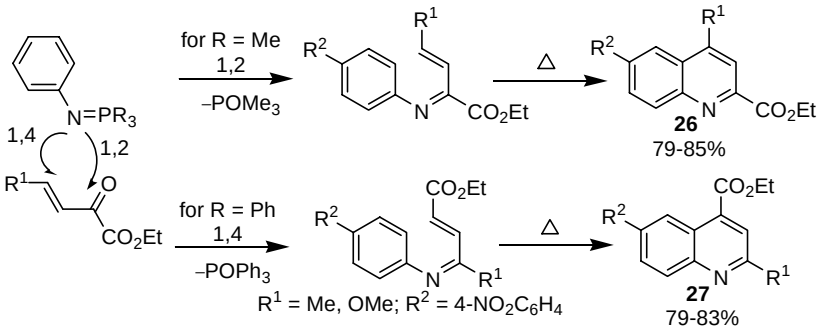
2.3 Other 3+ 3 cyclizations-

Besides, there have been other strategies too where the synthesis of quinolines were achieved utilizing C-C-N and C-C-C units. Jones and co-workers [34] obtained aryl substituted 2,4-dimethoxyquinolines **(25)** by reacting bromoanilines with malonic acid in the presence of $POCl_3$ followed by treatment with NaOMe and finally performing the Suzuki-coupling as shown in scheme 15. A few analogs were discovered to show promising activity against drug sensitive and drug resistant strains of an important nematode target.



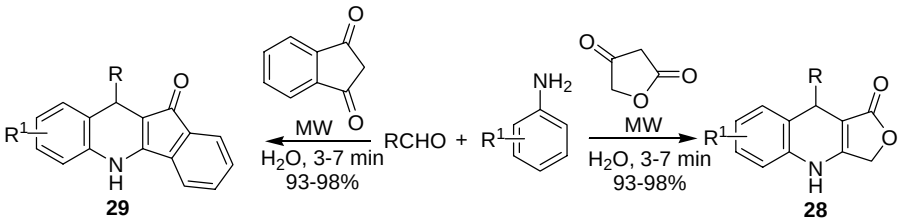
Scheme 15

A selective 1,4-addition of *N*-aryl phosphazenes, derived from PPh_3 to α,β-unsaturated carbonyl compounds to furnish 2-quinolinecarboxylates **(26)** was reported by Polacios *et al.* [35] However when a more reactive phosphazene species derived from PMe_3 was employed, it resulted in a 1,2-addition with their carbonyl carbon to provide *N*-aryl-1-azadienes which upon thermal 6-π electrocyclization afforded 4-quinoline carboxylate **(27)** as per the scheme 16.



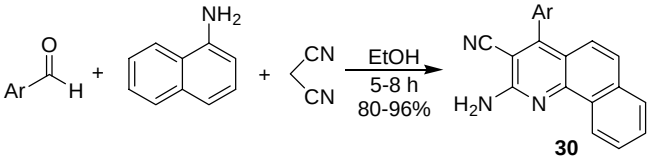
Scheme 16

Tu *et al.* [36] have reported the synthesis of 4-aza-podophyllotoxin via a three component reaction of an aldehyde, aniline and cyclic diones in H_2O under microwave irradiation. Use of tetronic acid as the cyclic diketone provided the 4-aza-podophyllotoxin derivatives **(28)** (scheme 17). The reaction proceeded via attack of Schiff's base, formed through the condensation between aldehyde and aniline, on tetronic acid resulting into an intermediate which underwent intramolecular cyclization and dehydration to yield the product. The scope of the strategy was enhanced by replacing tetronic acid with 1,3-indanedione to generate indenoquinoline derivatives **(29)**.



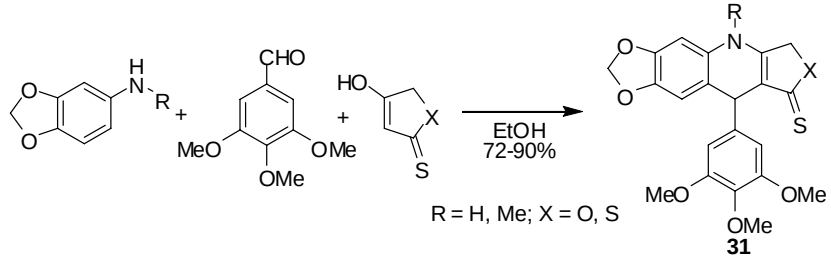
Scheme 17

More recently Tu and co-workers [37] described another multicomponent reaction wherein a series of 2-amino-4-aryl benzo[*g*]quinolin-3-carbonitrile derivatives **(30)** were synthesized via one-pot condensation of arylaldehyde, a naphthylamine and malononitrile in EtOH without catalyst (scheme 18).



Scheme 18

In contrast to Tu *et al*., [36] Labruere *et al.* [38] utilized the thio- and dithio-analogues of tetronic acid in their three component coupling reaction in EtOH in the absence of a catalyst to afford good yields of thio analogs **(31)** of 2,3-dihydropodophillotoxin as shown in scheme 19.



Scheme 19

3.0 4+2 Unit approach

3.1 From N-C-C-C+ C-C Units-

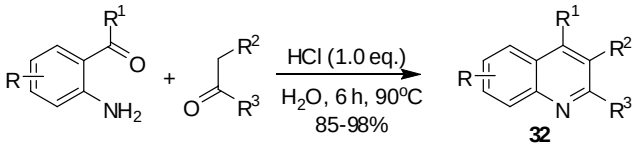
3.1.1 Friedlander Synthesis-

Friedlander synthesis for quinoline was originally described by Friedlander in 1882 and has been accepted to be one of the most convenient routes to this scaffold. [39] The reaction advances by the condensation of α-amino carbonyl compound (N-C-C-C unit) with a derivative having α-methylene group with respect to the carbonyl (C-C unit), in the presence of a suitable catalyst. During last couple of years there has been spurt in the number of publications describing the successful accomplishment of Friedlander reaction. This was achieved by making changes in the catalyst or reaction medium or physical parameters though the starting substrates were conceptually similar in these endeavors. These advances have been discussed in this particular section. The section has been

subdivided into different classes based on the catalyst employed to effect the Friedlander reaction.

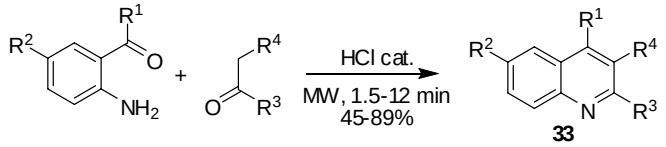
3.1.1.1 Acid-catalyzed Friedlander reaction-

Wang *et al.* [40] described an environmentally friendly and highly efficient procedure for the synthesis of substituted quinolines **(32)** by a simple Friedlander reaction of 2-aminoarylketone or 2-aminoarylaldehyde with carbonyl compounds in the presence of HCl utilizing H_2O as the solvent as delineated in scheme 20. Subsequently Asis and co-workers [41] also demonstrated the successful use of HCl as catalyst for similar reaction under microwave for quinoline synthesis **(33)**. Unlike the conventional heating under which the reaction took 6 h to go to completion, the use of microwave speeded up the reaction to be complete within 1.5 to 12 min (scheme 21).



R = H, 2,4-$(Br)_2$; R^1 = H, Me, 4-F-C_6H_4; R^2 = CO_2Et, COMe;
R^3 = Me, *n*-Pr; R^2 & R^3 = -$(CH_2)_2$-, -$(CH_2)_3$-, -$CO(CH_2)_2$-, -$COCH_2CMe_2CH_2$-

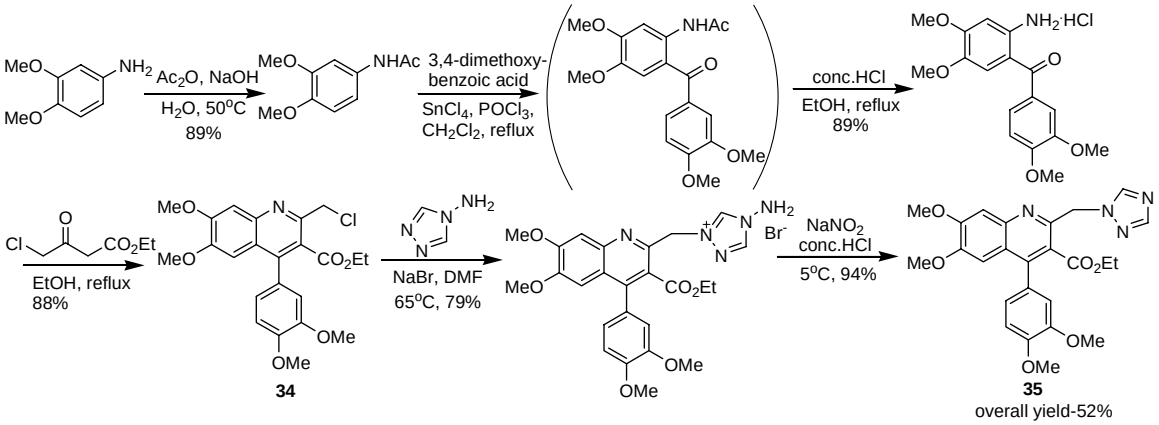
Scheme 20



R^1 = CH_3, C_6H_5; R^2 = H, Cl, NO_2; R^3 = Me, CH_2Cl, C_6H_5
R^4 = H, Me, COMe, CO_2Me, CO_2Et; R^3, R^4 = -$(CH_2)_4$-, -$(CH_2)_5$-

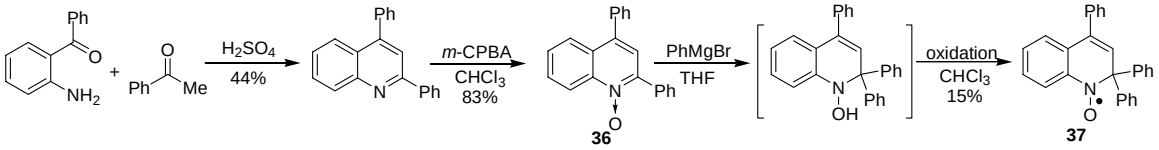
Scheme 21

Mizuno *et al.* [42] reported a convenient synthesis of the quinoline base of the antirheumatic drug TAK-603 **(35)** utilizing the Friedlander reaction as the key step as delineated in scheme 22. The hydrochloride salt form of the amino derivative provided sufficient acidity to act as catalyst in the reaction to afford the desired quinoline unit **(34)**. Subsequently they developed a convenient and efficient method for the generation of different metabolites of TAK-603 **(35)** in high yields. [43] Here too the Friedlander condensation was one of the key reactions although the required amino derivative for the reaction was generated in a slightly different fashion.



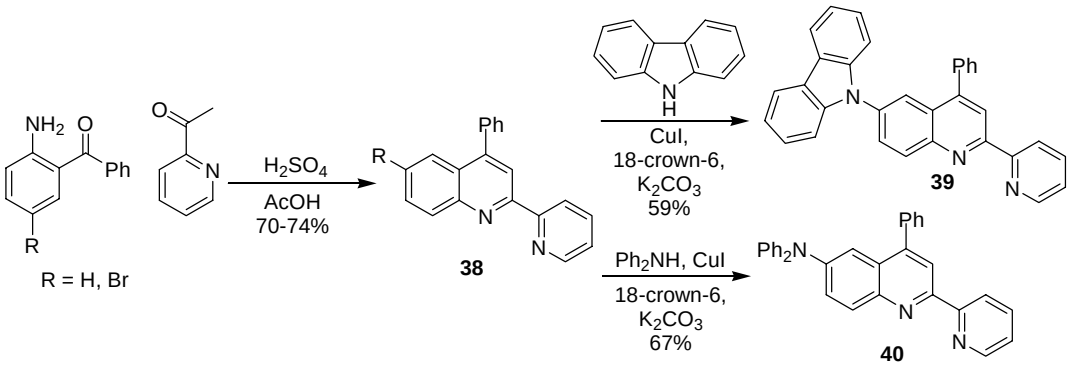
Scheme 22

Yoshioka and co-workers successfully accomplished the synthesis of 2,2,4-triphenyl-1, 2-dihydroquinoline-*N*-oxyl **(37)** from the *N*-oxide product of the quinoline **(36)** which was in turn obtained via Friedlander annulation in the presence of H_2SO_4 as shown in scheme 23. [44] These stable oxyl quinolines **(37)** were prepared with the intent to study their magnetic properties.



Scheme 23

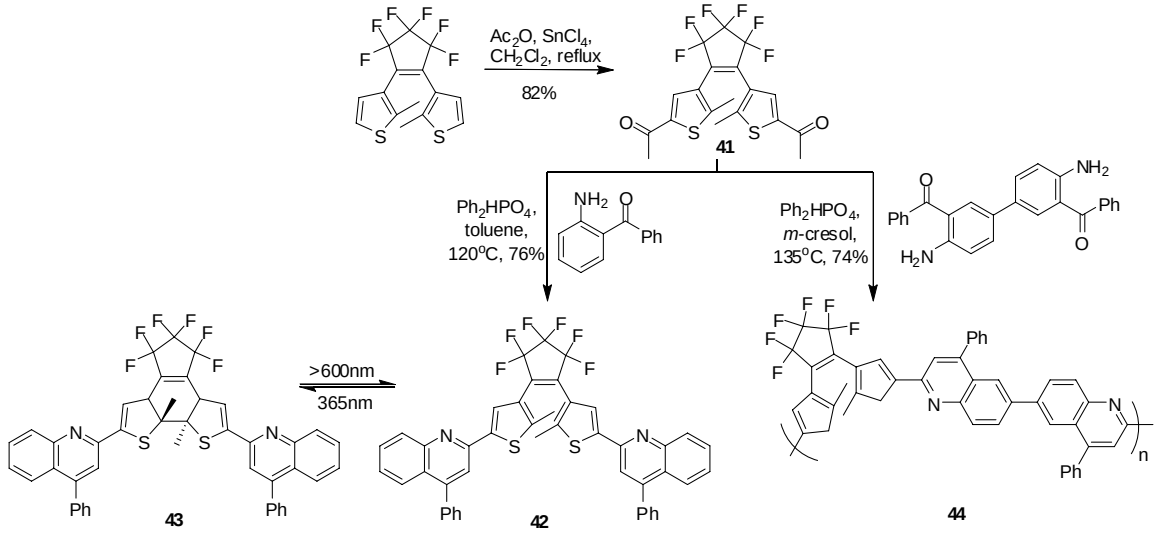
H_2SO_4-promoted Friedlander reaction of picoline with 5-bromo-2-amino benzophenone was also utilized by Cheng and co-workers [45] for the preparation of 6-bromo-4-phenyl-2-pyridin-2-yl-quinoline **(38)** which served as precursor for the synthesis of bidentate ligands **39,** and **40** via Ullmann reaction (scheme 24).



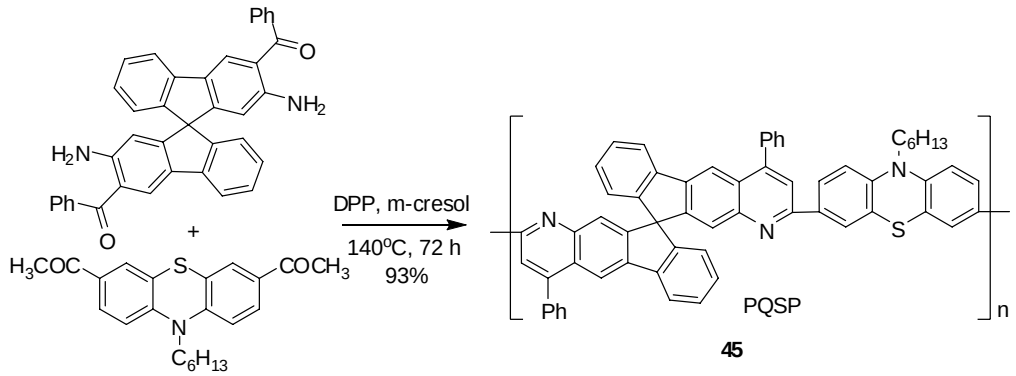
Scheme 24

Choi *et al.* [46] carried out the synthesis of a series of compounds bearing a phenylquinoline unit via the Friedlander annulation and studied their photophysical and

electric transport properties. The synthesis commenced with the preparation of diacetyl monomer **(41)** by the reaction of 1,2-bis-(2-methyl-3-thienyl) perfluoro cyclopentene with Ac_2O in the presence of $SnCl_4$. The resulting diacetyl monomer **(41)** upon heating at reflux temperature with 2-amino benzophenone in toluene in the presence of DPP generated the quinolinyl derivative **(42)**, whereas the reaction between diacetyl monomer and 3,3-dibenzoyl benzidine yielded 74% of the polymer **(44)** which was transformed to closed dyad **43** in UV light (λ = 365 nm) in CH_2Cl_2 (scheme 25). The synthesis of poly quinolines containing spiro bifluorene and phenathiazine units with excellent electroluminescence properties was achieved via Friedlander annulation by Liu *et al.* [47] As shown in the Scheme 26 bis (2-amino ketone) reacted with 2, 7-diacetyl-10-*n*-hexyl phenothiazine in an acidic medium comprising of DPP and *m*-cresol at 140°C for 3 d to afford the PQSP **(45)** in excellent yield.

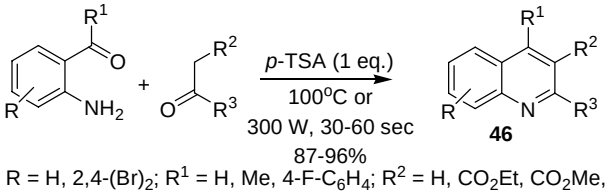


Scheme 25



Scheme 26

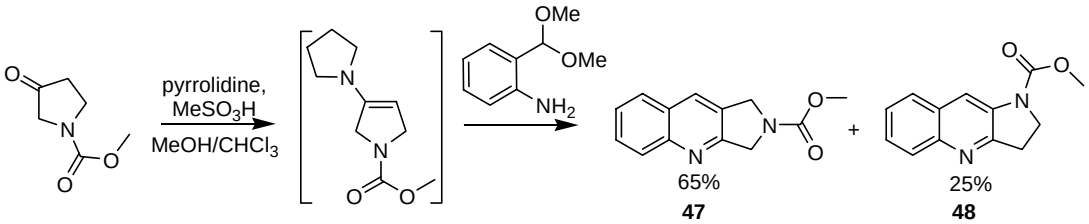
Wang *et al.* [48] utilized *p*-TSA as the catalyst to demonstrate the synthesis of quinoline derivatives **(46)** under solvent less condition. They carried out their reaction both under microwave and conventional heating. Although yields of the products were excellent under both conditions, the reaction accomplished in the influence of microwave was reported to be completed a few seconds only (scheme 27).



R = H, 2,4-$(Br)_2$; R^1 = H, Me, 4-F-C_6H_4; R^2 = H, CO_2Et, CO_2Me, COMe;
R^3 = Me, cy-Pr, i-Pr, C_6H_5, 4-Cl-C_6H_4; R^2 & R^3 = -$(CH_2)_3$-,
-$(CH_2)_4$-, -$CO(CH_2)_3$-, -$COCH_2CMe_2CH_2$-,

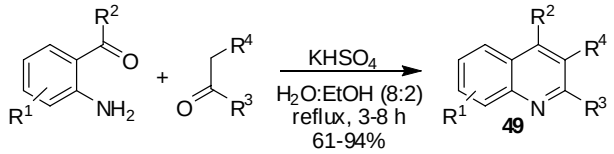
Scheme 27

Akue-Gedu *et al.* [49] described the synthesis of 1,3-dihydro-2*H*-pyrrolo[3,4-*b*]quinolin-2-carboxylate **(47)** and methyl 2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinoline-1-carboxylate **(48)** from the reaction of 3-oxo-pyrrolidine-1-carboxylic acid methyl ester with pyrrolidine, and 2-dimethoxymethyl-phenylamine in the presence of $MeSO_3H$ in MeOH or $CHCl_3$ in good yield (scheme 28).



Scheme 28

Perumal and co-workers [50] reported the reaction of 2-amino substituted aromatic ketones with α-methylene containing ketones in the presence of $KHSO_4$ in aqueous EtOH under heating at reflux to furnish 2,3,4-substituted quinolines **(49)** as shown in scheme 29.

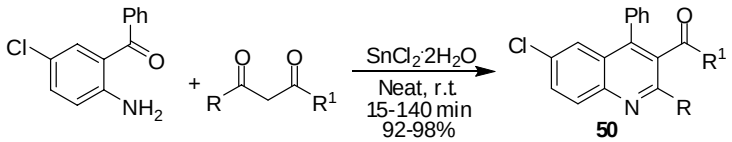


R^1 = H, 5-Cl; R^2 = Me, C_6H_5; R^3 = Me; R^4 = COMe, CO_2Et, CO_2CHMe_2;
R^3 & R^4 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$(CH_2)_5$-, -$(CH_2)_6$-, -$COCH_2CMe_2CH_2$-,

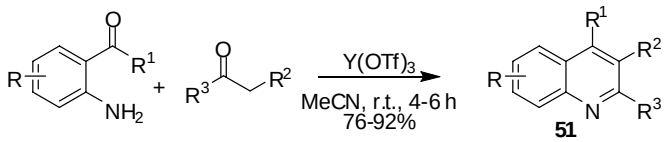
Scheme 29

3.1.1.2 Lewis acid-catalyzed Friedlander reaction-

In the recent times several Lewis-acids have been successfully employed for performing the Friedlander reaction. $SnCl_2 \cdot 2H_2O$ served as a suitable catalyst to initiate the reaction between the 2-aminoarylketones with different carbonyl compounds at room temperature yielding the corresponding 2,3,4-substituted quinolines **(50)** (scheme 30). [49] Use of cyclic ketones under the same reaction gave the tricyclic quinolines. This protocol was feasible only when both the substrates are solid and renders excellent yields. Similar quinolines **(51)** were generated in good yields by De and Gibbs by performing the reaction in the presence of $Y(OTf)_3$ at room temperature in MeCN for 4-6 h (scheme 31). [52] Wu and co-workers [53] generated identical quinolines **(52 & 53)** from similar starting substrates by carrying out reactions in the presence of $FeCl_3$ or $Mg(ClO_4)_2$. Strikingly, in the presence of $FeCl_3$ and EtOH the reaction proceeded at room temperature but the use of $Mg(ClO_4)_2$ as a catalyst required the reaction to be heated at 60°C to furnish quinolines **(53)** in good yield as delineated in scheme 32. Very recently, Sandhu *et al*. [54] too reported $FeCl_3$-promoted Friedlander synthesis of quinolines **(54)** under solvent less condition (scheme 33). Bose and Kumar demonstrated that $CeCl_3 \cdot 7H_2O$ can act as a reusable catalyst during similar reactions to afford quinolines **(55)** in good to excellent yields (scheme 34). [55] Simultaneously, Varala and associates, [56] demonstrated the utility of $Nd(NO_3)_3$ as catalyst in the Friedlander condensation to acquire substituted quinolines **(56)** (scheme 35). In another variation, Tolmachev *et al.* [57] recently showed that TMSCl in DMF was also successful to furnish quinolines **(57)** in excellent yields from same starting substrates (scheme 36). Subsequently, the same group [58] reported the synthesis of ethyl 2-chloro-methyl-3-quinoline carboxylates **(58)** from the condensation of 2-aminoacetophenone and 2-aminobenzophenone with ethyl 4-chloro-3-oxobutanoate in the presence of excess TMSCl, in high yields (scheme 37). Under the same reaction conditions, 1,3-dichloroacetone and 2-chlorocyclohexanone afforded the 3-chloro-2-(chloromethyl)quinolines and 4-chloro-1,2,3,4-tetrahydro-acridines, respectively.

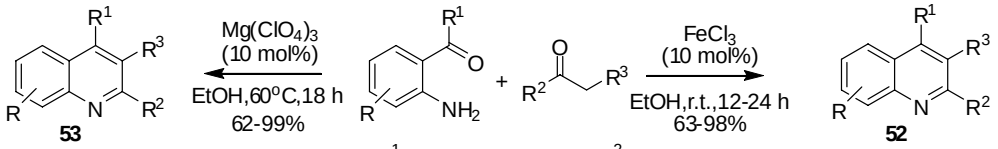


Scheme 30



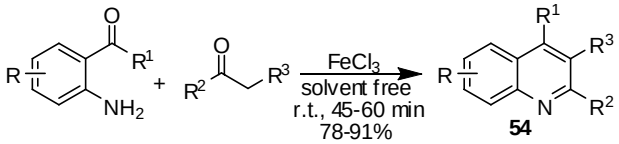
R = H, 4-Cl; R^1 = Me,C_6H_5; R^2 = CO_2Et, COMe; R^3 = Me;
R^2 & R^3 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$COCH_2CMe_2CH_2$-

Scheme **31**



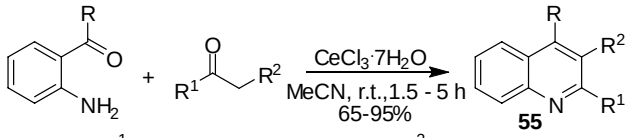
R = H, 5-Cl; R^1 = H, Me, 2-Cl-C_6H_4; R^2 = Me;
R^3 =CO_2Et, COMe; R^2 & R^3 = -$(CH_2)_3$-, -$CO(CH_2)_3$-

Scheme 32



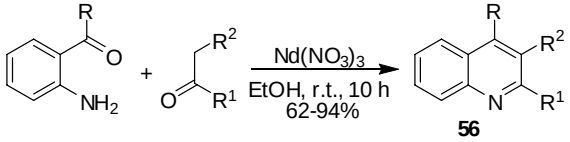
R = H, 4-Cl; R^1 = Me,C_6H_5, 2-Cl-C_6H_4; R^2 = Me; R^3 = CO_2Et,
COMe, $COCF_3$; R^2 & R^3 = -$(CH_2)_4$-, -$COCH_2CMe_2CH_2$-

Scheme **33**

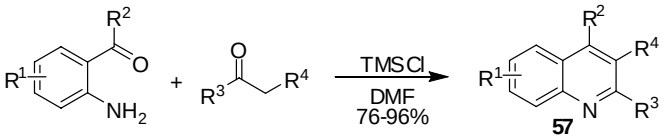


R = Me, C_6H_5; R^1 = Me, Et, $CH_2O(CH_2)_3$NPht; R^2 = Me, CO_2Et, CO_2Me, COMe
R^1 & R^2 = -$(CH_2)_6$-, -$COCH_2CMe_2CH_2$-, -$CH_2CH^tBu(CH_2)_2$-

Scheme 34

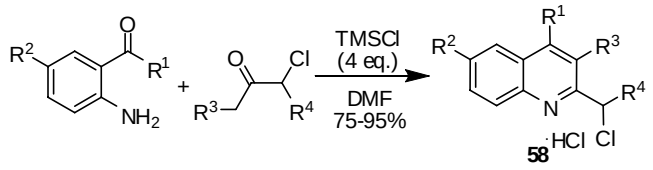


Scheme 35



R^1 = H, 4-Cl, 4-NO_2, 3,4-CH_2O_2; R^2 = Me, C_6H_5; R^3 = Me, CH_2Cl, *t*-Bu, CF_3,
CO_2Et, C_6H_5, 4-F-C_6H_4, 3-Pyridyl, 2-Thienyl, 2-Pyrrolyl, Adamantyl, 2-Furyl, 2-NH_2-C_6H_4;
R^4 = H, Me, CN, COMe, $CONH_2$, CO_2H, CO_2Et, CH_2CH_2Cl, 4-Cl-C_6H_4; R^3 & R^4 =
$(CH_2)_3$, $(CH_2)_6$, $(CH_2)_{10}$, $(CH_2)_4CHCO_2$Me, $COCH_2CMe_2CH_2$, $CH_2NBn(CH_2)_2$,

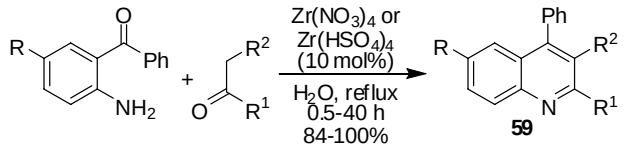
Scheme 36



58

Scheme 37

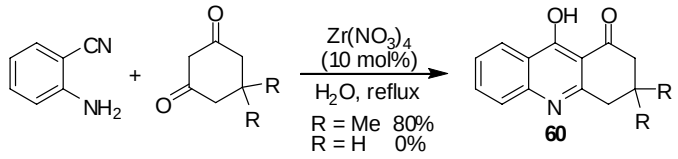
In their attempt to develop efficient environmentally benign protocol for obtaining polysubstituted quinolines, Zolfigol and co-workers [59] optimized the Friedlander annulation between 2-aminoarylketones or 2-aminobenzonitrile and ketones or β-diketones with several Lewis acids viz. $Al(HSO_4)_3$, $FeCl_3{\cdot}6H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, $Bi(NO_3)_3$, $Cr(NO_3)_3{\cdot}9H_2O$, $Ni(NO_3)_3{\cdot}6H_2O$, $Zr(NO_3)_4$ and $Zr(HSO_4)_4$. It was observed that $Zr(NO_3)_4$ and $Zr(HSO_4)_4$ in H_2O gave the desired products **(59 & 60)** in excellent yields (scheme 38). Unfortunately, the β-cyclohexanedione failed to react with 2-aminobenzonitrile under the described condition (scheme 39).



59

R = H, Cl; R^1 = Me; R^2 = COMe, COC_6H_4, CO_2Me
R^1 & R^2 = $-(CH_2)_2CO-$, $-(CH_2)_3CO-$, $-(CH_2)_4-$, $-COCH_2CMe_2CH_2-$,

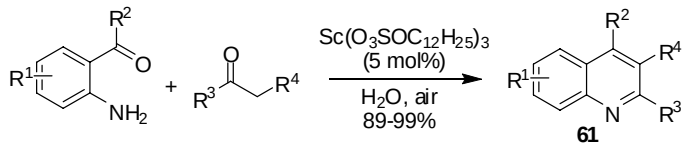
Scheme 38



60

Scheme 39

Zhang and Wu [60] recently performed successful Friedlander reaction by the use of a unique Lewis acid-surfactant-combined catalyst. Although during optimization they employed several such catalysts, the best yields of polysubstituted and polycyclic quinolines **(61)** were obtained when the condensation of 2-aminoarylketone and α-methylene ketone was carried out in the presence of $Sc(O_3SOC_{12}H_{25})_3$ in H_2O at 40°C (scheme 40).

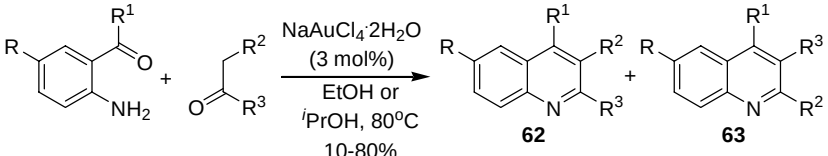


61

R^1 = H, 4-Cl; R^2 = Me, C_6H_5; R^3 = Me; R^4 = CO_2Et, CO_2Me, COMe; R^2 & R^3 = $-CO(CH_2)_3-$, $-COCH_2CMe_2CH_2-$

Scheme 40

Masciadri and co-workers [61] synthesize the substituted quinolines **(62 & 63)** via Au-catalyst promoted condensation of 2-aminoarylketones with several 1,3-diketones including β-keto-esters, β-diketones, β-keto-amides and β-keto-sulfones. When this reaction was performed with 1,1,1-trifluoro-2,4-pentanedione or 1-cyclopropyl-1,3-butanedione produced only one regioisomer. The regioselectivity with the trifluoro-derivative was rationalized on the basis of preferred hydrate formation of the carbonyl group next to the CF_3 whereas the regioselectivity of the cyclopropyl group reflected lower reactivity of the carbonyl group adjacent to the cyclopropyl residue (scheme 41).

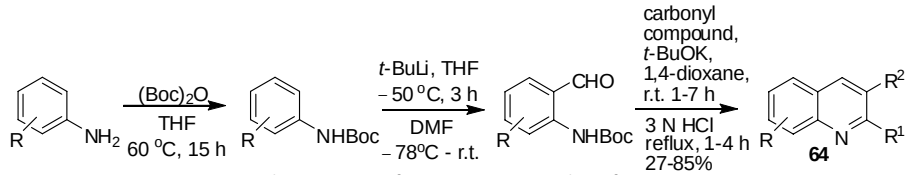


R = Br, OCF_3, R^1 = CH_2Cl, C_6H_5, R^2 = Me, Et, ^{i}Pr, ^{t}Bu, CH_2OMe; R_3 = COMe, COEt, CO_2Et, CO^{i}Pr, CO^{t}Bu, $COCF_3$, CF_3, ^{c}Pr, COC_6H_5, CONHMe, $CONMe_2$, $CONHC_6H_5$, CONH-4-Cl-C_6H_4, $COCH_2OMe$; R_2 = R_3 = $CO(CH_2)_2$, $CO(CH_2)_3$, $CO(CH_2)_4$, $CONH(CH_2)_3$,

Scheme 41

3.1.1.3 Base-catalyzed Friedlander reaction-

Chelucci *et al.* [62] reported a successful protocol for generating quinolines substituted on both pyridine and benzo-fused rings **(64)**. As represented in scheme 42 their method was based on the formylation of a substituted *N*-(Boc)aniline followed by direct cyclization and aromatization of the intermediate product obtained by condensation of the formed *N*-Boc-2-aminobenzaldehyde with an enolizable carbonyl compound in the presence of *t*-BuOK. The Boc group was finally removed with 3 N HCl to generate the substituted quinolines.

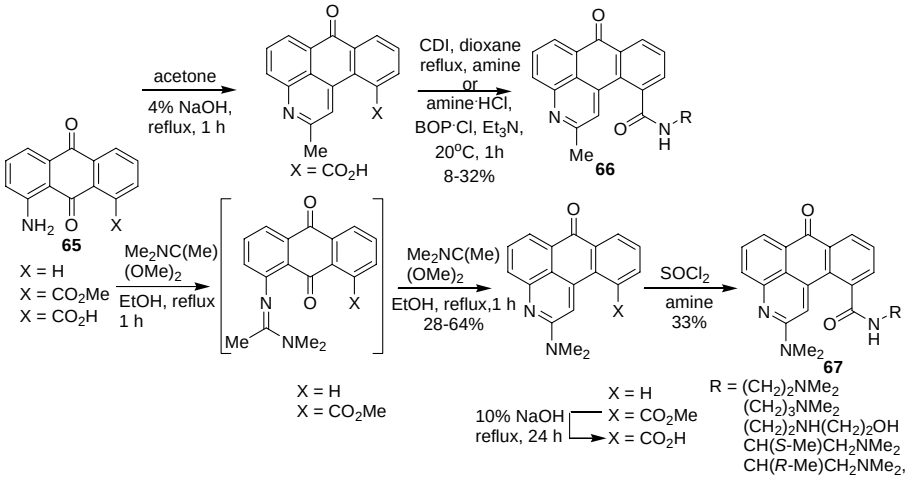


R = H, 2-F, 4-F, 3- CF_3; R^1 = H, C_6H_5; R^2 = Me, Bu; C_6H_5; R^1 & R^2 = $-(CH_2)_4-$, $-CO(CH_2)_3-$

Scheme 42

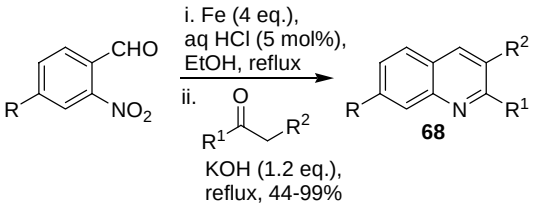
Denny and co-workers [63] demonstrated an innovative synthetic approach for the preparation of 7-oxo-7*H*-naptho[1,2,3-*de*] quinoline-11-carboxamide **(66, 67)** and

analogs using 1-amino-8-chloro anthraquinone **(65)** as the synthon for the Friedlander annulation reaction with acetone in the presence of NaOH as depicted in scheme 43.



Scheme 43

Li *et al.* [64] disclosed a highly effective one-pot Friedlander synthesis by reaction of 2-nitrobenzaldehyde with excess of Fe in aq. HCl for the *in situ* generation of 2-aminobenzaldehyde followed by reaction with aldehyde or ketone in the presence of KOH to obtain quinolines **(68)** in high yields. This procedure was demonstrated to be successful even for the aldehyde containing an active methylene group (scheme 44).

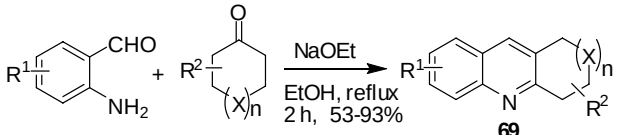


R = H, CO_2Me, NMe_2; R^1 = Me, t-Bu, C_6H_5, $(CH_2)_4CH_3$,
Cinnamyl, 2-Pyridyl, 2-Thienyl; R^2 = H, Me, OMe, $(CH_2)_4CH_3$

Scheme 44

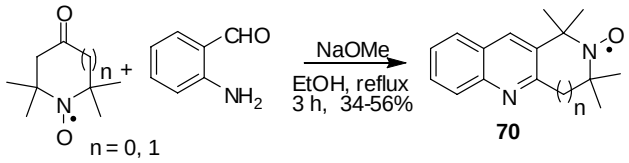
Yang and group [65] recently reported an efficient Friedlander reaction under basic conditions by treatment of substituted 2-aminobenzaldehyde with an appropriate cyclic ketone in the presence of EtONa to afford the substituted quinolines **(69)** in moderate to excellent yields (scheme 45). Similarly, MeONa-mediated reaction was reported by Hideg and his group for the synthesis of paramagnetic quinolines **(70)** in low yields as per the scheme 46. [66] They also demonstrated that the reaction of β-bromo-α,β-unsaturated aldehyde with 2-benzyloxyaniline in DMF under nitrogen atmosphere

followed by hydrogenation gave the paramagnetic 8-hydroxyquinoline derivative **(71)** (scheme 47).

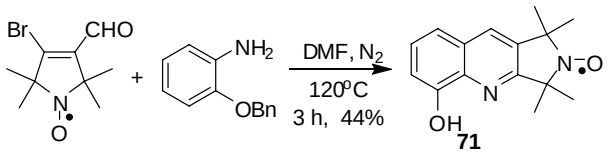


R^1 = H, OCH_2O, OMe; R^2 = H, Ar
X = O, S, NMe, $N(CH_2)_2$, NCO_2Et; n = 0, 1

Scheme 45



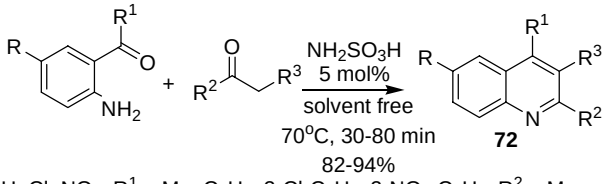
Scheme 46



Scheme 47

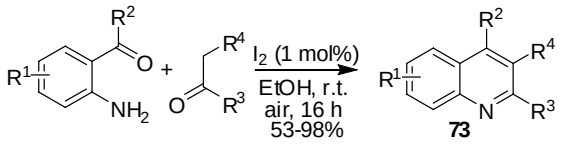
3.1.1.4 Solid catalyst-mediated Friedlander reaction-

Yadav and co-workers [67] utilized the Friedlander annulation to synthesize 4-phenyl quinolines from 2-aminoarylketones and α-methylene ketones using sulfamic acid, a recyclable solid catalyst. The reaction proceeded smoothly at 70°C under solvent free conditions to furnish quinolines **(72)** in good yields as presented in scheme 48. Wu *et al.* [68] demonstrated that identical quinolines **(73)** can also be easily generated in milder fashion via reaction of same substrates in the presence of molecular iodine (scheme 49).



R = H, Cl, NO_2; R^1 = Me, C_6H_5, 2-Cl-C_6H_4, 2-NO_2-C_6H_4; R^2 = Me, cyclopropyl;
R^3 = Me, COMe, CO_2Me, CO_2Et; R^2, R^3 = -$(CH_2)_3$, -$(CH_2)_4$-, -$(CH_2)_3$CO-

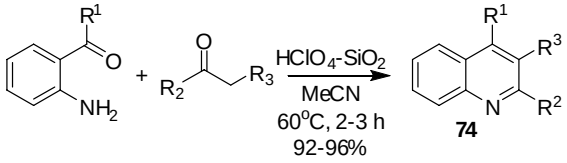
Scheme 48



R^1 = H, 4-Cl; R^2 = Me, C_6H_5, 2-Cl-C_6H_4; R^3 = Me;
R^4 = COMe, CO_2Et; R^3 & R^4 = -$(CH_2)_3$-, -$(CH_2)_3$CO-

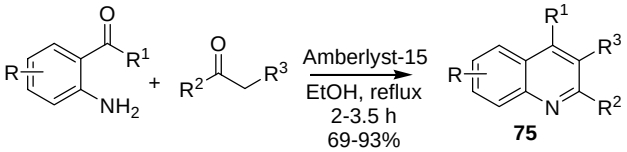
Scheme 49

Recently, Venkateswarlu and co-workers [69] performed rapid one-pot two component condensation of 2-aminoarylketone with carbonyl compound or β-keto ester using heterogeneous solid-silica-supported-$HClO_4$ as an efficient recyclizable catalyst (scheme 50). On the contrary, Das *et al.* [70] during their study with several heterogeneous catalysts observed that Amberlyst-15 gave better results **(75)** than several silica-supported-acids to affect Friedlander synthesis for the synthesis of quinolines (scheme 51).



R^1 = Me, C_6H_5, R^2 = Me; R^3 = Me, OEt, OMe, COMe, *i*-Pr
R^2 & R^3 = -$(CH_2)_3$-,-$(CH_2)_4$-,-$(CH_2)_3$CO-

Scheme 50



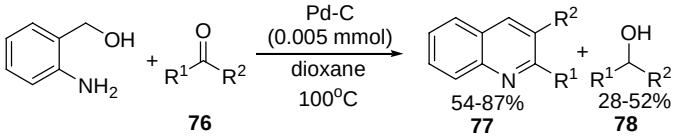
R = H, 4-Cl; R^1 = C_6H_5, 2-Cl-C_6H_4; R^2 = Me
R^3 = CO_2Et, COMe; R^2 & R^3 = -$(CH_2)_4$-

Scheme 51

3.1.1.5 Modified Friedlander reaction-

A reaction wherein the starting 2-aminobenzaldehyde is generated *in situ* from 2-aminobenzyl alcohol has been generally termed as modified Friedlander reaction in the literature. Cho and co-workers have reported several catalysts and conditions to obtain quinolines through this strategy. They discovered that Pd-C in dioxane acts as effective catalyst for the generation of 2-substituted quinolines **(77)** from the reaction of 2-aminobenzyl alcohol and aryl alkyl ketones **(76)** (scheme 52). [71] It was observed that hydrogenated ketone **(78)** as the side product was also formed during the reaction. Simultaneously they unfolded similar reaction between alcohol and aliphatic aldehyde to

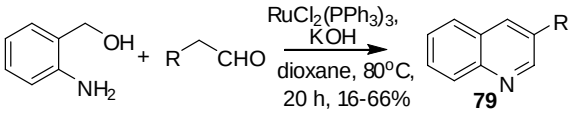
generate 3-substituted quinoline **(79)** in the presence of $RuCl_2(PPh_3)_3$, albeit in moderate yields (scheme 53). [72] Extending their study further they found that 2-aminobenzyl alcohol also reacts with ketones in the presence of Rh-catalyst along with KOH in dioxane yielding 2-substituted quinolines **(80)** through oxidative coupling reaction followed by dehydrative cyclization (scheme 54). [73] Subsequently they also demonstrated the utility of Cu-catalyst for similar reactions. [74] 2-Aminobenzyl alcohol on treatment with several ketones in dioxane in the presence of a catalytic amount of $CuCl_2$ along with KOH under O_2 atmosphere afforded the corresponding 2,3-substituted quinolines **(81)** (scheme 55). Similar reaction when carried out by adding aldehyde as a reactant in the place of ketone under inert atmosphere led to the formation of 3-substituted quinolines **(81)** (scheme 55).



76 **77** **78**

R^1 = C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 3-CF_3-C_6H_4, 4-CN-C_6H_4, 2-Thienyl, 2-Naphthyl, $(CH_2)_4CH_3$, $(CH_2)_2C_6H_5$; R^2 = H, $(CH_2)_3CH_3$,

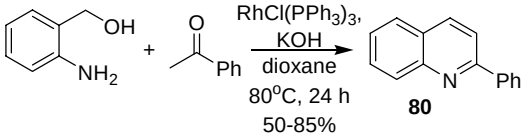
Scheme 52



79

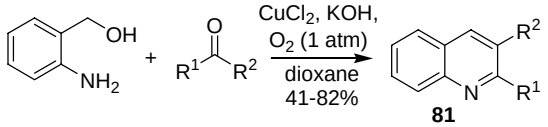
R = $(CH_2)_2CH_3$, $(CH_2)_5CH_3$, $(CH_2)_2CH_3$, $CH_2C_6H_5$, $CH(Me)C_6H_5$, ^{i}Pr, ^{t}Bu, C_6H_5

Scheme 53



80

Scheme 54



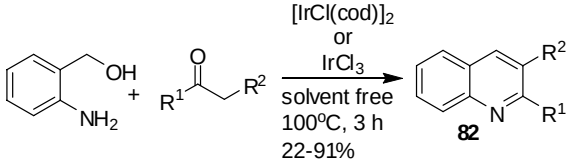
81

R^1 = C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 4-F-C_6H_4, 3-CF_3-C_6H_4, 4-CN-C_6H_4, 2-Thienyl, 2-Napthyl, $(CH_2)_4CH_3$, $(CH_2)_2C_6H_5$; R^2 = H, $(CH_2)_3CH_3$,

Scheme 55

Indirect Friedlander condensation in the presence of [IrCl(cod)] or $IrCl_3$ as catalyst was described by Ishii and his group. [75] Their approach involved treatment of 2-

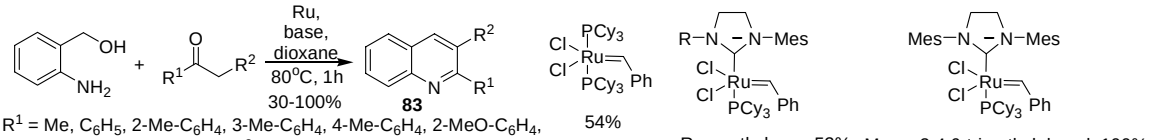
aminobenzyl alcohol with different ketones in the presence of KOH under solvent less condition to obtain 2,3-disubstituted quinolines **(82)** (scheme 56). The reaction mechanism included the ketimine formation from 2-aminobenzyl alcohol and corresponding ketone followed by oxidation to the respective aldehyde and subsequent intramolecular aldol condensation to provide 2,3-disubstituted quinolines **(82)**.



R^1 = Me, Et, i-Bu, *n*-Hex, C_6H_5; R_2 = H, Me
R_1 & R_2 = -$(CH_2)_5$-, -$(CH_2)_3$CHMe-

Scheme 56

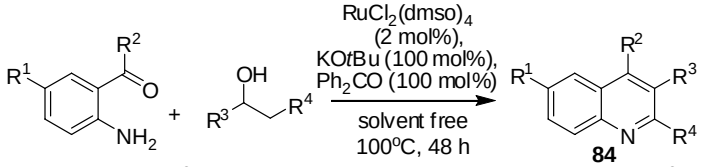
More recently Verpoort *et al.* [76] after examining several Ru-catalysts to accomplish modified Friedlander reaction reported that the Grubb's second generation catalyst was the most efficient surpassing the efficiency of first generation even to effect this reaction for the synthesis of quinoline **(83)** (scheme 57).



R^1 = Me, C_6H_5, 2-Me-C_6H_4, 3-Me-C_6H_4, 4-Me-C_6H_4, 2-MeO-C_6H_4, 4-MeO-C_6H_4, 4-NO_2-C_6H_4; R^2 = H, Me, -$(CH_2)_4$-,-CHMe$(CH_2)_2$-

Scheme 57

In a variation from the reported strategies for the modified Friedlander reaction, very recently Yus and co-workers described the first synthesis of polysubstituted quinoline derivatives **(84)** from reaction of 2-aminoacetophenone or benzophenones with aromatic and aliphatic alcohols in the presence of $RuCl_2(dmso)_4$ as a catalyst under solvent free conditions. Their protocol involved the *in situ* oxidation of alcohols to the corresponding carbonyl compounds through hydrogen transfer followed by Friedlander's condensation as shown in scheme 58. It was shown that the reaction was mild and efficient and independent of the nature of alcohol. [77]

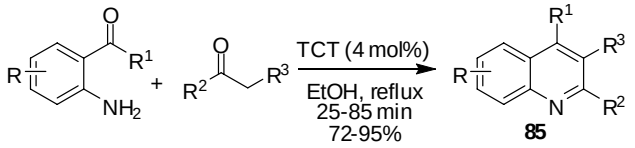


R^1 = H, Cl, NH_2; R^2 = Me, C_6H_5, 2-F-C_6H_4, 2-Cl-C_6H_4, 4-MeO-C_6H_4; R^3 = H, C_6H_5, 4-Me-C_6H_4, 4-CF_3-C_6H_4, 2-Furyl, t-Bu, $(CH_2)_4CH_3$; R^4 = H, Me, C_6H_5

Scheme 58

3.1.1.6 Miscellaneous-

Recently, Das *et al.* [78] successfully performed the Friedlander reaction to generate quinolines **(85)** utilizing TCT as the catalyst as depicted in scheme 59.

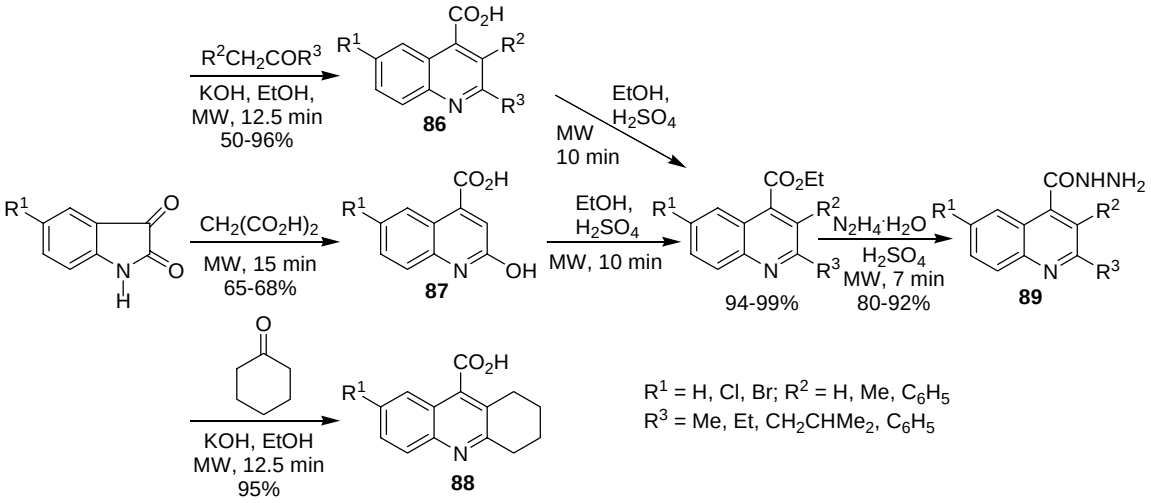


R = H, 4-Cl; R^1 = Me, C_6H_5, 2-Cl-C_6H_4; R^2 = Me; R^3 = CO_2Et, CO_2Me, COMe, CH_2COMe; R^2 & R^3 = -$(CH_2)_3$-, -$(CH_2)_4$-, -$COCH_2CMe_2CH_2$-

Scheme 59

3.1.2 Pfitzinger synthesis-

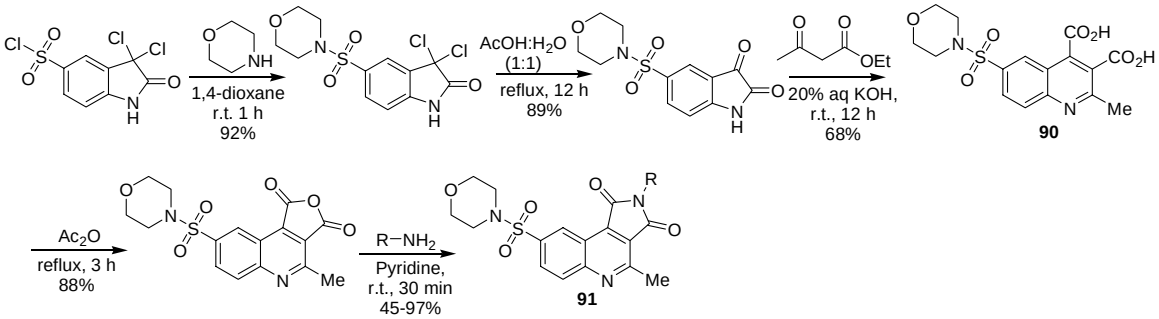
Pfitzinger synthesis for quinolines involves reaction between isatin (N-C-C-C) and carbon nucleophile (C-C) in the presence of a base. [79] Ashry and his group [80] reacted isatin with acyclic and cyclic ketones to obtain quinolines-4-carboxylic acids **(86 & 88)**. Replacing ketones with malonic acid provided quinoline-2-hydroxy-4-carboxylic acid **(87)** as per the scheme 60.



Scheme 60

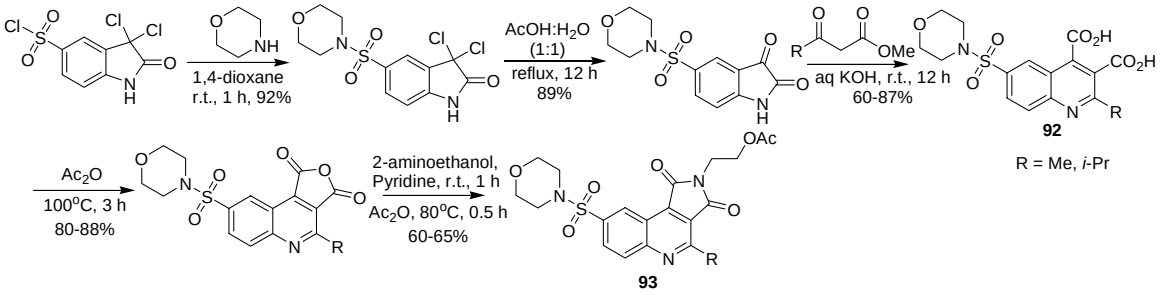
Ivachtcheko *et al.* [81] utilized the Pfitzinger reaction between isatin-5-sulphonimide and methylacetoacetate to generate quinoline-3,4-dicarboxylic acid **(90)** as a synthetic intermediate in the synthesis of pyrrolo[3,4-c]quinolin-1,3-diones **(91)**, which were identified as potent caspase-3 inhibitors (scheme 61). Similar methodology was adopted by these workers [82] for the synthesis of 2-(2-acetyloxyethyl)-8-(morpholine-4-sulfonyl) pyrrolo [3,4-*c*]quinoline-1,3-diones **(92)** from the isatin derivatives. The formation of

furandiones and their condensation with 2-aminoethanol followed by treatment with Ac_2O provided the desired product in good yields (scheme 62). Subsequently they broadened the scope of Pfitzinger reaction for the generation of 2,3,4-tricarboxylic acid **(89)** of quinoline by employing 2-oxosuccinate as the nucleophile. Indeed they obtained the isatin from 3,3-dichloro-2-oxo-2,3-dihydro-1*H*-indole derivative **(93)** and described it to be the first report of utilizing indole as an indirect substrate for Pfitzinger reaction. They further demonstrated the utility of this strategy for the synthesis of series of annulated quinolines **(95)** as caspase-3-inhibitors to be used for apoptosis as out lined in scheme 63. [83] An alternative method for the generation of same series of compounds was also described. The initial reaction of 2,3-dioxo-2,3-dihydro-1*H*-indole-5-sulfonate initially with ketoesters afforded the corresponding dicarboxylic acid **(96)**. These acids were transformed to furandiones via treatment with Ac_2O. As discussed in above sequence, the reaction of furandione with 2-aminoethanol and treatment with $POCl_3$ and morpholine yielded the 2-(2-acetyloxyethyl)-8-(morpholine-4-sulfonyl) pyrrolo [3,4-*c*]quinoline-1,3-diones **(97)** (scheme 64). In another strategy the condensation reaction of sulfamoyl isatin was performed with malononitrile. Further hydrolysis to afford the corresponding dicarboxylic acid **(98)** and conversion to the imides and finally to the chloro derivative **(99)** was conducted as described above (scheme 65). These were considered to be viable precursors for the various nucleophilic substitution reactions. These compounds exhibited the inhibition of caspase-3 enzyme.

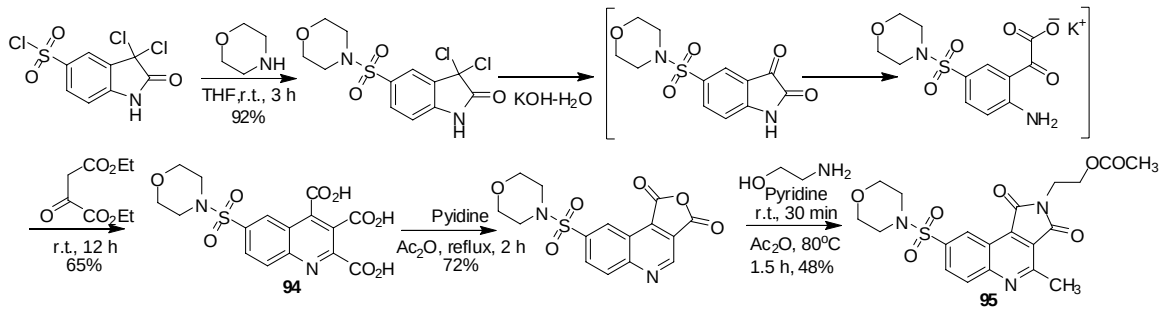


R = H, Me, $(CH_2)_2OH$, $(CH_2)_2OCOCH$, $(CH_2)_2NMe_2$, $(CH_2)_3OH$, $(CH_2)_2CO_2Me$, $CH(CO_2H)CH_2C_6H_5$, $CH(CO_2Me)CH_2C_6H_5$, CH_2CO_2Me, CH_2CO_2t-Bu, $CH(CO_2Me)CH_2OH$, $CH(CO_2Me)CH_2SH$

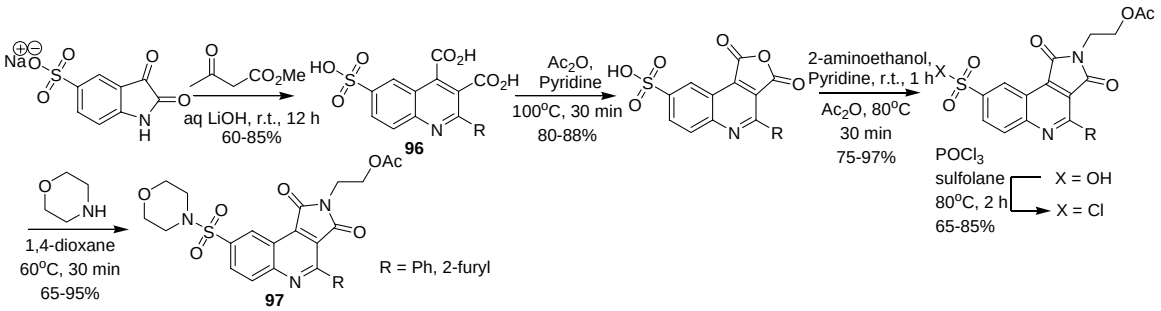
Scheme 61



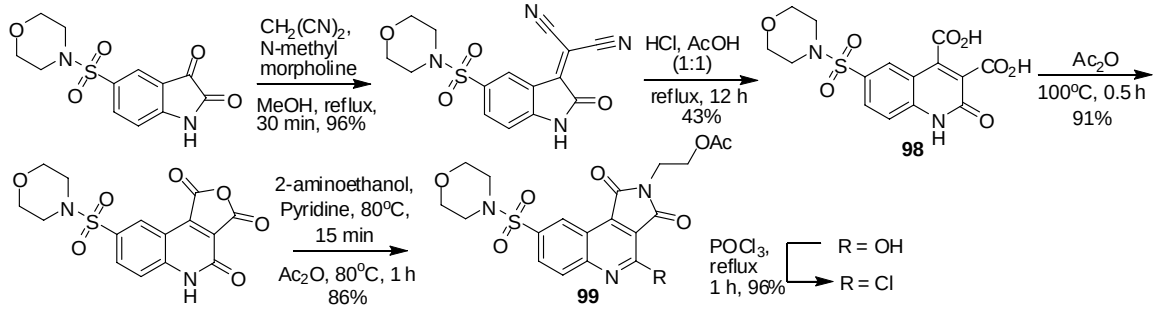
Scheme 62



Scheme 63

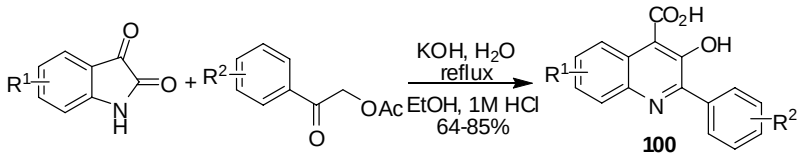


Scheme 64



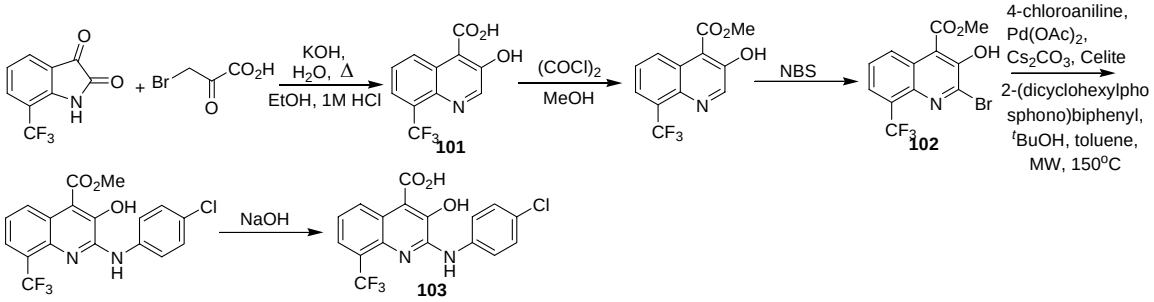
Scheme 65

Kaila *et al.* [84,85] demonstrated the synthesis of quinoline salicylic acid derivatives **(100, 103, 104)** via Pfitzinger reaction for p-selectrin activity (scheme 66, 67 and 68). The precursors for the reaction *viz*. isatin and α-keto acetates were synthesized by various synthetic routes. The 2-bromoquinoline derivatives **(102)** were further modified to 2-benzyl quinoline derivatives using Heck reaction as described in scheme 67.

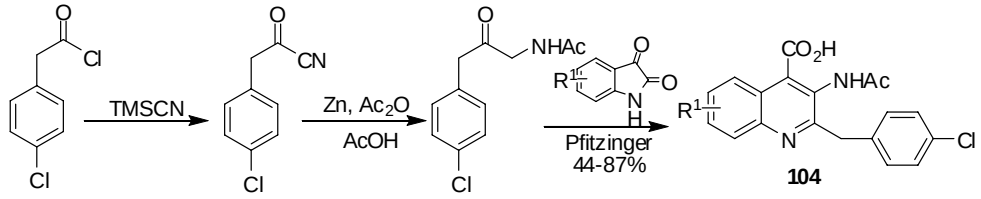


R^1 = H, 4-OH, 5-CF_3, 7-CF_3, 4-Me, 5-Me, 6-Me, 7-Me, 7-Et, 5-OMe, 6-OMe, 7-OMe, 5-OCF_3, 7-OCF_3, *i*-Pr; R^2 = H, Cl, OH, OC_6H_5, SC_6H_5, 4-OHC_6H_4

Scheme 66



Scheme 67

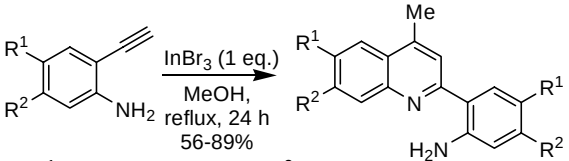


R^1 = H, 6-Me, 7-Me, 6-Et, 7-Et, 7-OCF_3, 7-CF_3, 7-Br, 7-Cl, 7-F, 7*i*-Pr

Scheme 68

3.1.3 From Alkynes-

Sakai *et al.* [86] reported the first dimerization reaction between the identical molecules for the synthesis of quinolines. The 2-ethynyl anilines undergo dimerisation and intermolecular cyclization in the presence of $InBr_3$ to yield the quinoline compounds **(105)** in excellent yield as shown in scheme 69.

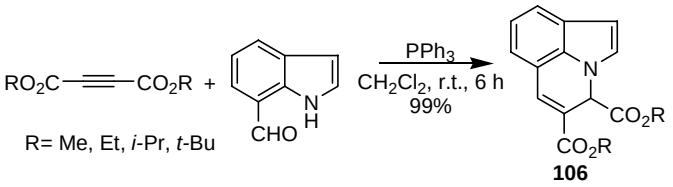


R^1 = H, Me, F, CN, NO_2; R^2 = H, Me

Scheme 69

The reaction of acetylenic esters with indole-7-carboxaldehyde in the presence of PPh_3 to produce dialkyl 4*H*-pyrrolo[3,2,1-*ij*]quinoline-4,5-dicarboxylates **(106)** proceeded smoothly in CH_2Cl_2 at ambient temperature as reported by Adib and Sayahi (scheme 70). [87] This method generated products in quantitative yields simply under neutral

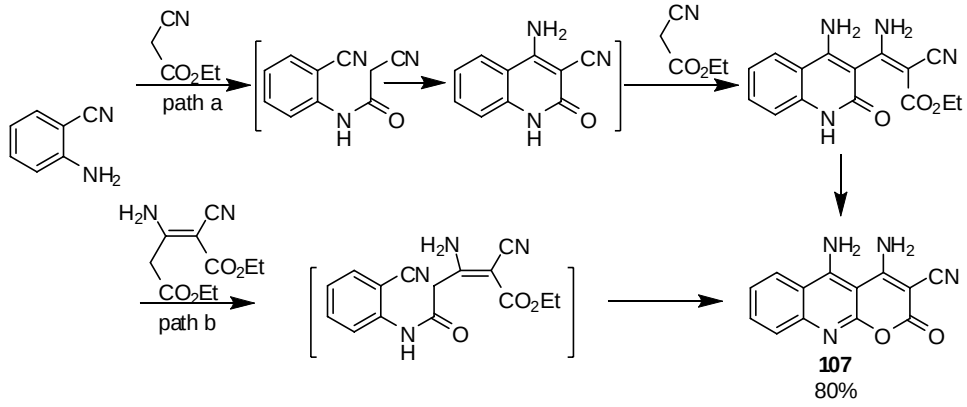
conditions within a few hours. They claimed it to be an unconventional approach towards compound **106** as compared to the formerly used multi-step synthesis.



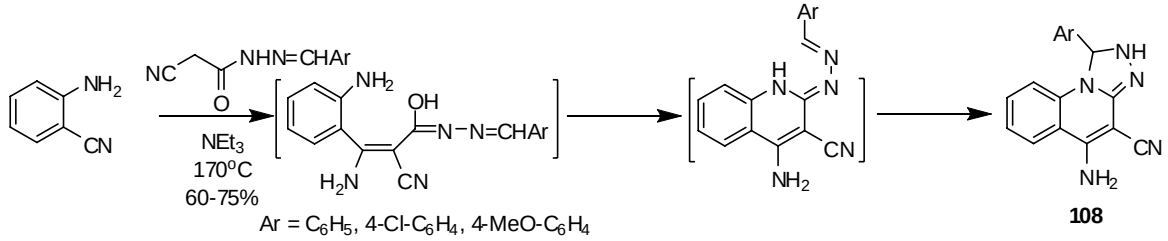
Scheme 70

3.1.4 Other 4+2 approaches-

Highly functionalized quinolines were prepared from anthranilonitrile by Metwally and Abdelrazek. [88] Anthranilonitrile reacted with ethylcyanoacetate and its dimer to furnish pyrano[2,3-*b*]quinoline **(107)** (scheme 71), while reaction with *N*-acylidene cyanoacetohydrazides afforded triazolo[4,3-*a*]quinolines **(108)** as shown in scheme 72.

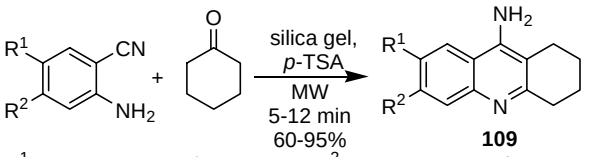


Scheme 71



Scheme 72

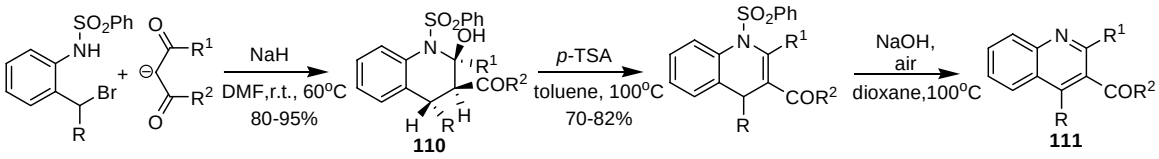
Recently Khalilzadeh and co-workers [89] also utilized anthranilonitrile as a precursor for the synthesis of substituted tacrines **(109)**. This was achieved by the condensation of substituted anthranilonitriles with cyclohexanone in the presence of silica gel/ *p*-TSA as catalyst under microwave irradiation (scheme 73).



R^1 = H, Me, OMe, Cl, NO_2, NH_2; R^2 = H, Me, OMe, Cl, NO_2, F

Scheme 73

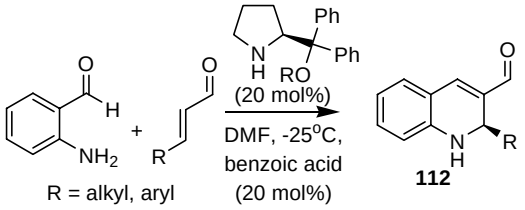
Croce and co-workers [90] transformed *N*-phenylsulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinolines to dihydroquinolines in the presence of *p*-TSA followed by deprotection under basic conditions to generate quinolines **(111)**. The required *N*-phenyl sulfonyl-2-hydroxy-1,2,3,4-tetrahydroquinolines **(110)** were obtained from enolates of 1,3-dicarbonyl compounds and *N*-(2-bromomethylphenyl) benzenesulfonamides in highly stereoselective manner (scheme 74).



R = H, Me, C_6H_5; R^1 = Me, C_6H_5; R^2 = Me, OMe, $OEtC_6H_5$

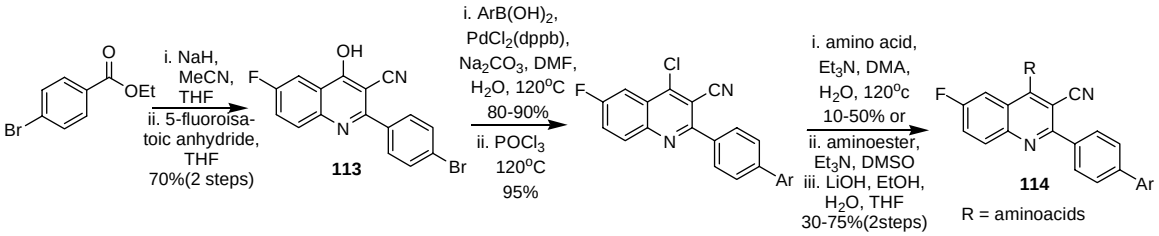
Scheme 74

Cordova and co-workers [91] reported highly enantioselective organocatalytic domino aza-Michael/aldol reaction between 2-aminobenzaldehydes and α,β-unsaturated aldehydes for the synthesis of 1,2-dihydro quinolidines **(112)** (scheme 75).



Scheme 75

Cantin *et al.* [92] described the reaction of bromobenzoate with MeCN in the presence of NaH to yield enolate, which upon treatment with 5-fluoroisatoic anhydride furnished 2,3,4-substituted quinolines **(113)**. The quinolines were transformed to quinoline amino acids **114** as per the reaction sequence shown in scheme 76. These quinoline amino acids were identified as PDE-10A inhibitors as insulin secretagogues *in vitro*.



Scheme 76

3.2 From C-N-C-C+ C-C Units

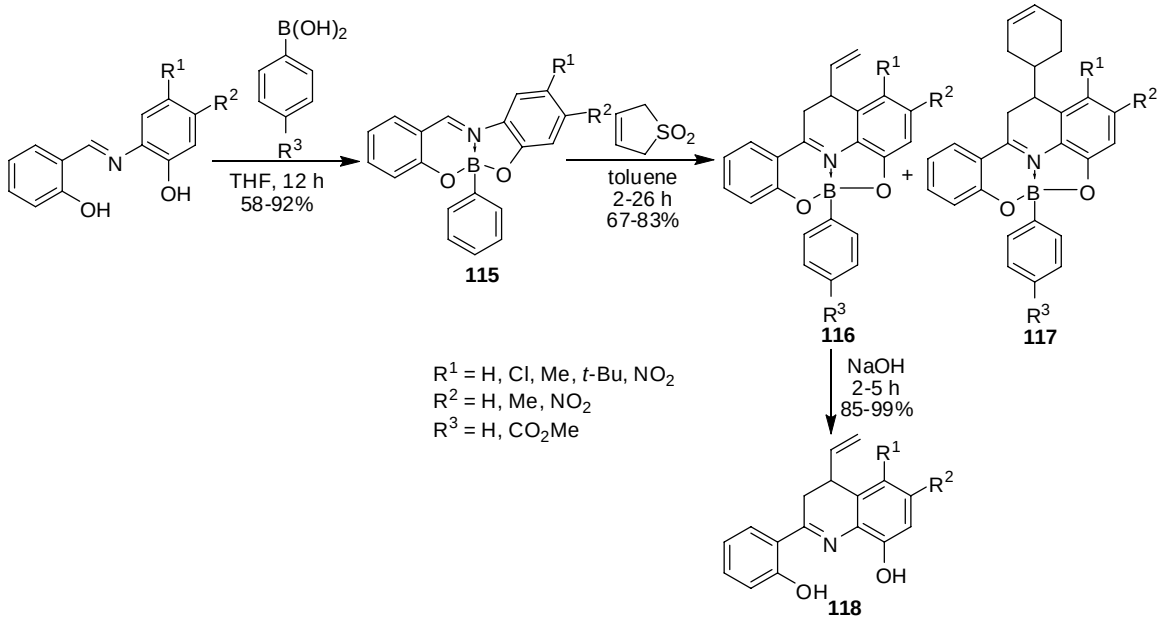
The syntheses of quinolines have been widely accomplished via imines. The two strategies generally adopted for the purpose include either imino-Diels-Alder reaction also termed as Povarov reaction or by the route where it is not the Diels-Alder type reaction though the imine is present in the form of enamine or enaminone. Both these methodologies are being discussed separately.

3.2.1 Aza-Diels-Alder reaction-

The Aza-Diels-Alder reaction for quinoline synthesis comprises of formation of a Schiff's base initially which acts as diene (C-N-C-C) to react with the alkene (C-C) that behaves as a dienophile. Generally when the formation of Schiff's base takes place *in situ* the strategy is one-pot multicomponent whereas if it is formed separately and reacted with the alkene it becomes a two-step procedure.

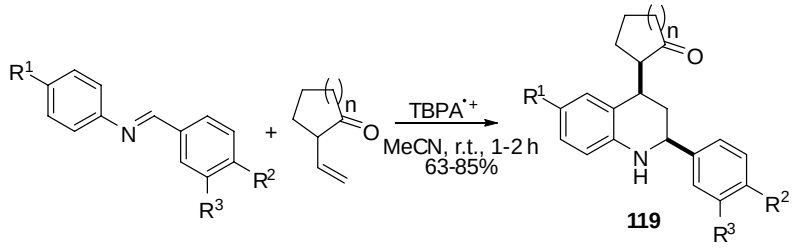
3.2.1.1 From Aldimine- Two-step procedure-

Santillan and co-workers [93] put forward a novel imino-Diels-Alder reaction for the synthesis of 3,4-dihydroquinolines and quinolines by the reaction between boron adducts **(115)** derived from Schiff's bases and sulfolene. The reactions were reported to be highly regioselective yielding 4-substituted dihydroquinolines **(116 & 117)** with *cis* relative stereochemistry between the phenyl group on the boron atom and vinyl substitution at 4-position as shown in scheme 48. Compounds **116** were treated with a base to furnish quinolines **(118)** in good yields (scheme 77).

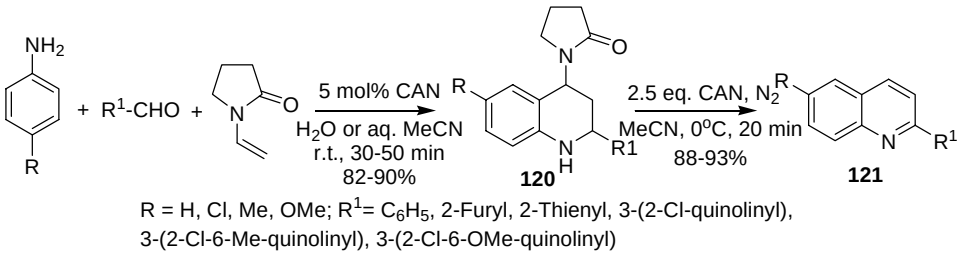


Scheme 77

Jia *et al.* [94] reported the tris-TBPA cation radical catalyzed Aza-Diels-Alder reaction of *N*-arylamines with *N*-vinyl lactams for the synthesis of cis 2-aryl-4-(lactam-*N*-yl) 1,2,3,4-tetrahydroquinolines **(119)** in good yields (scheme 78). Simultaneously, Savitha and Perumal [95] demonstrated that the formation of similar tetrahydroquinolines **(69)** could be achieved in one-pot by the reaction between anilines, hetero arylaldehydes, and *N*-vinylpyrrolidin-2-one in the presence of CAN, in H_2O or aq. MeCN (Scheme 79). These conditions were mild and reactions were completed in a short reaction time affording good yields and excellent selectivity. The resulting tetrahydroquinolines **(120)** could be readily aromatized to substituted quinolines **(121)** through CAN in MeCN under the nitrogen atmosphere at 0°C.

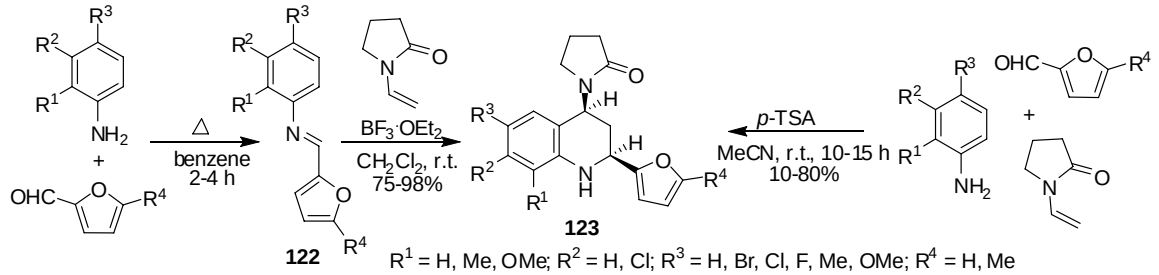


Scheme 78



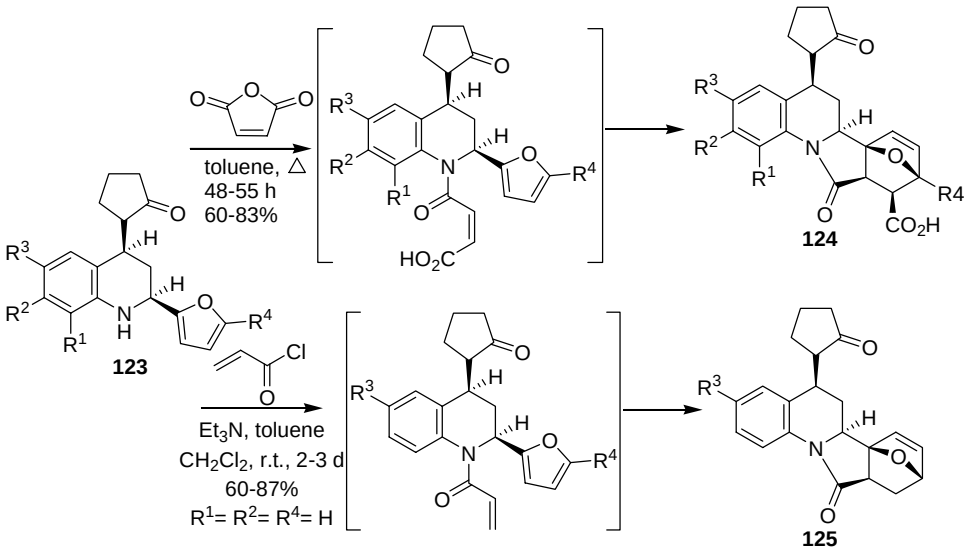
Scheme 79

Recently, Kouznetsov and co-workers [96] developed a straightforward synthesis of new isoindolo[2,1-*a*]quinolines **(123)** utilizing analogous intramolecular Diels-Alder reaction as the key step. The 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment at 2-position was obtained by the reaction between the Schiff's base **(122)** and *N*-vinylpyrrolidin-2-one in the presence of $BF_3 \cdot OEt_2$ (scheme 80). Alternatively, one pot reaction between aniline, 2-furfuraldehyde and *N*-vinylpyrrolidin-2-one in the presence of *p*-TSA furnished the same product **(123)** albeit in lower yields (scheme 81). Interestingly both routes were highly diastereoselective in nature. The resulting 2-furyltetrahydroquinolines **(123)** were *N*-acylated with maleic anhydride and acryloyl chloride and subsequent intramolecular Diels-Alder reaction with furan moiety yielded 11-oxo-5-(2-oxopyrrolidin-1-yl)-hexahydro-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acids **(124)** and epoxyisoindolo[2,1-a]quinolines **(125)** in good yields as shown in scheme 80.

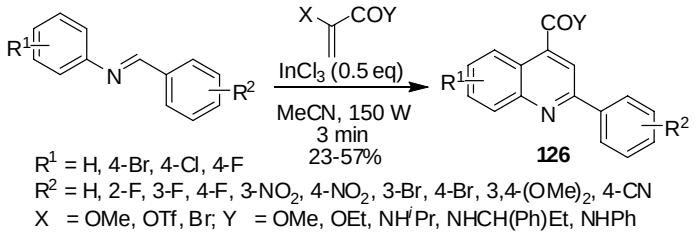


Scheme 80

A rapid synthesis of quinoline carboxylic acid **(126)** by the reaction of *N*-arylbenzalimines with 2-methoxy acrylates or acrylamides in the presence of $InCl_3$ was achieved by Duvelleroy and co-workers [97] under microwave irradiation. Although they investigated several Lewis acids including $Yb(OTf)_3$, $InBr_3$, InI_3, $In(OTf)_3$, $Sc(OTf)_3$ as catalyst, the reaction proceeded better with $InCl_3$ in MeCN (scheme 82).

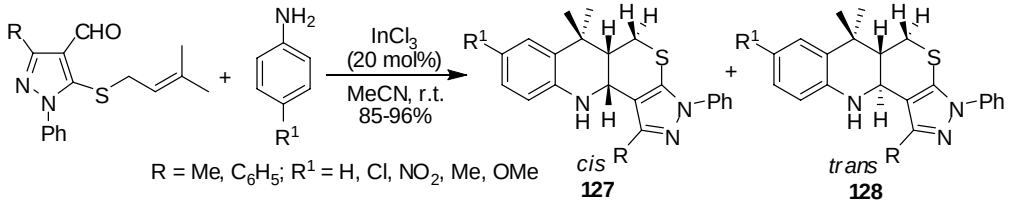


Scheme 81

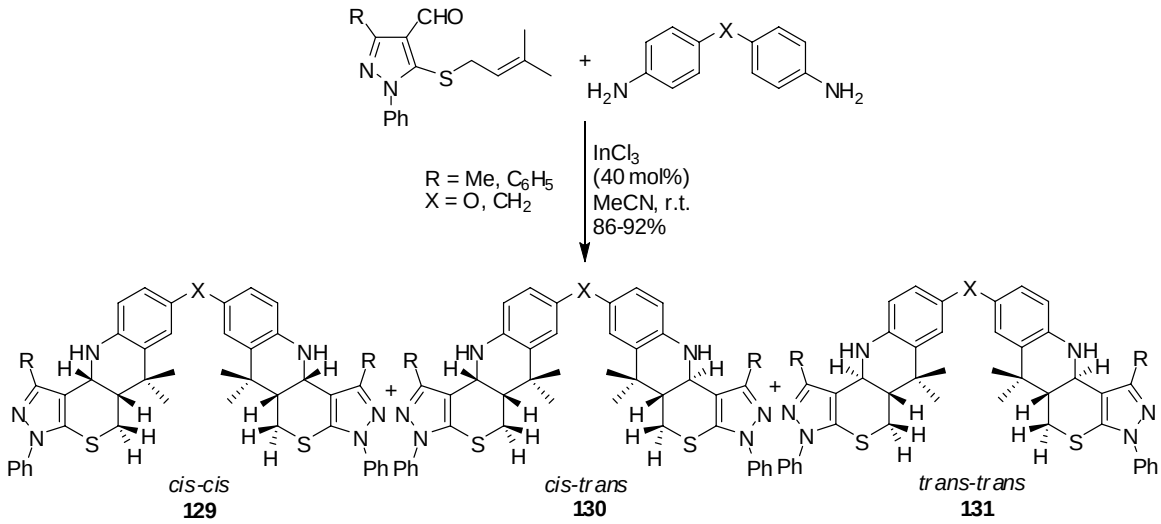


Scheme 82

Raghunathan and co-workers [98] also utilized $InCl_3$ in MeCN to achieve the synthesis of bis-tetrahydropyrazolo[4',3':5,6]thiopyrano[4,3-*b*]quinolines **(127** & **128)** via imino-Diels-Alder reaction. Strategically the initial formation of imine was followed by intramolecular Diels-Alder with the S-prenyl chain (scheme 83). They reported their reaction to be diastereoselective to yield only *cis* product. Use of 4,4'-methylene or 4,4'-oxo bis anilines led to bis-quinoline structure **(129-131)** wherein *cis-cis* isomer **(129)** predominated as outlined in scheme 84.

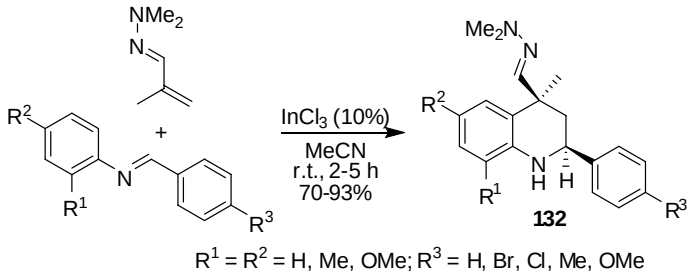


Scheme 83



Scheme 84

Recently Menendez and co-workers [99] described the first Aza-Diels-Alder reaction involving an α,β-unsaturated hydrazones as the dienophile and catalyzed by $InCl_3$ for the stereoselective synthesis of 1,2,3,4-tetrahydroquinoline **(132)** substituted at 4-position. The process was domino that involved a reaction of 2-stereocenters, one of these quaternary with complete diastereoselectivity and in a single operation (scheme 85). They termed this process as vinylogous aza-Povarov reaction.

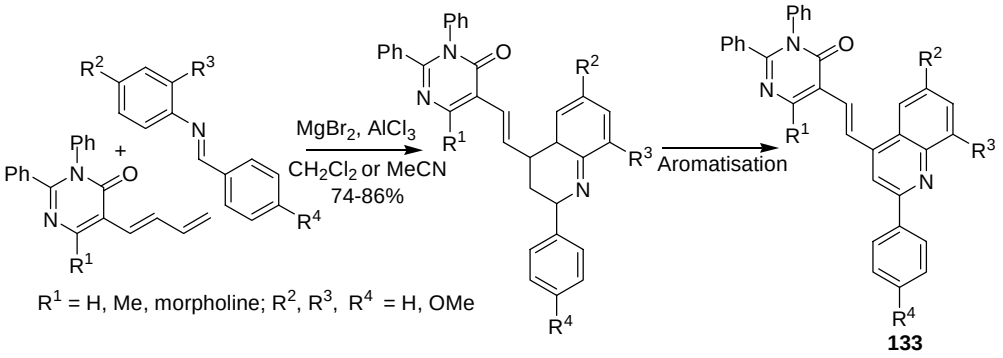


Scheme 85

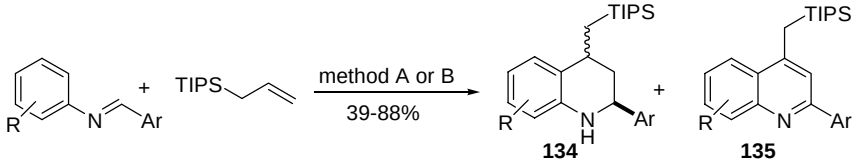
More recently, Bhargava and co-workers [100] successfully developed a Lewis acid-mediated Aza-Diels-Alder reaction employing $MgBr_2$ and a catalytic amount of $AlCl_3$ as catalyst for the reaction between acyclic-5-dienyl pyrimidinones and *N*-arylamines to provide the quinolines **(133)** in good yields as shown in scheme 86.

Takasu *et al.* [101] demonstrated a cascade one-pot strategy which included inverse electron hetero Diels-Alder reaction and oxidative aromatization initiated by Tf_2NH to furnish the quinoline derivative **(135)** from aldimine and allyl silane. The

tetrahydroquinolines **(134)** obtained as additional minor product was easily aromatized with DDQ to yield quinolines **(135)** (scheme 87).



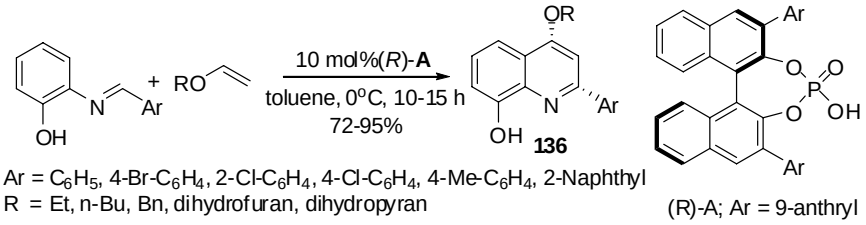
Scheme 86



method A: imine(3 eq.), allyl silane (1 eq.), Tf_2NH (10 mol%), toluene, 60°C, 24 h.
method B: imine (1.25 eq.), allyl silane (1 eq.), Tf_2NH (15 mol%), DCE, 60°C, 3 h, then DDQ (2 eq.), r.t., 10 min.
R = H, 2-Br, 4-Br, 4-Cl, 4-OMe, 4-NO_2; Ar = C_6H_5, 4-NO_2-C_6H_4, 2-NO_2-C_6H_4

Scheme 87

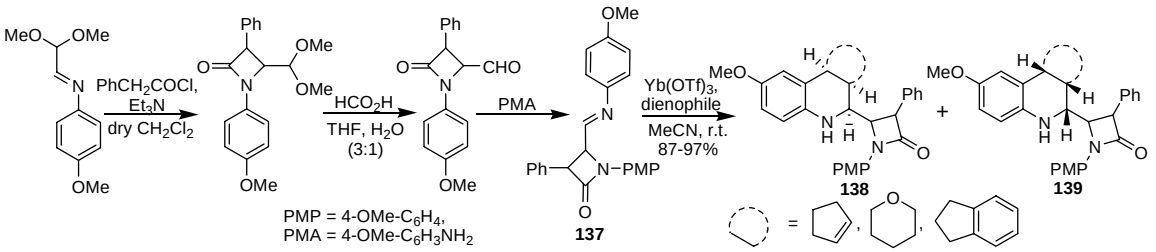
Akiyama and co-workers [102] reported the chiral Bronsted acid-catalyzed enantioselctive tetrahydroquinolines **(131)** via Aza-Diels-Alder reaction of aldimines with electron-rich alkenes in toluene at 0°C (scheme 88).



Ar = C_6H_5, 4-Br-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-Me-C_6H_4, 2-Naphthyl
R = Et, n-Bu, Bn, dihydrofuran, dihydropyran

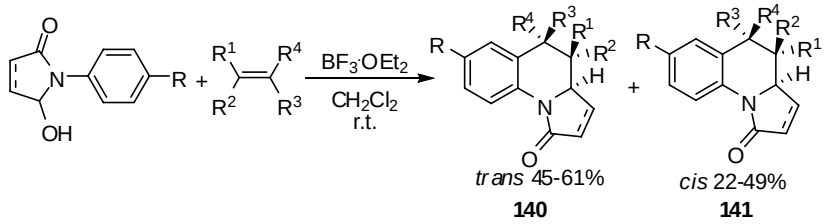
Scheme 88

Ramesh *et al*. [103] described the synthesis of quinoline-β-lactams **(138 & 139)** from the reaction of β-lactam imines **(137)** and various electron-rich dienophiles via intermolecular imino-Diels–Alder reaction in the presence of $Yb(OTf)_3$ in MeCN at room temperature in excellent yields. The β-lactam imine **(137)** was in turn obtained from the reaction of glyoxal dimethylacetal imine with 2-phenylacetyl chloride to furnish 4-dimethylacetal β-lactams **(138 & 139)** followed by hydrolysis and condensation with 4-methoxy aniline (scheme 89).



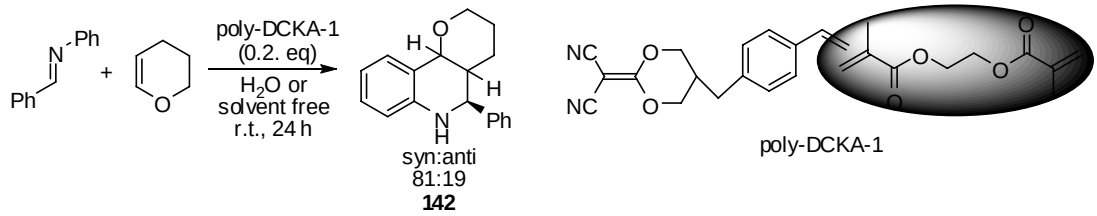
Scheme 89

Zhang and co-workers [104] developed a mild and efficient synthesis of pyrrolo- and pyrrolidino[1,2-*a*]quinolin-1-ones **(140 & 141)** from the reaction of 5-hydroxy-1-arylpyrrol-2-ones and 5-hydroxy-1-arylpyrrolidin-2-ones with olefins in the presence of $BF_3{\cdot}OEt_2$ via formation of *N*-acyliminium cations followed by Aza-Diels-Alder reaction (scheme 90).



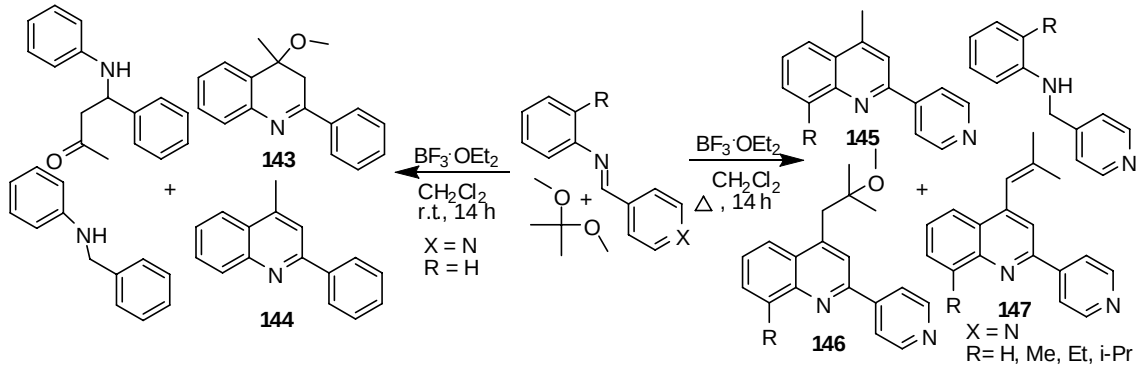
Scheme 90

Recyclable polymer-supported π-acid catalyzed inverse-electron-demand Aza-Diels-Alder reaction between an imine and 3,4-dihydro-2-*H*-pyran to afford pyrano-[3,2-*c*]quinolines **(142)** was reported by Masaki *et al*. [105] in H_2O and solvent free conditions (scheme 91).



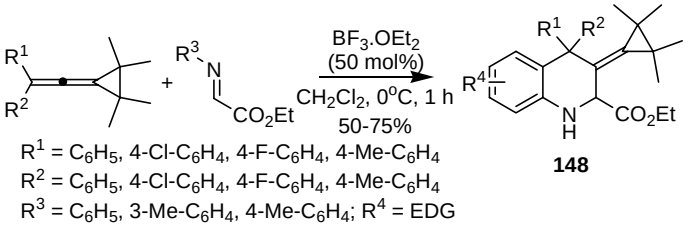
Scheme 91

Kouznetsov and co-workers [106] performed $BF_3{\cdot}OEt_2$ mediated Kametani reaction, an example of [4+2] imino-Diels-Alder cycloaddition reaction, on *N*-(4-pyridinyliden) anilines and *N*-benzylidene anilines with 2,2-dimethoxypropane to obtain quinolines **(143-147)** as shown in scheme 92.



Scheme 92

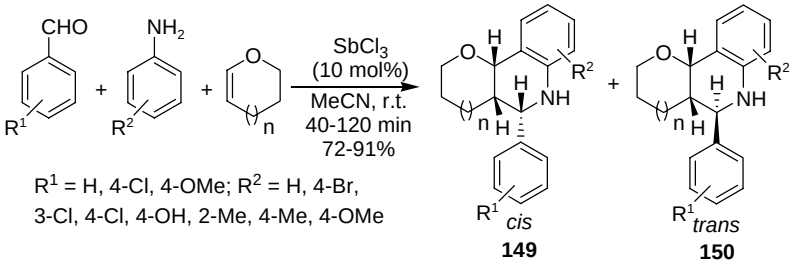
Lu and Shi demonstrated Lewis acid catalyzed reaction between arylvinylidenecyclopropanes and ethyl (arylimino) acetates for the synthesis of 1,2,3,4-tetrahydroquinoline derivatives **(148)**. [107] However the formation of the product took place only when the R^3 in iminoacetates was an electron rich group (scheme 93).



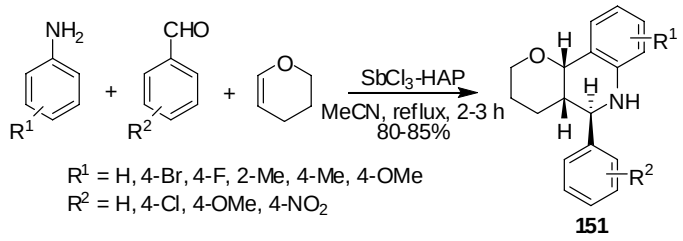
Scheme 93

3.2.1.2 Multicomponent– One step procedure-

The inverse electron demand imino-Diels-Alder reactions of *in situ* generated *N*-benzylidenes with 3,4-dihydro-2-*H*-pyran and 2,3-dihydro furan to obtain pyrano and furano[3,2-*c*]quinolines **(149 & 150)** was efficiently performed in the presence of $SbCl_3$ by Maiti and Kundu as shown in scheme 94. [108] Subsequently Mahajan *et al.*[109] also reported similar synthesis of pyrano[3,2-*c*]quinolines **(151)** using $SbCl_3$-HAP as the catalyst as delineated in scheme 95.

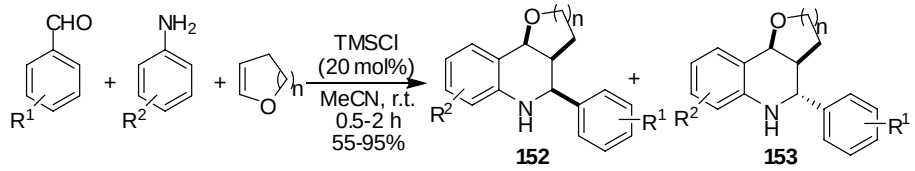


Scheme 94

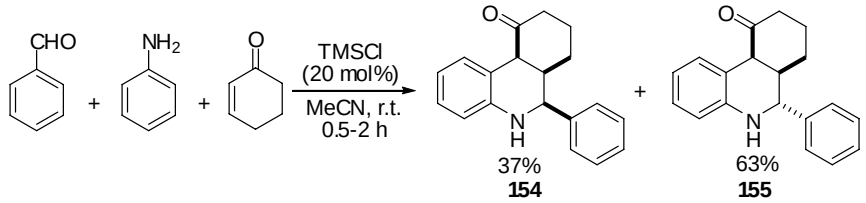


Scheme 95

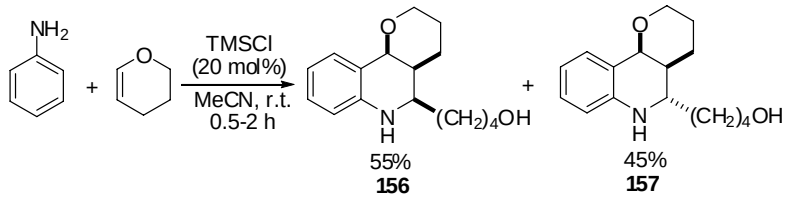
Synthesis of furano- and pyrano-quinolines **(152 & 153)** by a TMSCl-catalyzed three-component coupling of several aldehydes, anilines and either 2,3-dihydrofurans or 3,4-dihydro-2[*H*]-pyran, respectively in MeCN was reported by More and co-workers (scheme 96). [110] They further demonstrated that same reaction with cycloalkenone yielded phenanthridone derivatives **(154 & 155)** as delineated in scheme 97. Interestingly, the reaction of aniline with excess of 3,4-dihydro-2[*H*]-pyran in the absence of benzaldehyde yielded a mixture of new pyranoquinolines **(156 & 157)** under similar conditions (scheme 98). Subsequently Semwal and Nayak also reported analogous synthesis of pyrano- and furano[3,2-*c*]quinolines **(158 & 159)** using $CuBr_2$ as the catalyst as shown in scheme 99. [111]



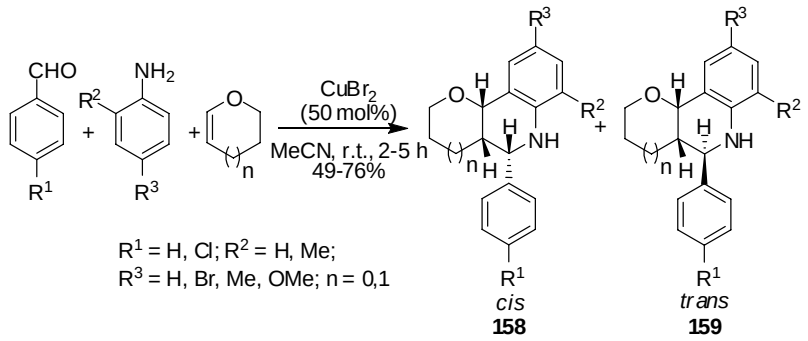
Scheme 96



Scheme 97

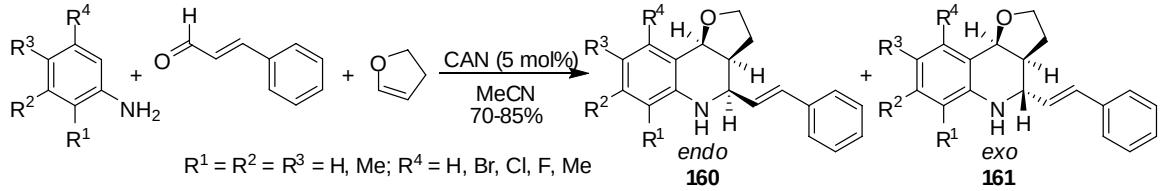


Scheme 98



Scheme 99

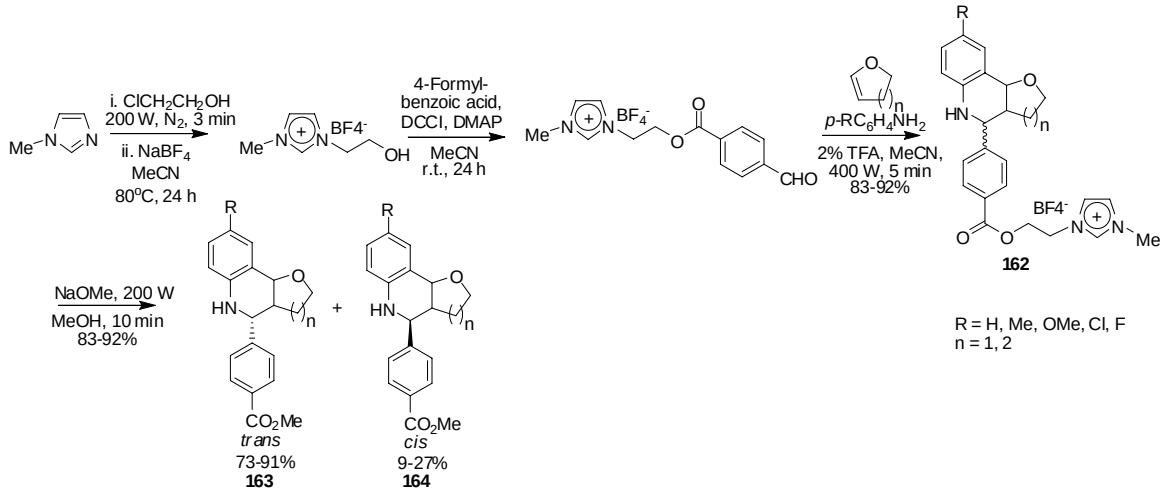
Menendez and his group [112] successfully accomplished the synthesis of styryl tetrahydroquinoline **(160 & 161)** via Povarov reaction of anilines, cinnamaldehyde, and cyclic vinyl ether in the presence of CAN as a catalyst (scheme 100). They observed that in the case of non-cyclic vinyl ether, the products were obtained stereoselectively having a *cis*-conformation between the styryl and alkoxy groups.



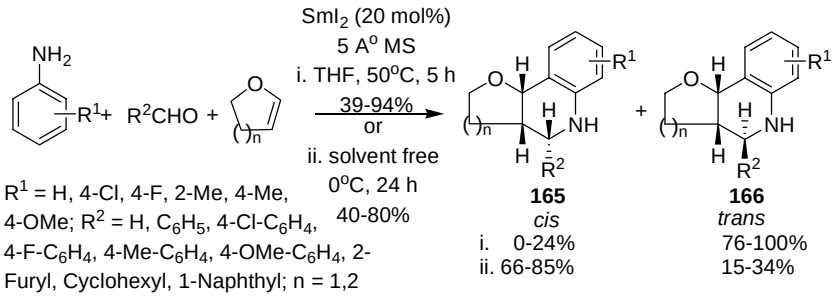
Scheme 100

Li and co-workers [113] reported the synthesis of tetrahydropyrano- and tetrahydrofurano-quinolines in the presence of ionic liquid. Reaction of ionic liquid bounded aldehyde, p-substituted aniline and either 2,3-dihydrofurans or 3,4-dihydro-2[*H*]-pyrans in 2% TFA in MeCN under microwave irradiation followed by treatment of resulting ionic liquid bound adduct **(162)** with NaOMe in MeOH furnished mixture of *trans* and *cis* isomers of tetrahydroquinolines **(163 & 164)** with high diastereoselectivity (scheme 101).

A three component imino-Diels-Alder reaction of aromatic aldehydes, aromatic amines and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of SmI_2 yielded pyrano- and furano[3,2-*c*]quinolines as reported by Zhou *et al.* recently. [114] Interestingly they concluded from their study that higher temperatures and lower substrate concentrations give more of the thermodynamically stable *trans* products **(166)**, whereas lower temperatures and higher substrate concentrations led to fast formation of the kinetically favored *cis* products **(165)** (scheme 102).

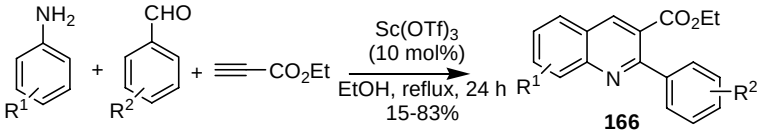


Scheme 101



Scheme 102

Synthesis of 2,3-disubstituted quinoline bearing an ester group at 3-position **(166)** by the reaction of aniline, aldehyde and ethyl propionate in the presence of $Ga(OTf)_3$ in refluxing EtOH was achieved by Fukuzawa and co-workers. [115] During this endeavor they investigated catalytic influence of several Lewis acids including $Yb(OTf)_3$, $InBr_3$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $Ga(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$ and discovered that $Ga(OTf)_3$ and $Sc(OTf)_3$ were most effective. In contrast to the ortho- or meta- substituted anilines, the para-substituted anilines gave better yields of the envisaged quinolines (scheme 103).

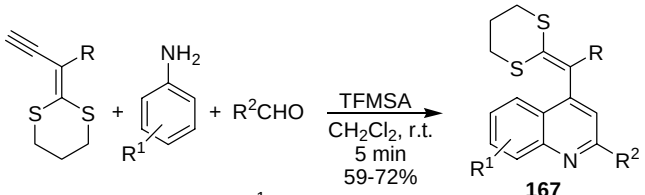


R1 = H, 4-Cl, 2-Me, 3-Me, 4-Me, 4-OMe, 4-Et, 4-*i*Pr; R2 = H, 4-Cl, 4-F

Scheme 103

Zhao *et al*. [116] reported a highly innovative and efficient one-pot procedure for the synthesis of 4-functionalized quinolines **(167)** by the reaction of ethynyl ketene-S-S-acetals with various arylamines and aldehydes in the presence of TFMSA as per the

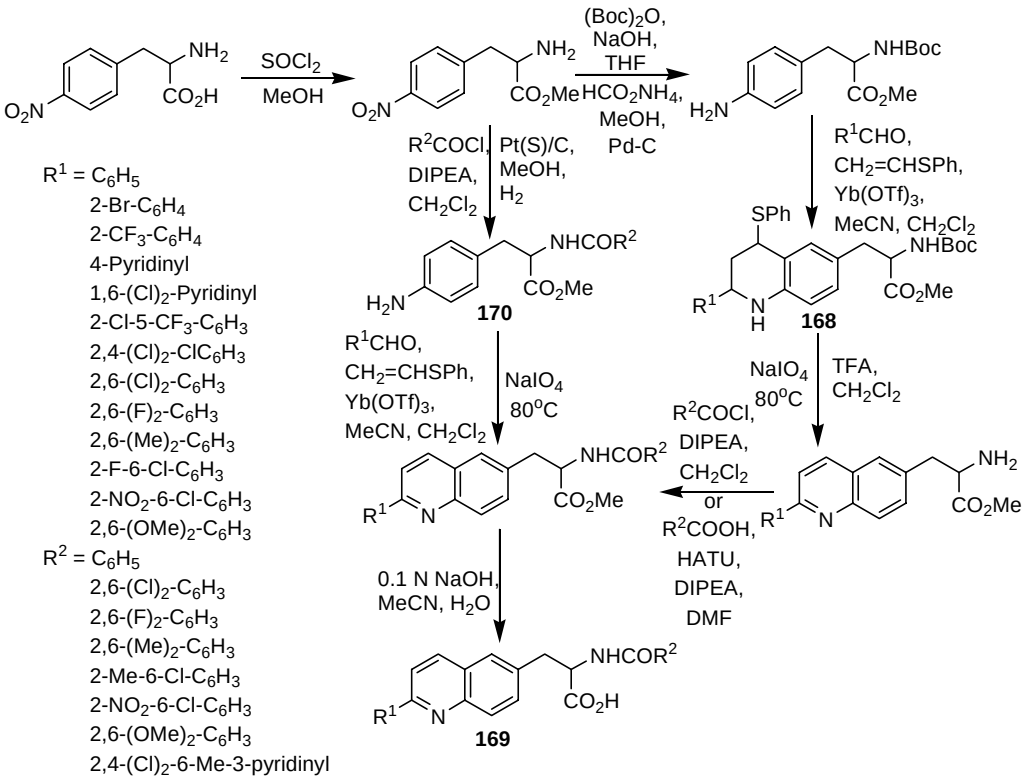
reaction sequence delineated in scheme 104. Here too the reaction proceeded through imino-Diels-Alder in the first step.



R = CO_2H, CO_2Et; R^1 = H, 4-C, 4-F, 3-Me, 4-Me,
R^2 = *t*-Bu, C_6H_5, 4-Cl-C_6H_4, 4-F-C_6H_4, 3,4-(OCH_2O)-C_6H_3,
4-OMe-C_6H_4, 4-NO_2-C_6H_4, $CH_2C_6H_4$, 4-Pyridyl, 4-Thienyl

Scheme 104

Provins and co-workers [117] described the synthesis of 2,6-disubstituted quinoline derivatives that acted as orally bioavailable VLA-4/VCAM antagonists. Their synthesis commenced with the esterification of 4-nitro phenylalanine and protection of the amino group with Boc moiety. Reduction of nitro group with HCO_2NH_4 in the presence of Pd-C gave the amino derivative, which reacted with alkene and aldehydes to produce the tetrahydroquinolines **(168)**, subsequent oxidation and deprotection followed by aroylation and hydrolysis yielded the substituted quinolines **(169)**. Alternatively, similar final

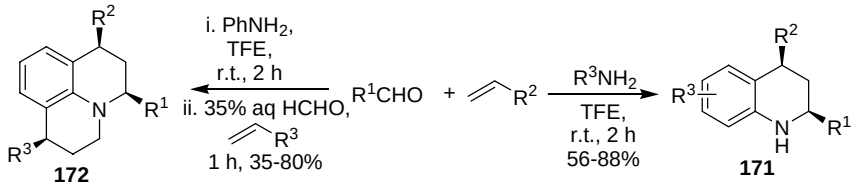


R^1 = C_6H_5
2-Br-C_6H_4
2-CF_3-C_6H_4
4-Pyridinyl
1,6-$(Cl)_2$-Pyridinyl
2-Cl-5-CF_3-C_6H_3
2,4-$(Cl)_2$-ClC_6H_3
2,6-$(Cl)_2$-C_6H_3
2,6-$(F)_2$-C_6H_3
2,6-$(Me)_2$-C_6H_3
2-F-6-Cl-C_6H_3
2-NO_2-6-Cl-C_6H_3
2,6-$(OMe)_2$-C_6H_3
R^2 = C_6H_5
2,6-$(Cl)_2$-C_6H_3
2,6-$(F)_2$-C_6H_3
2,6-$(Me)_2$-C_6H_3
2-Me-6-Cl-C_6H_3
2-NO_2-6-Cl-C_6H_3
2,6-$(OMe)_2$-C_6H_3
2,4-$(Cl)_2$-6-Me-3-pyridinyl

Scheme 105

products **(169)** were obtained from the 4-nitro (D,L) phenylalanine ester. Acylation of the ester followed by reduction of the nitro group by hydrogenation led to formation of corresponding amine **(170)** which reacted with the alkene and aldehydes (scheme 105).

Legros *et al*. [118] reported a simple and efficient protocol for the synthesis of tetrahydroquinolines **(171)** via Aza-Diels-Alder reaction of alkyl aldehydes, anilines and electron rich olefins (vinyl ethers) in TFE (scheme 106). It was observed that when the reaction was performed in the presence of formaldehyde and excess of dienophile, the resulting tetrahydroquinoline undergo second Povarov reaction furnishing new julolidine derivative **(172)**.

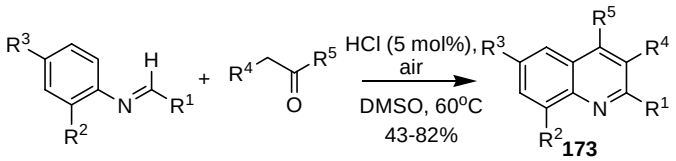


R^1 = *i*-Pr, *n*- C_5H_{11}; R^2 = OEt; R^3 = OEt R^1 = *i*-Pr, *i*-Bu, *n*- C_5H_{11}, C_6H_5; R^2 = OEt; R^3 = 4-OEt, 4-Me

Scheme 106

3.2.2 From aldimines-

Beside Aza-Diels-Alder approach, the imines have been utilized for quinoline synthesis in various fashions. These examples are being included in this section. Baba and co-workers [119] reported a simple and practical synthesis of a variety of substituted quinolines **(172)** from imine (afforded by aniline and aromatic aldehyde) and enolizable carbonyl compounds in the presence of HCl under aerobic conditions. However as the imines afforded from alkyl aldehydes are unstable and difficult to isolate, they demonstrated the success of their strategy by taking 2.5 eq. of the alkylaldehyde and aryl amine in the reaction to obtain quinoline **(173)** in moderate to excellent yield as shown in scheme 107.

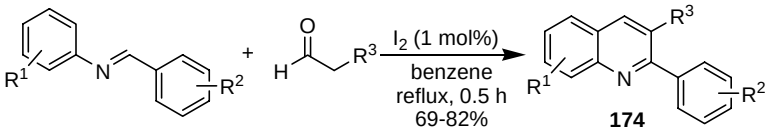


R^1 = Furyl, C_6H_5, 4-Br-C_6H_4, 4-OMe-C_6H_4, 4-CO_2H-C_6H_4; R^2 = H, OMe; R^3 = H, Br, OH, OMe; R^4 = H, C_6H_5, $CH_2C_6H_4$, $(CH_2)_4CH_3$; R^4 = H, C_6H_5, CO_2Me

Scheme 107

Wang and his group [120] reported the molecular iodine-catalyzed general method of quinoline **(174)** synthesis from imines and enolizable aldehydes in refluxing benzene.

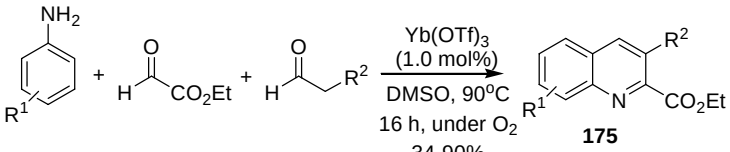
They observed that out of DCE, MeCN, THF, MeOH, DMSO, benzene, best results were obtained when benzene containing 1 mol% of iodine was used for the purpose (scheme 108).



R^1 = H, 4-Br, 4-Me, 4-OMe, 4-OEt; R^2 = H, 4-Br, 4-Cl, 4-Me, 3,4-$(Me)_2$;
R^3 = C_6H_5, *i*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, *n*-C_6H_{13}, *n*-C_7H_{15}, *n*-C_8H_{17},

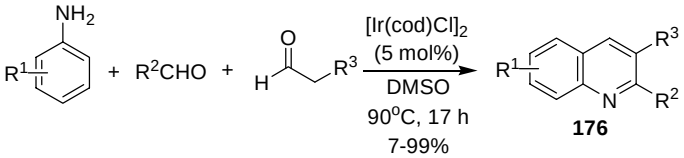
Scheme 108

Shimizu and co-workers [121] described several variants of three component reaction using transition metal and Lewis-acid catalysts to generate quinolines. Initially they demonstrated a one-step synthesis of ethylquinaldates **(175)** by Lewis acid mediated reaction between aromatic amines, aliphatic aldehydes and ethylglyoxalate. During this work they investigated the effect of several Lewis-acids including $SnCl_2$, $ZnCl_2$, $TiCl_4$, $La(OTf)_3$, and $Yb(OTf)_3$ and found that these all gave comparable yields though 1.0 mol% of $Yb(OTf)_3$ was the most suitable for this reaction (scheme 109). Subsequently they demonstrated the success of this strategy with Ir-catalyzed three component coupling reaction. [122] A reaction between an arylamine, an aromatic aldehyde or aliphatic aldehyde and an aliphatic aldehyde in the presence of 5 mol% $[Ir(cod)Cl]_2$ yielded quinoline **(176)** in moderate to good yields (scheme 119). Here they studied as well the effect of several Lewis-acids and reported that $Yb(OTf)_3$ gave comparable yields but $AlCl_3$, $TiCl_4$, and $HfCl_4$ furnished lower yields of quinolines.



R^1 = H, 4-Br, 4-F, 4-Me, 2-OMe, 4-OMe, 4-CO_2Me
R^2 = H, Bn, Et, Me, *n*-Pr, *i*-Pr

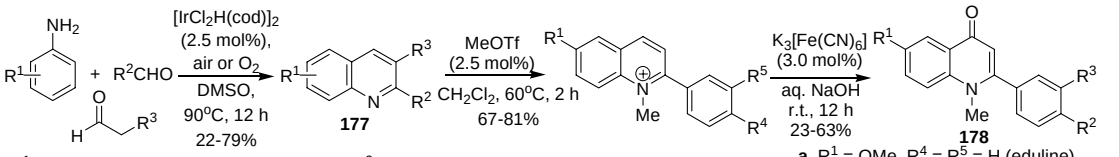
Scheme 109



R^1 = 4-F, 2-Me, 2-OMe, 4-OMe; R^2 = Me, Et, Pr, *i*-Bu, C_6H_5, 2-OMe-C_6H_4, 3-OMe-C_6H_4, 4-CO_2H-C_6H_4, 2-Pyridyl, 2-Furyl; R^3 = H, Me, Et, *i*-Pr, C_6H_5

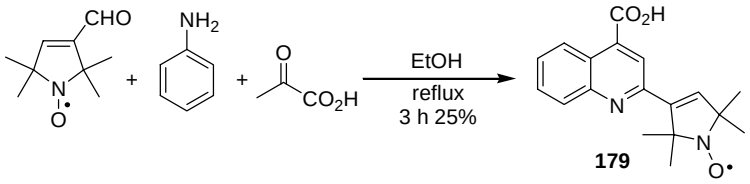
Scheme 110

Later they showed that this coupling could be accomplished in the presence of another Ir-catalyst under oxygen as oxidant. [123,124] The reaction proceeded with Mannich-type imine formation followed by nucleophilic addition to give β-aminoaldehydes which undergo dehydrative cyclization to give dihydroquinoline. This upon dehydrogenation via aerobic oxidation yielded 2-aryl-3-alkyl quinolines **(177)**. Some of the natural products (Eduline **(178a)** and Graveoline **(178b)**) were obtained from these quinolines via methylation followed by oxidation (scheme 111).



Scheme 111

Kalai *et al.* [66] reported the different synthetic routes for the synthesis of paramagnetic quinolines. The aniline was treated with paramagnetic aldehyde and pyruvic acid in EtOH to furnish the 2-substituted paramagnetic cinchoninic acid **(179)** (scheme 112).



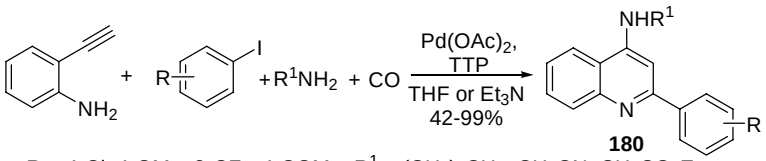
Scheme 112

4.0 5+1 Unit approach

4.1. From N-C-C-C-C+ C Units

4.1.1 From Alkynes-

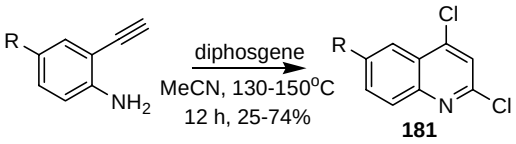
Rossi and co-workers [125] reported a highly innovative Pd-mediated multicomponent domino reaction to obtain 2-aryl-4-amino quinolines **(180)** starting from carbon monoxide, 2-ethynylarylamines, aryl iodides and primary amines. Strategically the Pd-mediated process involved a triple domino sequence including carbonylative coupling between 2-ethynylarylamines and aryl iodides followed by inter- and intramolecular nucleophilic addition to a carbon-carbon triple bond and carbon-oxygen double bond, respectively (scheme 113).



R = 4-Cl, 4-OMe, 3-CF_3, 4-COMe; R^1 = $(CH_2)_3CH_3$, CH_2CN, CH_2CO_2Et, $CH_2C_6H_4$, *cy*-Hex, $CH(C_2H_5)CO_2Et$, $CH(CHMe_2)CO_2Et$

Scheme 113

The successful synthesis of 2,4-dichloroquinoline **(181)** was accomplished in good yield from 2-ethynylaniline using diphosgene in MeCN under high temperature (130-150°C) as reported by Chi and his group (scheme 114). [126]

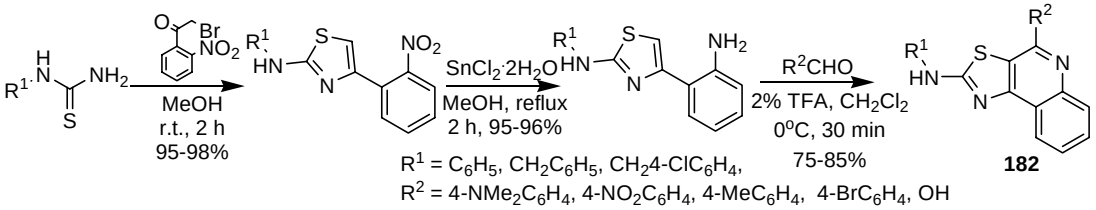


Scheme 114

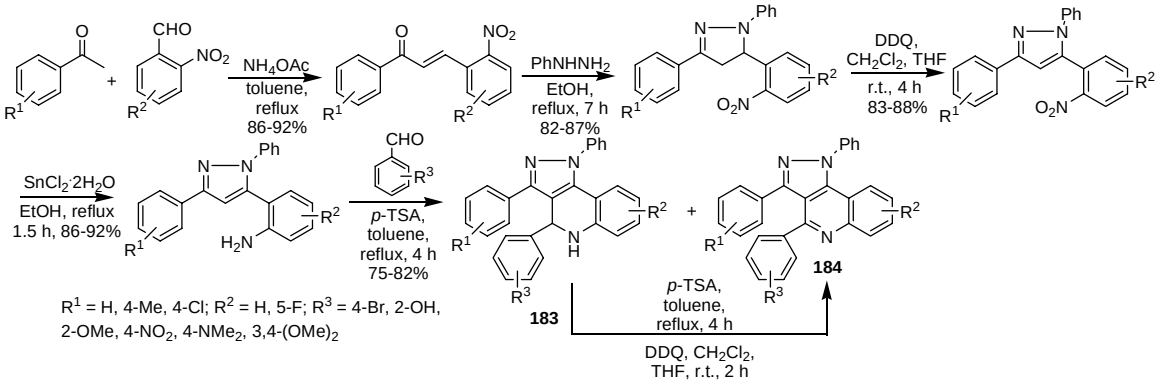
4.1.2 From modified Pictet-Spengler reaction-

Kundu and his group [127] described application of modified Pictet-Spengler reaction for the synthesis of thiazolo- and pyrazolo-quinolines **(182 & 184)** from thiazolo and pyrazolo amines. A reaction of substituted thiourea with 2-nitrophenacyl bromide yielded [4-(2-nitro phenyl)-thiazol-2-yl]-phenyl amine, which upon reduction followed by Pictet-Spengler reaction in the presence of TFA afforded thiazoloquinolines (scheme 115). In another variation of their work condensation of substituted acetophenone and 2-nitrobenzaldehydes in the presence of ammonium acetate in refluxing toluene followed by treatment with phenylhydrazine resulted in a chalcone which led to pyrazoles. Reduction of the aryl nitro group in pyrazoles followed by Pictet-Spengler cyclization with different aldehydes under the influence of *p*-TSA in toluene yielded pyrazoloquinolines **(184)** along with dihydropyrazoloquinolines **(183)**. DDQ mediated oxidation of dihydropyrazoloquinoline **(183)** afforded pyrazoloquinolines **(184)** (scheme 116). Adopting a similar approach of modified Pictet-Spengler reaction, El-Abdelah and co-workers [128] recently demonstrated successful synthesis of indolo [2,3-*c*] quinolines **(185)** (scheme 117). More recently Lemaire's group [129] reported the synthesis of a series of 6-arylbenzo thieno[3,2-*c*]quinolines via Heck-type coupling of benzo[*b*]thiophene with 2-nitroarylbromides to generate the 2-(2-nitroaryl)-

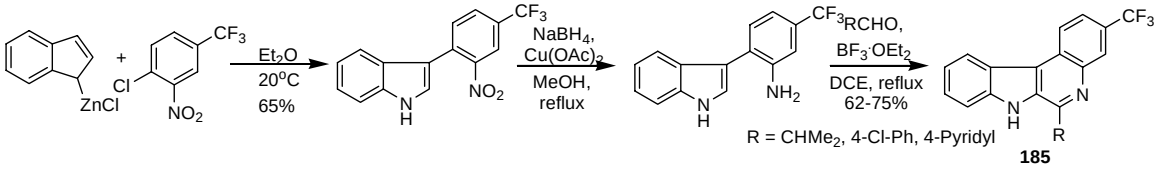
benzo[*b*]thiophenes which upon reduction followed by Pictet-Spengler reaction yielded the quinoline derivatives **(186)** as per the sequence depicted in scheme 118.



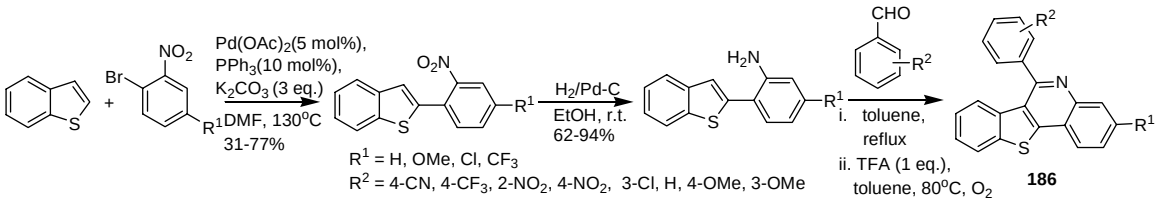
Scheme 115



Scheme 116



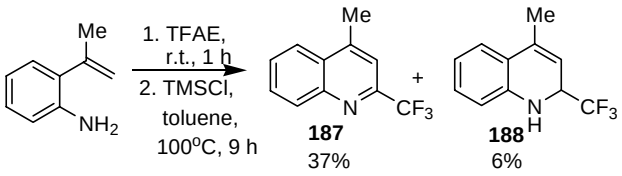
Scheme 117



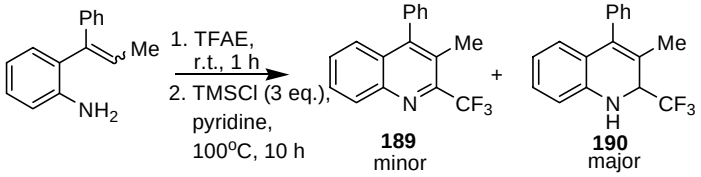
Scheme 118

4.1.3 Other N-C-C-C-C+ C approaches-

A convenient synthesis for 2-polyfluoromethylquinolines **(187-190)** via reaction between 2-vinyl anilines with perfluorinated hemiacetals or aldehydes in the presence of TMSCl in toluene (scheme 119) was reported by Taguchi *et al.* [130] However they observed that if the reaction was performed in pyridine, the 1,2-dihydroquinoline **(190)** was afforded as the major product (scheme 120).

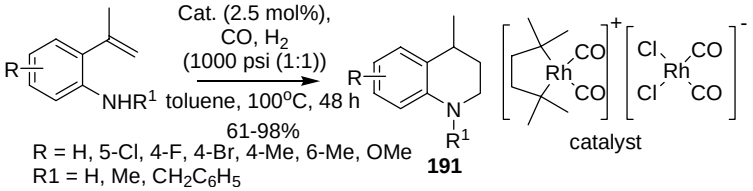


Scheme 119



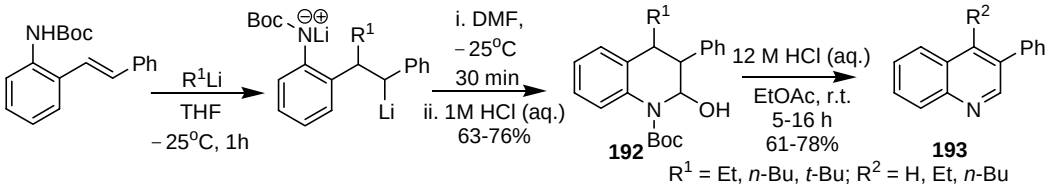
Scheme 120

Vieira and Alper described a new atom economical approach for the preparation of 1,2,3,4-tetrahydroquinolines **(191)** via intramolecular hydroaminomethylation of 2-isopropenylanilines mediated by an ionic domino Rh-catalyst. [131] The use of this catalyst did not require phosphines and the reaction was found to be highly chemo- and regioselective (scheme 121).

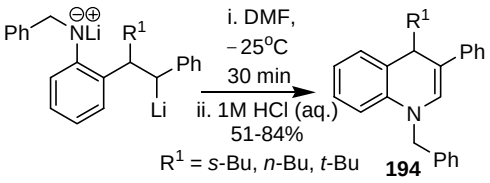


Scheme 121

The substituted *N*-Boc 2-amino stilbenes reacted with alkyl lithium to furnish lithiated intermediates which further reacted with DMF and subsequently acidified with dilute acid to obtain 1,2,3,4-tetrasubstituted tetrahydroquinolines **(192)** as shown in scheme 122. The generated tetrahydroquinolines when treated with dilute HCl provided the fully aromatized quinolines **(193)**. [132] If this reaction was performed with *N*-benzyl amino stilbene instead of *N*-Boc amino stilbene 1,4-dihydroquinolines **(194)** were formed (scheme 123).



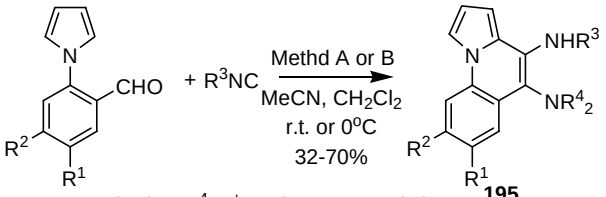
Scheme 122



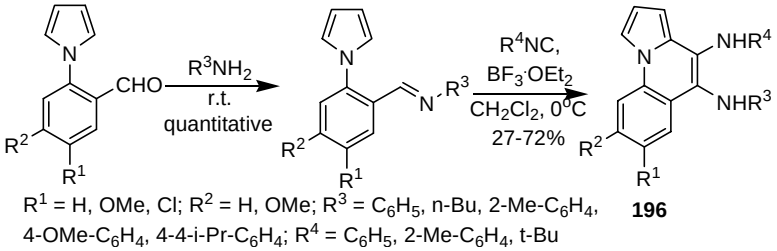
Scheme 123

4.2 From C-N-C-C-C+ C Units

Kobayashi and co-workers [133] developed a new synthetic strategy for the synthesis of 4,5-diamino-pyrrolo[1,2-*a*]quinolines **(195)** by reaction of secondary amine hydrochloride with 2-(pyrrol-1-yl)-benzaldehydes and isocyano compounds in the presence of NaI, Et_3N and TMSCl. They also exemplified their methodology for the synthesis of desired compounds using secondary amines along with $Et_3N{\cdot}HCl$ instead of secondary amine hydrochloride (scheme 124). In a variation to this strategy, subsequently they reported that 4,5-diamino-pyrrolo[1,2-*a*]quinolines **(196)** could also synthesized from *N*-alkyl/*N*-aryl-2-(pyrrol-1-yl) benzaldimines obtained via reaction of 2-(pyrrol-1-yl) benzaldehydes with primary amines which on reaction with aromatic or aliphatic isocyanides in the presence of $BF_3{\cdot}OEt_2$ yielded the final product **(196)** in moderate yields (scheme 125). [134]



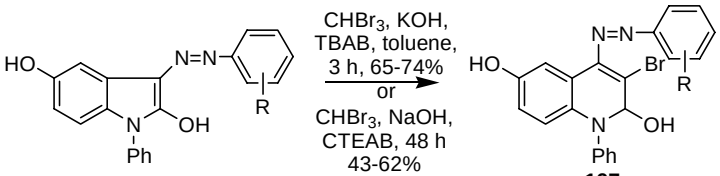
Scheme 124



Scheme 125

Sharma *et al.* [135] utilized the phase transfer catalyst for the synthesis of quinoline derivatives. The cycloaddition reaction of *N*-phenyl-2,5-dihydroxy-3-arylazo indoles with

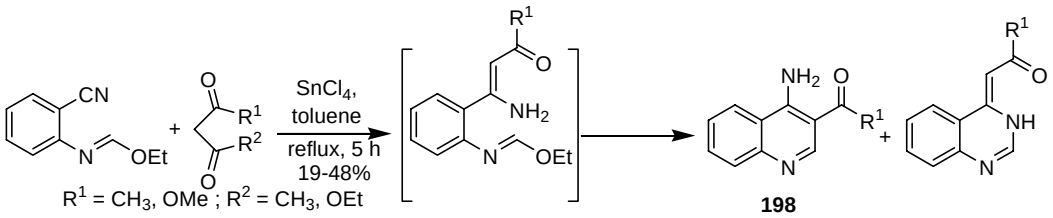
dibromocarbene (obtained from $CHBr_3$ and KOH) in the presence of TBAB produced the *N*-phenyl-2,6-dihydroxy-4-arylazo quinolines **(197)** which possess good antibacterial activity (scheme 126).



R = H, 4-Me, 2-NO_2, 3-NO_2, 4-NO_2, 2-Cl, 3-Cl, 4-Cl, 3-OH

Scheme 126

Chattopadhyay and co-workers [136] obtained quinolines **(198)** as a side product during the $SnCl_4$-catalyzed 5+1 annulation of β-dicarbonyl compounds and 2-ethoxymethyleneamidinonitriles in refluxing toluene (scheme 127).

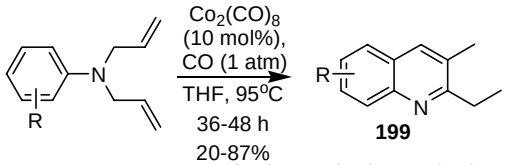


R^1 = CH_3, OMe ; R^2 = CH_3, OEt

Scheme 127

4.3 From C-C-N-C-C+ C Units

Recently Li and Jones demonstrated the synthesis and mechanism of the 2,3-disubstituted quinolines **(199)** in moderate to good yields from the diallylanilines in the presence of $Co_2(CO)_8$ catalyst in THF (scheme 128). [137] Yields of products was dependent on electronic and steric factors. For example electron donating group at *p*-position of diallylaniline favoured the reaction, whereas an electron withdrawing group inhibited the reaction.

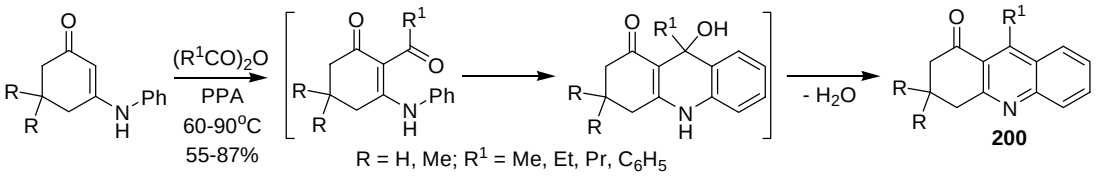


R = H, 2-Me, 4-Me, 2,3-$(Me)_2$, 3,4-$(Me)_2$, 3,5-$(Me)_2$,
2-Me-4-OMe, 3,5-$(OMe)_2$, 2-CF_3, 4-CF_3, 3,5-$(CF_3)_2$, CN

Scheme 128

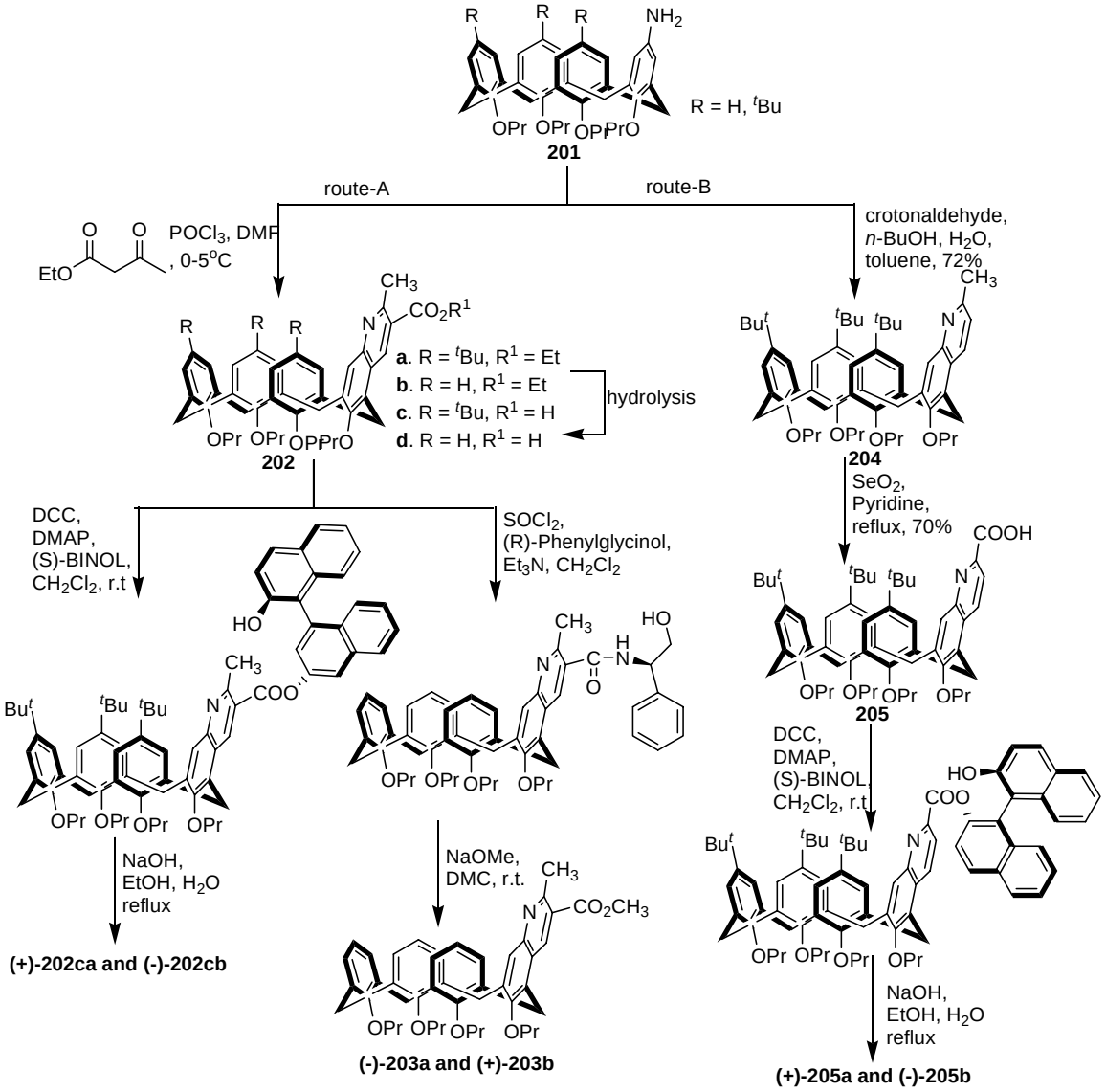
Kim and co-workers [138] conducted the synthesis of quinolines **(200)** from *N*-phenyl enaminones through reaction with acid anhydrides in PPA. The reaction proceeded via

sequential acylation at α-position of enaminone, cyclization and dehydration as shown in scheme 129.



Scheme 129

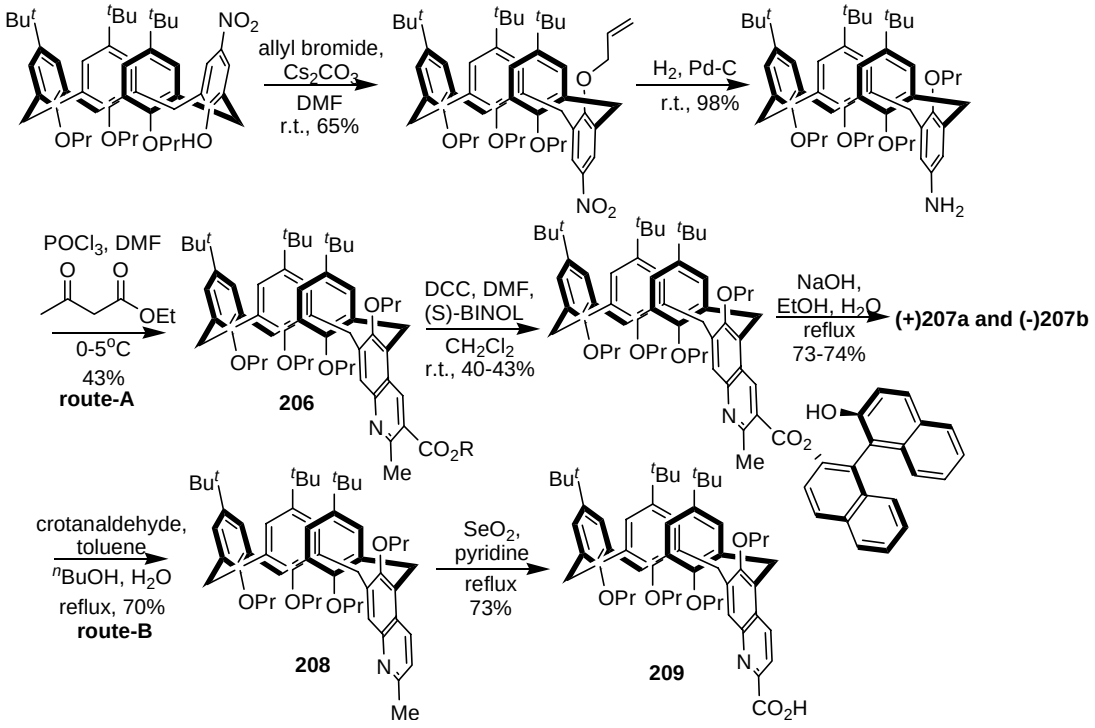
Miao *et al.* [139] described the synthesis of cone and partial cone conformations of substituted 2 or 3-carboxylic group substituted chiral calix[4]quinolines from amines. Aniline **(201)** reacted with a mixture of ethylacetoacetate and Vilsmeier reagent to afford the racemic



Scheme 130

chiral calix [4] quinolines **(202)** which hydrolyzed to a racemic mixture of 3-carboxylic acid quinolines **((+)-202ca & (-)-202cb)** on treatment with NaOH in EtOH and H_2O.

Alternatively the aromatic amine **(201)** upon condensation with crotonaldehyde in toluene furnished 2-methylquinoline **(204)** containing chiral calix. On oxidation with SeO_2 in pyridine the racemic 2-carboxylic group substituted chiral calix[4]quinolines **(205)** were formed in good yields as depicted in scheme 130. In a slight variation to their strategy they also demonstrated the synthesis of substituted 2- or 3-carboxylic acid chiral calix [4] quinolines **((+)-207a, (-)-207b & 209)** having partial cone conformations via two separate routes A and B. This was possible due to the inversion of configuration of the hydroxyl group at the time of allylation under the influence of $CsCO_3$ (scheme 131).



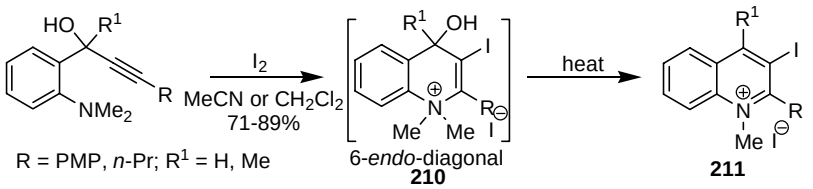
Scheme 131

5.0 6 Unit Approach

5.1 From N-C-C-C-C-C Unit

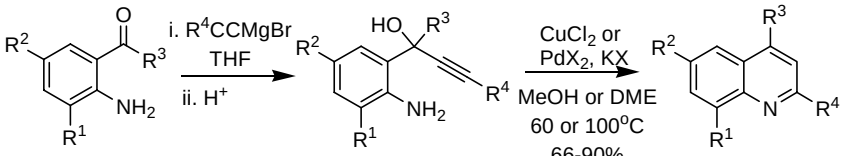
5.1.1 From alkyne-

Hessian and Flynn [140] demonstrated the synthesis of 3-iodoquinoline **(211)** via iodocyclization of 6-endo-diagonal product **(210)** obtained from the reaction between 2-(*N*,*N*-dimethylamino)benzaldehyde and lithium acetylides (scheme 132).



Scheme 132

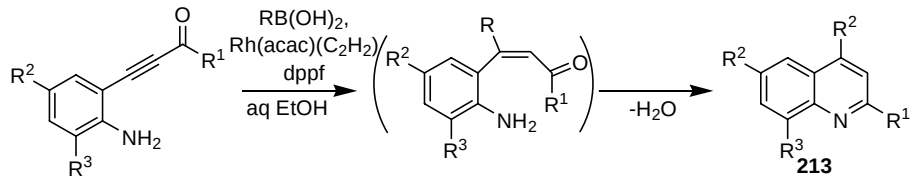
Gabriele and his collaborators [141] reported an innovative practical synthesis of substituted quinolines **(212)** through a two-step procedure involving Grignard addition of alkynylmagnesium bromides to 2-aminoarylketones followed by regioselective Cu- or Pd-catalyzed 6-*endo-dig* cyclodehydration of the analogous 1-(2-aminophenyl)-2-yn-1-ols as shown in scheme 133.



R1 = H, OMe; R2 = H, Cl; R3 = Me, Ph; R4 = Bu, *t*-Bu, Ph

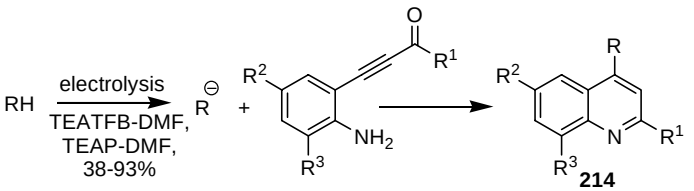
Scheme 133

A new synthetic approach was developed by Marinelli and co-workers [142] for the synthesis of functionalized quinolines from β-(2-aminophenyl)-α,β-ynones scaffold via sequential hydroarylation or hydrovinylation and heterocyclization. The reaction of β-(2-aminophenyl)-α,β-ynones with arylboronic acid or potassium aryl and vinyl trifluoroborates, followed by nucleophilic attack of amino group on carbonyl in the presence of Rh(acac)(C_2H_2), dppf in aqueous EtOH at 80-100°C furnished the desired functionalized quinolines **(213)** regioselectively as shown in scheme 134. Subsequently Arcadi *et al.* [143] reacted carbanions obtained from electrolysis of nitroalkanes or MeOH, with β-(2-aminophenyl)-α,β-ynones under solvent free conditions to obtain substituted quinolines **(214)** in moderate to good yields (scheme 135).



R = C_6H_5, 4-F-C_6H_4, 4-Me-C_6H_4, 3-COMe-C_6H_4, CH=CHC_6H_5, 3-Thiophenyl, 2-Furyl; R^1 = 2,4-Me_2-C_6H_3, 2-OMe-C_6H_4, 4-OMe-C_6H_4, 3-COMe-C_6H_4, 3-CF_3-C_6H_4, napthyl; R^2 = H, F; R^2 = H, F

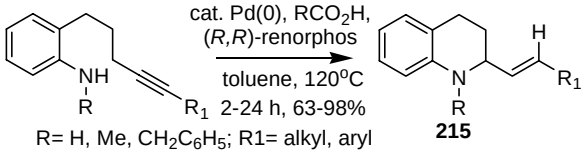
Scheme 134



R = MeOH, $MeNO_2$, *n*-$PrNO_2$, *i*-$PrNO_2$, $CH(CO_2Me)_2$; R^1 = 2-OMe-C_6H_4, 4-OMe-C_6H_4, 3,5-Me_2-C_6H_4, naphthyl; R^2 = H, F; R^3 = H, F

Scheme 135

Recently Yamamoto *et al.* [144] reported the preparation of 2-substituted tetrahydroquinolines via Pd-catalyzed intramolecular hydroamination of anilino alkynes. They extended the scope of the strategy by developing an asymmetric variant of the reaction using chiral Pd-catalyst to obtain tetrahydroquinolines **(215)** with *R*-configuration (scheme 136).



R= H, Me, $CH_2C_6H_5$; R1= alkyl, aryl

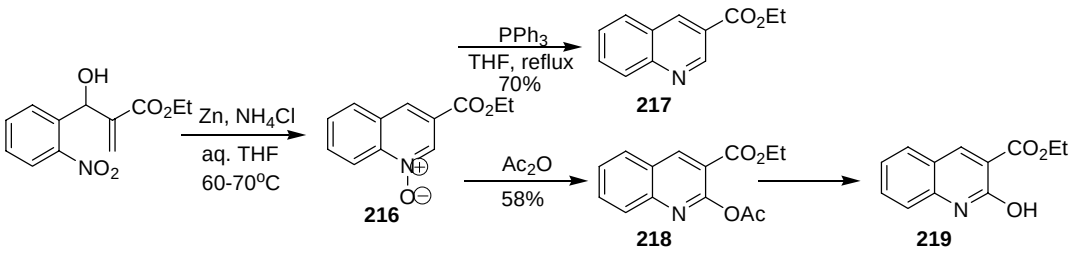
Scheme 136

5.1.2 From reductive cyclization-

A reductive cyclization strategy involving the reduction of 2-nitro or 2-azido group in aromatic ring to amino group followed by its cyclization with appropriate carbonyl or alkene has been widely applied towards the synthesis of quinoline and quinoline annulated heterocycles.

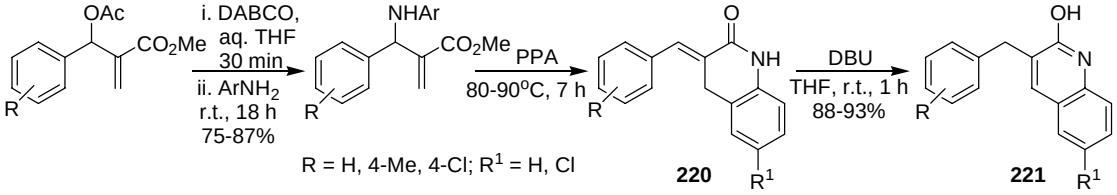
5.1.2.1 From Baylis-Hillman chemistry-

The Baylis-Hillman derivatives originating from 2-nitrobenzaldehyde have been extensively utilized for quinoline synthesis utilizing the reductive cyclization methodology. Kim Lee *et al.* [145] reported the synthesis of quinoline-*N*-oxide **(216)** from Baylis-Hillman adducts of 2-nitrobenzaldehyde via conjugate addition of nitroso intermediate in the presence of Zn and NH_4Cl in aqueous THF at 60-70°C. The resulting quinoline-*N*-oxides **(216)** were refluxed with PPh_3 in THF to furnish the corresponding quinolines **(217)**. Alternatively these *N*-oxides reacted with Ac_2O to provide the 2-acetoxy derivatives **(218)** which spontaneously transformed to 2-hydroxy quinolines **(219)** (scheme 137).



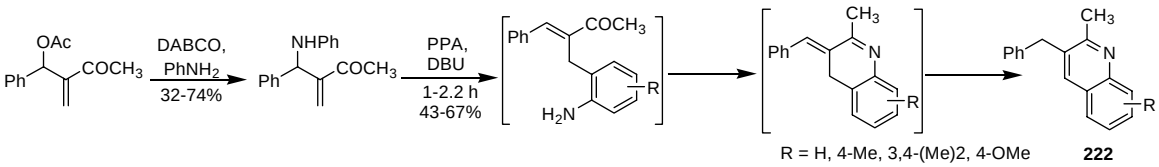
Scheme 137

Kim and co-workers [146] demonstrated the transformation of the Baylis-Hillman adducts to 3-benzylquinolin-2-ols. The synthetic pathway included the S_N2 nucleophilic substitution reaction between Baylis-Hillman acetate and aryl amines leading to the formation of 3-arylamino-2-methylene-3-phenylpropanoates, which upon treatment with PPA resulted in of 3-benzylidene-3,4-dihydro-1*H*-quinolin-2-ones **(220)**. Finally, isomerization in the presence of DBU yielded the 3-benzylquinolin-2-ols **(221)** as outlined in scheme 138.

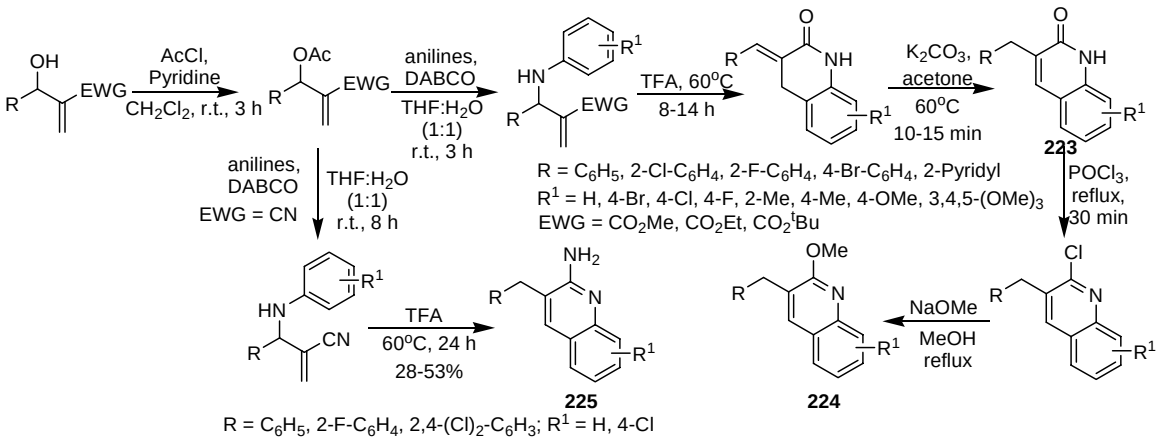


Scheme 138

They [147] also described the synthesis of 2-methyl-3-benzyl quinolines **(222)** in good yields from the Baylis-Hillman acetate via S_N2'- S_N2' displacement reaction of substituted aniline followed by PPA-mediated Claisen rearrangement and intramolecular cyclization (scheme 139). Subsequently in our attempts to synthesize 2-methoxy quinoline **(224)**, the starting substrate for antitubercular compound JJ-207910, we demonstrated that the same reaction could be accomplished in the presence of TFA to obtain 3-benzyl-2-quinolinols **(223)** in excellent yields as per the scheme 140. [148] These compounds were



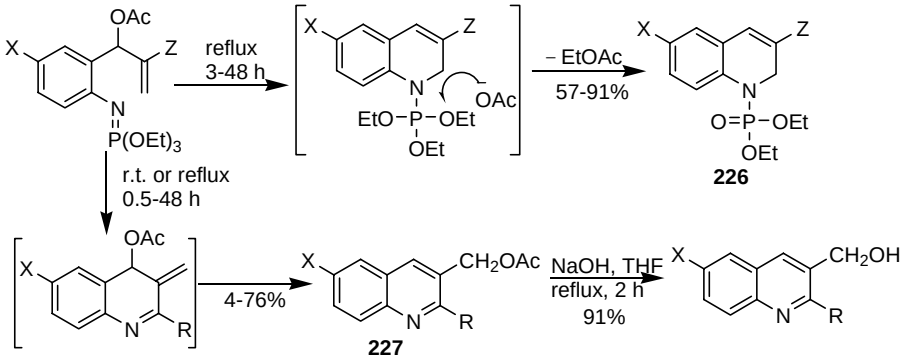
Scheme 139



Scheme 140

transformed to 2-methoxyquinolines **(224)** in excellent yields without the use of column chromatography. We observed that the Baylis-Hillman adduct of acrylonitrile undergo similar reaction to yield 2-aminoquinolines **(225)**.

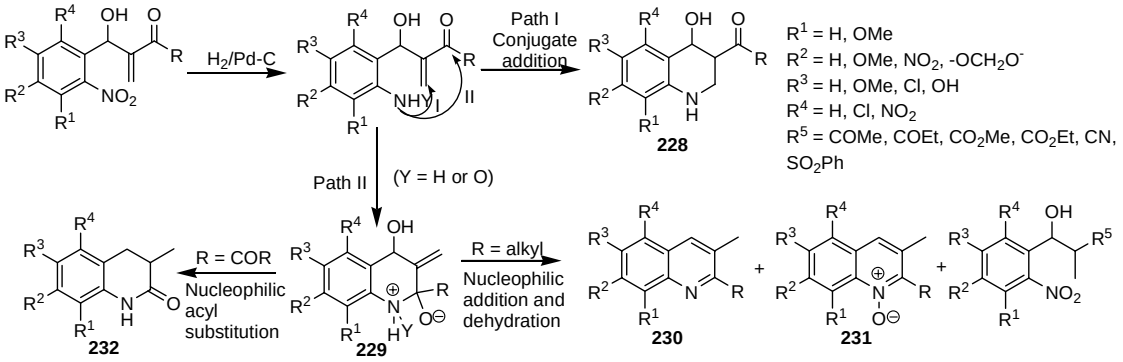
The acetoxy derivative of Baylis-Hillman adduct of 2-azidobenzaldehyde on Staudinger reaction led to imino phosphorane which after S_N2'-displacement reaction of the acetate afforded an intermediate that undergo Michaelis-Arbuzov rearrangement to furnish a mixture of 1-diethyl phosphono-1,2-dihydro quinoline **(226)** and 3-acetoxy methylquinolines **(227)**. It was reported that in case of adducts originating from acrylate the diethyl phosphonoquinoline **(226)** was the major product while for adducts derived from methyl vinyl ketone the amount of 3-acetoxymethylquinoline **(227)** was afforded in better quantities (scheme 141). [149]



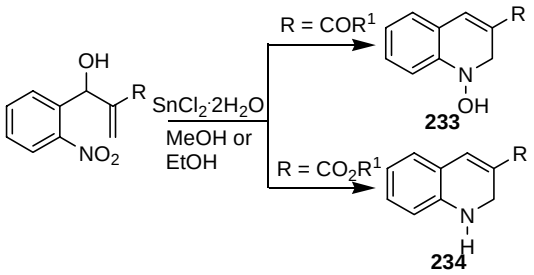
Scheme 141

Kaye and co-workers [150] demonstrated the synthesis of quinolines **(228-234)** from the Baylis-Hillman adducts of 2-nitrobenzaldehyde via reductive cyclization as per the sequence shown in scheme 142. The reduction was accomplished either by catalytic

hydrogenation or by $SnCl_2$ (scheme 143). They suggested that though the formation of products may take place via path-I or II, in most of the cases Path-II predominates.

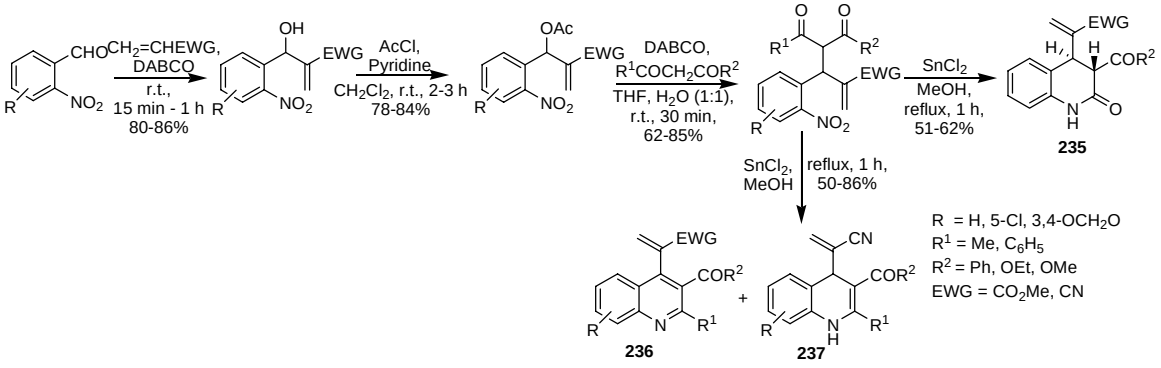


Scheme 142



Scheme 143

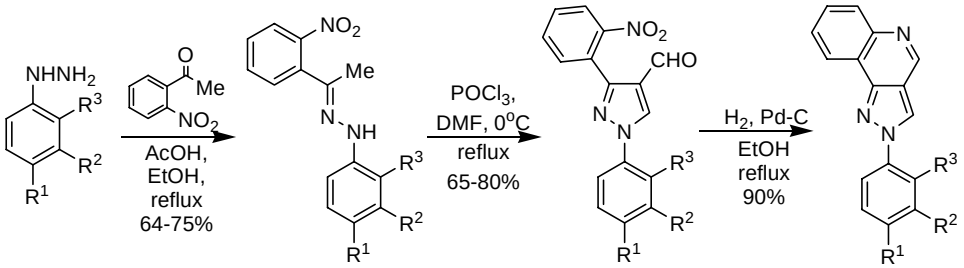
We have also demonstrated the synthesis of 4-vinyl-quinoline derivatives **(235-237)** utilizing Baylis-Hillman chemistry through the S_N2'-S_N2'displacement reaction of Baylis-Hillman acetate of 2-nitrobenzaldehyde with carbonyl group containing nucleophiles. [151] The $SnCl_2$-mediated reduction of the nitro group triggered a subsequent intramolecular cyclization yielding the final quinoline derivatives **(235-237)** as shown in scheme 144.



Scheme 144

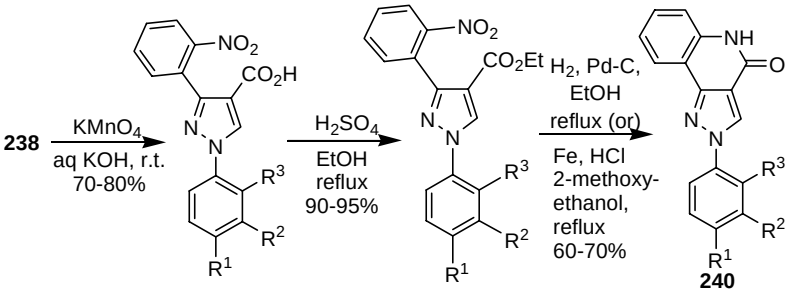
5.1.2.2 Other reductive cyclizations-

Baraldi *et al.* [152] described the synthesis of novel 2-arylpyrazolo[4,3-*c*]quinolines **(239-244)** starting from phenyl hydrazines. As shown in scheme 145, the condensation of substituted phenylhydrazines with 2-nitroacetophenone afforded the corresponding phenylhydrazones which on treatment with Vilsmeier reagent furnished the pyrazole-4-carbaldehydes **(238)**. Reduction of the nitro group followed by intramolecular cyclization in EtOH produced the pyrazoloquinolines **(239)**. The generated pyrazole-4-carbaldehydes were also converted to their acids by $KMnO_4$ to obtain pyrazoloquinolones **(240)** via sequential esterification, reduction and cyclization (scheme 146). These quinolones **(240)** were used as precursors for the pyrazoloquinolines **(240-244)** by treating them with $POCl_3$ in the presence of PCl_5 followed by reaction with amines or MeONa to afford the corresponding pyrazoloquinolines **(241)**. The reaction of 4-chloro-pyrazoloquinolines with 4-chlorobenzoic acid hydrazide in EtOH at 70ºC yielded **242** whereas the same reaction when performed at 120ºC resulted in the corresponding tetracyclic compounds **(243)**. The 4-thiomethyl pyrazoloquinolines **(244)** were also obtained from the corresponding quinolones on reaction with Lawesson's reagent followed by methylation (scheme 147). The compounds generated during the endeavor were found to be potent and selective human A3 adenosine receptor antagonists.

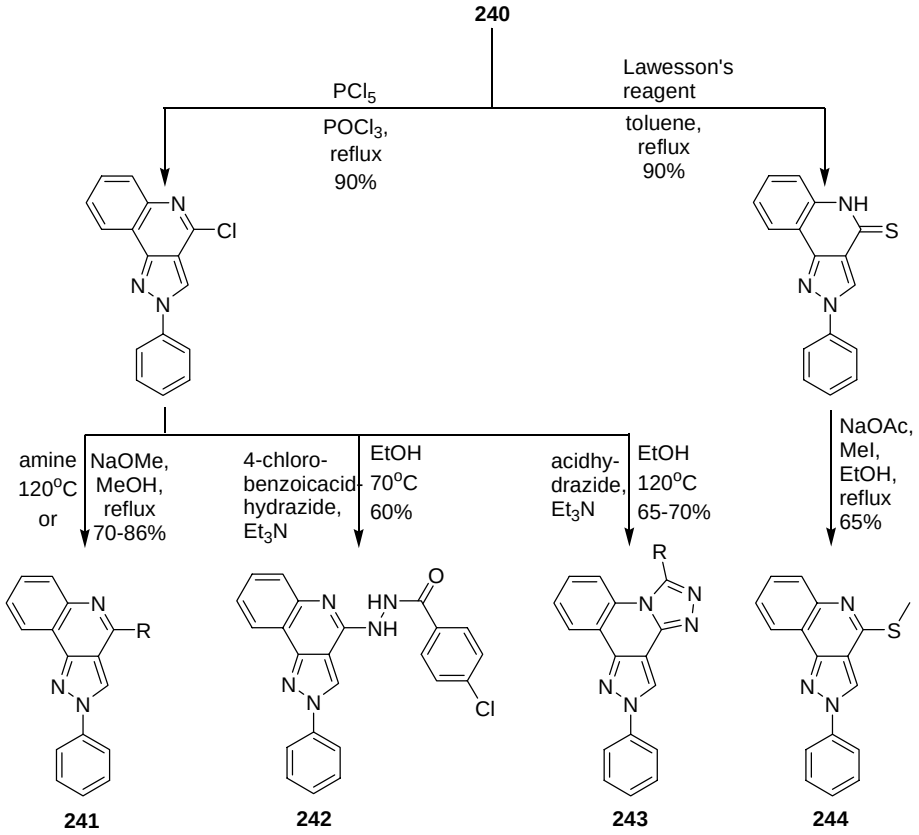


R^1 = H, Cl, F, OMe, Me, Et, *n*-Bu, *i*-Pr; R^2 = H, Cl; R^3 = H, Cl

Scheme 145

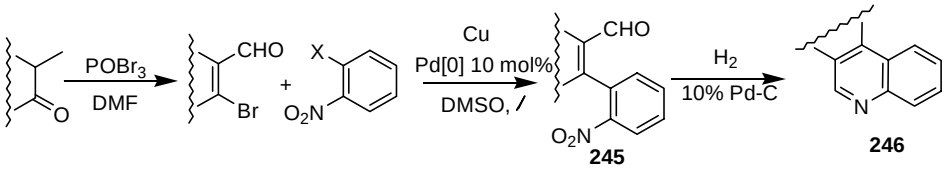


Scheme 146

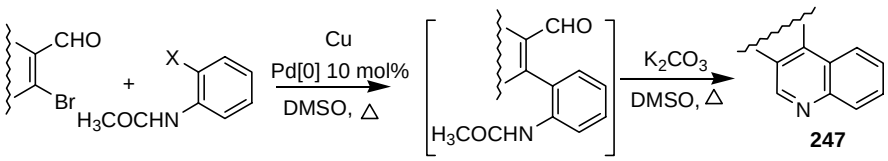


Scheme 147

Some *et al.* [153] described a new protocol involving Pd(0)-mediated Ullman cross-coupling of β-bromo-α, β-unsaturated aldehydes with 1-bromo-2-nitrobenzene to produce the β-(2-nitrophenyl)-α, β-unsaturated aldehydes **(245)**, which upon reductive cyclization using either In-NH_4Cl or Raney-Ni with hydrogen furnished the quinolines **(246)** (scheme 148). They developed another route for the synthesis of same set of quinolines **(257)** utilizing the 2-bromoacetanilides instead of 1-bromo-2-nitrobenzene as shown in the scheme 149.

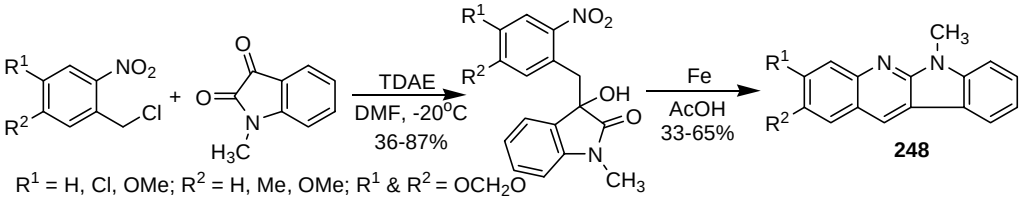


Scheme 148



Scheme 149

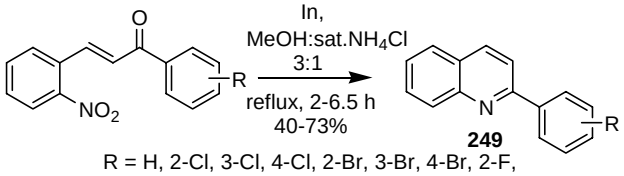
Vanelle and co-workers [154] performed an original and rapid synthesis of new substituted 6*H*-indolo[2,3-*b*]quinolines **(248)**. The reaction of substituted 2-nitrobenzylchloride with 1-methyl isatin in the presence of TDAE generated the α-hydroxy lactams, which were transformed to indoloquinolines by the reduction of nitro group followed by intramolecular cyclization and dehydration in the presence of Fe in AcOH (scheme 150).



R^1 = H, Cl, OMe; R^2 = H, Me, OMe; R^1 & R^2 = OCH_2O

Scheme 150

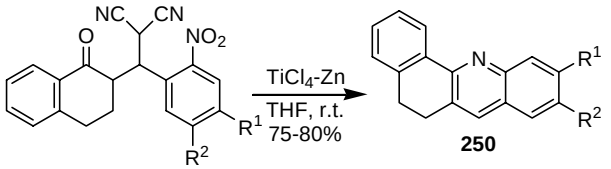
2-Nitrochalcones were successfully transformed to 2-aryl quinolines by Kim *et al*. [155] A reductive cyclization triggered by reduction of nitro group of 2-nitrochalcone in the presence of In-NH_4Cl afforded quinoline **(249)** in moderate to good yields (scheme 151).



R = H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-F, 3-F, 4-F, 2-Me, 4-Me, 3-OMe, 4-OMe

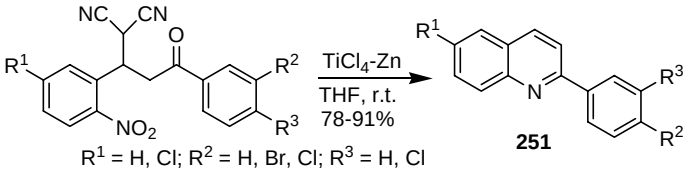
Scheme 151

Shi *et al.* [156] described that intramolecular reductive cyclization of ketomalononitriles induced by a low valent Ti-reagent made by $TiCl_4$-Zn provided acridines **(250)** and quinolines **(251)** as shown in scheme 152, 153.



R^1 = H, OMe; R^2 = H, OMe, Cl; R^1 & R^2 = OCH_2O

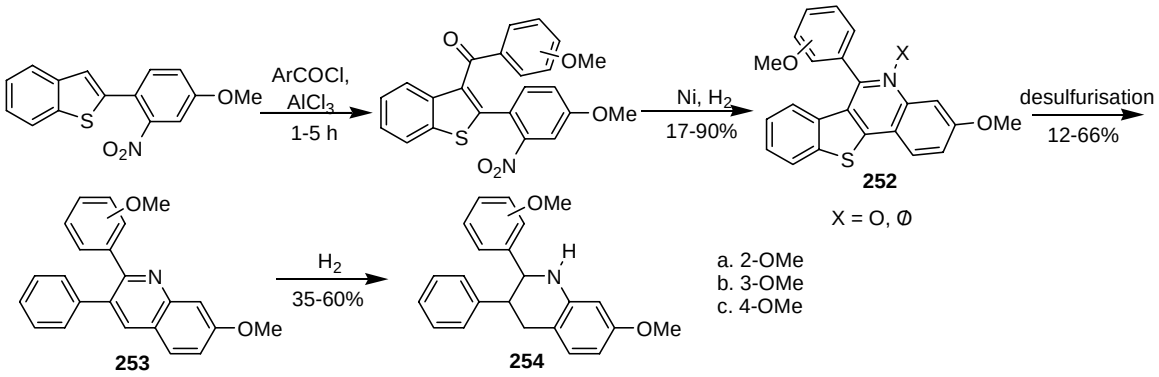
Scheme 152



R^1 = H, Cl; R^2 = H, Br, Cl; R^3 = H, Cl

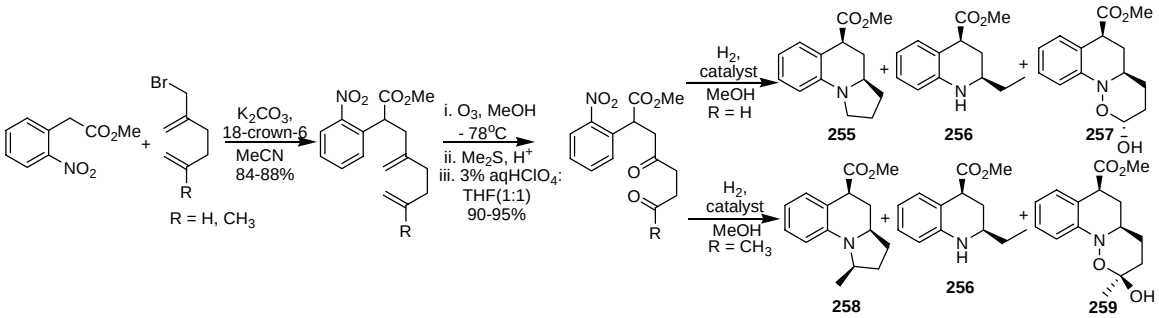
Scheme 153

Lemaire also demonstrated that benzo[*b*]thiophene acts as a template for the synthesis of substituted quinolines **(253)** and tetrahydroquinolines as **(254)** shown in scheme 154. [157]



Scheme 154

A diastereoselective synthesis of hexahydropyrrolo[1,2-*a*]quinolines **(255 & 258)** was described by Bunce *et al.* [158]. Synthetic sequence involved the alkylation of methyl (2-nitrophenyl) acetate with 2-bromomethyl-1,5-hexadiene derivatives using K_2CO_3 and 18-crown-6 in MeCN to produce the nitro dienoic esters, which upon ozonolysis furnished the nitro dicarbonyl compounds. Catalytic hydrogenation of nitro derivative afforded the hexahydropyrrolo [1,2-*a*] quinolines-5-carboxylic ester **(255 & 258)** as a single isomer with *cis*-geometry along with deacetylated product **(256)** and a fused hemiacetal adduct **(257 & 259)** (scheme 155). The ratio of the product depended on the catalyst used and the hydrogen pressure applied as shown in table-1.



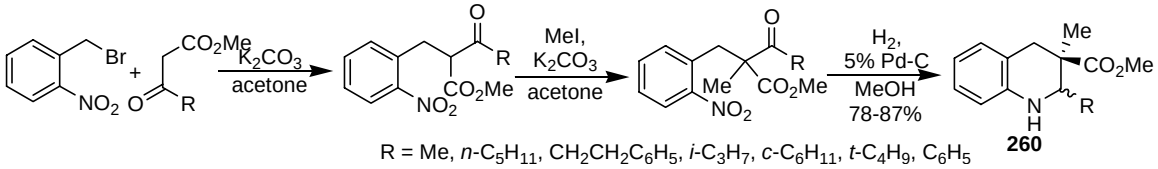
Scheme 155

Table-1

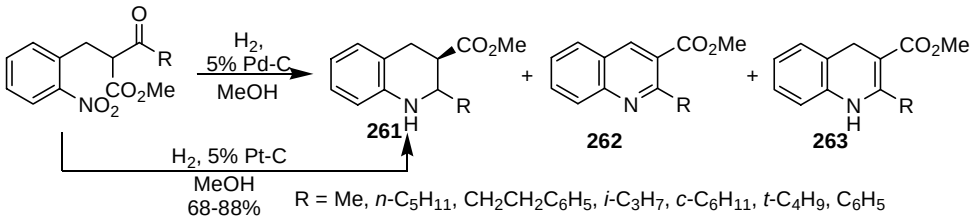
Conditions	yield% **255**	yield% **256**	yield% **257**	yield% **258**	yield% **259**

5% Pd/C (3 atm, purged)	36	29 (7)	3	58	4
PtO_2 or Pt/C (3 atm, purged)	20-25	0 (0)	48-53	34	36
5% Pd/C (1 atm, purged)	29	37 (16)	3	48	4
5% Pd/C (5 atm, not purged)	66	5 (4)	3	64	3

Very recently they introduced another synthetic sequence for (±)2-alkyl-1,2,3,4-tetrahydroquinoline-3-carboxylic esters **(260)** by reductive cyclization of 2-methyl-2-(2-nitrobenzyl)-substituted-β-keto ester derivatives (scheme 156). [159] The reaction was conducted using different hydrogenation conditions to synthesize the quinoline derivatives **(261-263)** and to understand the importance of the ester group for outcome of the diastereoselectivity in the procedure (scheme 157). [160] It was observed that even though the final reductive cyclization was not as selective as that observed earlier for (±)2-alkyl-1,2,3,4-tetrahydroquinoline-4-carboxylic esters **(255-259)**, it supported the product having a *cis* relationship between the alkyl and ester.



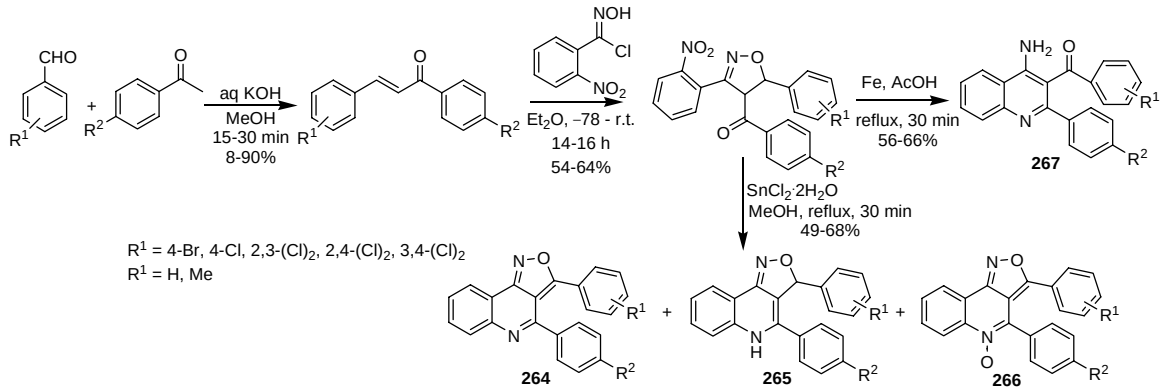
Scheme 156



Scheme 157

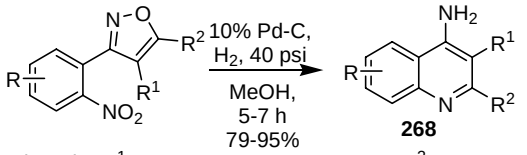
We have successfully achieved the synthesis of poly functionalized isoxazolo[4,3-*c*] quinolines **(264-266)** from chalcones. [161] As shown schematically 1,3-dipolar cycloaddition of chalcones with 2-nitrobenzonitrile oxide afforded the 2-isoxazolines, which upon reduction of nitro group by $SnCl_2{\cdot}2H_2O$ in MeOH, followed by intramolecular cyclization furnished a mixture of isoxazolo[4,3-*c*]quinolines **(264)** and 3,5-dihydroisoxazolo[4,3-*c*]quinolines **(265)** (scheme 158). Under similar reaction conditions compounds originating from 4-bromobenzaldehyde afforded the quinoline-*N*-oxide **(266)** along with isoxazolo[4,3-*c*]quinolines **(264)** and 3,5- dihydroisoxazolo[4,3-

c]-quinolines **(265)**. In contrast, when the reduction was performed with Fe in AcOH the 3-benzoylquinolin-4-ylamine derivatives **(267)** were obtained in good yields.



Scheme 158

We have also reported the synthesis of substituted 4-aminoquinolines **(268)** from 3-(2-nitrophenyl)isoxazoles via Pd-C-catalyzed hydrogenation which proceeded through sequential reduction of the nitro group, isoxazole ring cleavage and regiospecific cyclization of aromatic amino group with the keto of β-amino ketone (scheme 159). [162]

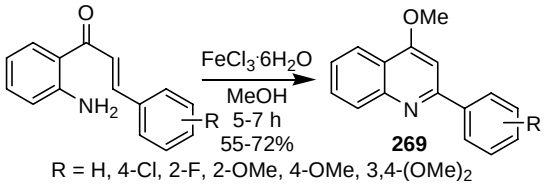


R = H, 6,7-$(OMe)_2$; R^1 = H, CHO, CH_2OH, CO_2Me; R^2 = H, Me, CH_2OH, CF_3, CH(OH)CH(CH_2(4-Me-piperazin-2-yl)CO_2Me, CH(OH)CHMeCO_2Me

Scheme 159

5.1.3 Other N-C-C-C-C-C approaches-

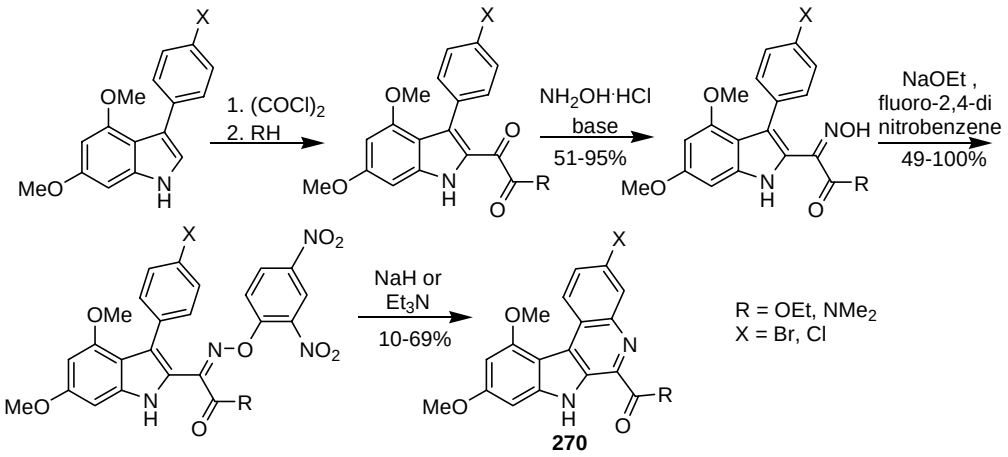
Kumar and Perumal [163] successfully accomplished the synthesis of 4-alkoxy-2-arylquinolines **(269)** via one-pot oxidative cyclization of 2'-aminochalcones employing $FeCl_3 \cdot 6H_2O$ as the catalyst as shown in scheme 160. They reported that out of several solvents attempted for optimization, the reaction proceeds in MeOH or EtOH only.



R = H, 4-Cl, 2-F, 2-OMe, 4-OMe, 3,4-$(OMe)_2$

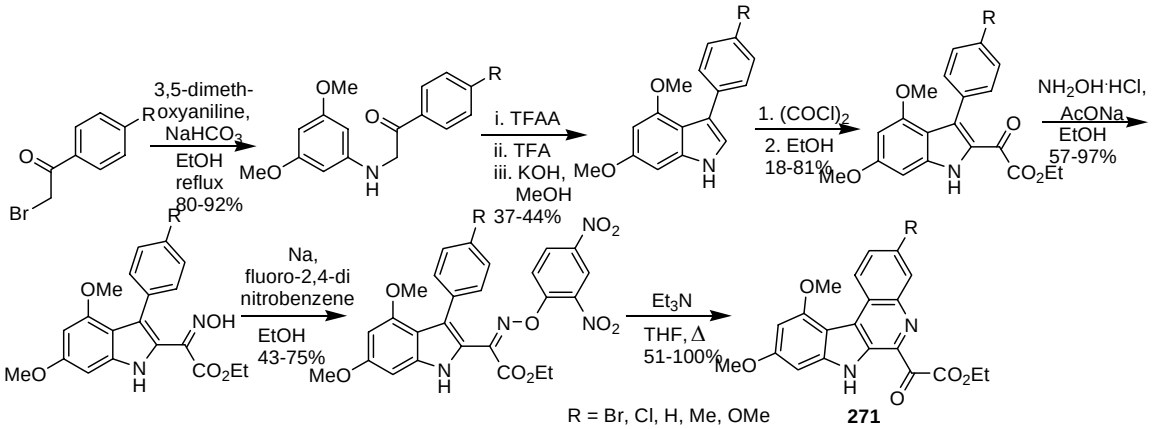
Scheme 160

Black and co-workers [164] conducted the reaction of 2,4-dinitrophenyl ethers of 3-arylindole-2-ketoximes in the presence of NaH or Et_3N resulting in indolo[2,3-*c*]quinolines **(270)** as per the reaction sequence shown in scheme 161.



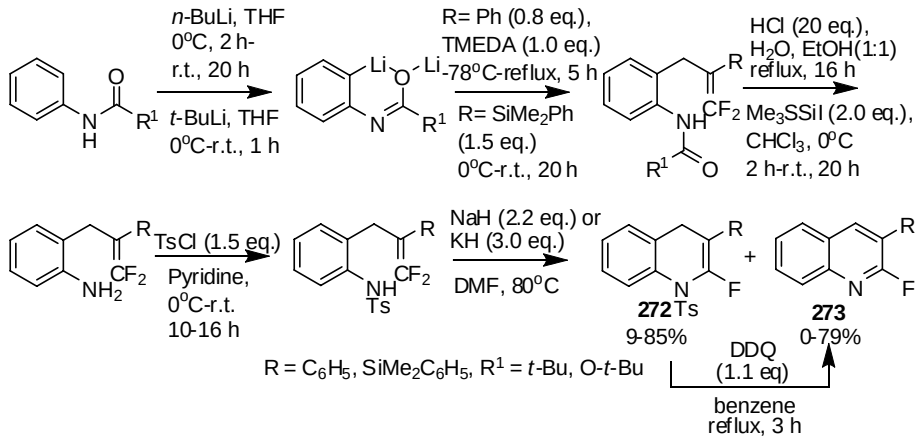
Scheme 161

Very recently they have extended their synthetic methodology and carried out the mechanistic studies to explain the final step consisting of unusual base-promoted cyclization. [165] They reported that the ester group was responsible for stabilising the intermediate in the electrocyclic process thus facilitating the reaction (scheme 162).



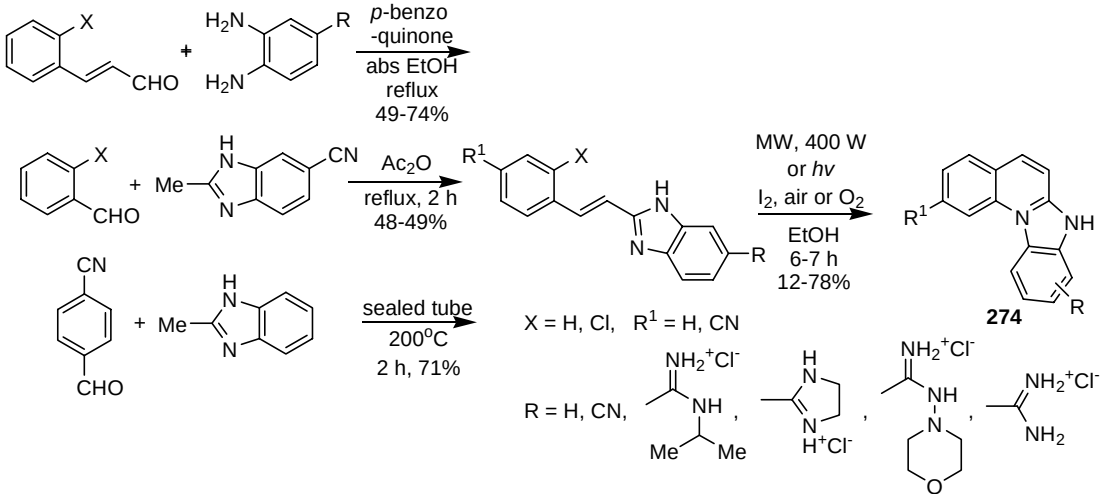
Scheme 162

Ichikawa and co-workers [166] disclosed the synthesis of 2-fluoro quinolines from *N*-[2-(3,3-difluoroallyl)phenyl]-substituted *p*-toluenesulfonamide obtained from the *N*-protected anilines upon treatment with lithiated base followed by S_N2' reaction with 1-(trifluoromethyl)vinyl compounds, deprotection and subsequent tosylation. The intramolecular substitution reaction of tosylamide nitrogen and vinylic fluorines in 1,1-difluoro-1-alkene in the presence of a base such as NaH or Et_3N yielded corresponding 2-fluoro tosylated dihydroquinolines **(272)** and quinolines **(273)** as illustrated in scheme 163. The dihydroquinolines **(272)** obtained during the process were reacted with DDQ to afford the quinolines **(273)**.



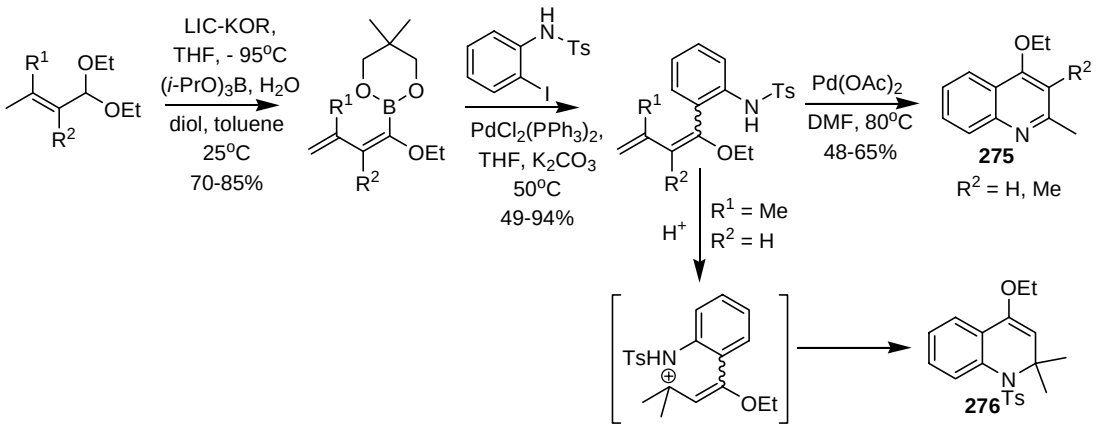
Scheme 163

Hranjec and co-workers [167] reported the synthesis of benzimidazo[1,2-a]quinolines **(274)** from *N*-amidino-and cyano-substituted *E*-2-styryl-1*H*-benzimidazoles (obtained from various methods) via photochemical dehydrocyclization and dehydrohalogenation in the presence of molecular iodine and O_2 in EtOH (scheme 164).



Scheme 164

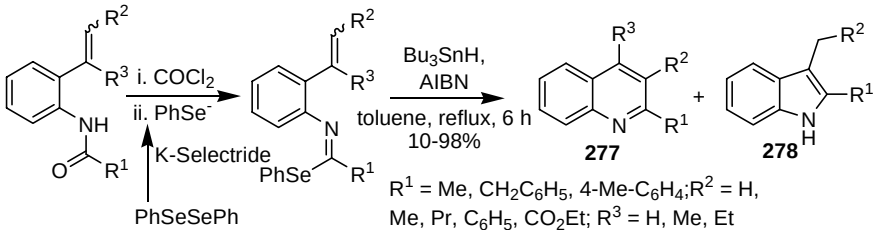
Deagostino *et al*. [168] demonstrated a novel metal-catalyzed synthesis of quinoline **(275 & 276)** from *N*-tosyl protected dienylaniline under mild conditions. The cyclization reaction proceeded via formation of a π-complex between Pd and dienyl fragment which underwent heterocyclization to form a σ-complex. This complex underwent β-elimination followed by re-addition of HPdX to the exocyclic bond followed by elimination of Pd(OAc)TS to furnish quinoline (scheme 165). Notably this process does not require reoxidation.



Scheme 165

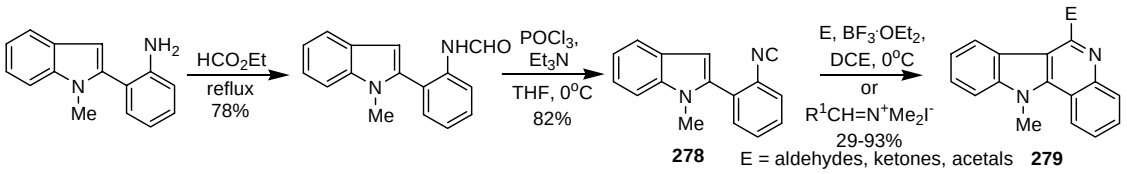
5.2 From C-N-C-C-C-C Unit

Bowman and co-workers [169] described a new route for the synthesis of quinolines from amides. Their protocol involved reaction of amides with phosgene followed by diphenyl diselenide in the presence of K-selectride to generate imidoyl selanides. The imidoyl selenides yielded the corresponding indoles (5-*exo*) **(278)** and quinolines (6-*endo*) **(277)** via imidoyl radical cyclization with alkene in the presence of Bu_3SnH. The reaction of imidoylselenides with Bu_3SnH and triethyl borane selectively gave the quinolines **(277)** (scheme 166).



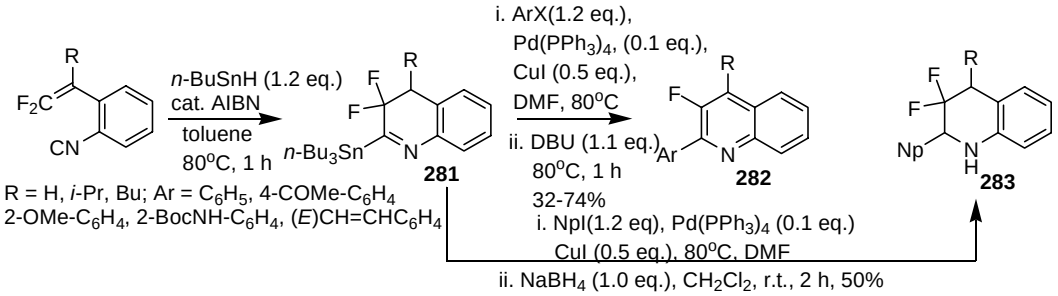
Scheme 166

Kobayashi *et al*. [170] demonstrated the synthesis of 6-substituted indolo[3,2-*c*]quinolines **(280)**. As depicted in the scheme 167, reaction of 2-(2-aminophenyl)-1-methyl-*H*-indole with ethylformate led to the formation of *N*-formyl derivative, which was treated with $POCl_3$ and Et_3N in THF at 0°C to afford 2-(2-isocyanophenyl)-1-methyl-1*H*-indole **(279)**. The 2-(2-isocyanophenyl)-1-methyl-1*H*-indole was treated with aldehydes, ketones, and acetals in the presence of catalytic amount of $BF_3{\cdot}OEt_2$ or *N*,*N*-dimethyliminium salts to furnishes the 6-(1-hydroxy or alkoxy alkyl or 1-dimethylaminoalkyl)-11*H*-indolo[3,2-*c*]quinolines **(280)** in satisfactory yields.



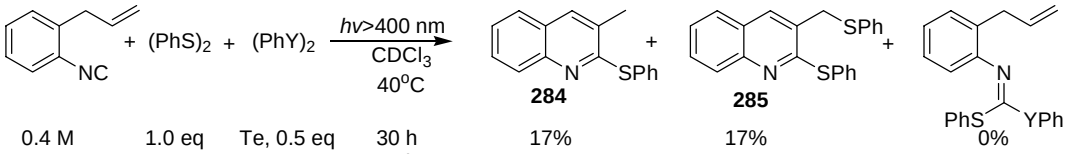
Scheme 167

A successful facile synthesis of 3-fluoro quinolines **(281-283)** through Sn-mediated radical cyclization was reported by Mori and Ichikawa. [171] Radical cyclization of 2-cyano substituted β,β-difluorostyrenes in a endo-trig fashion followed by transformation of C-Sn bond and dehydrofluorination or reduction as depicted in scheme 168. They further demonstrated that an appropriately substituted 3-fluoroquinoline **(281-283)** served as excellent precursor for cryptolepines.



Scheme 168

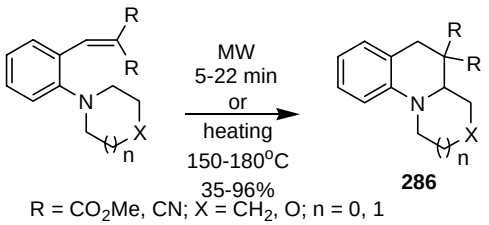
The isocyanides bearing an electron withdrawing group undergo a highly selective thiotelluration by the use of a disulfide-ditelluride mixture upon irradiation by visible light. Ogawa and co-workers applied this photoinduced reaction to radically cyclize 2-allylsubstituted phenylisocyanides to generate quinolines derivatives **(284 & 285)** as per the reaction sequence shown in scheme 169. [172]



0.4 M	1.0 eq	Te, 0.5 eq	30 h	17%	17%	0%
0.2 M	1.2 eq	Te, 1.0 eq	30 h	13%	22%	0%
0.4 M	2.0 eq	Te, 0.5 eq	15 h	14%	31%	0%
0.4 M	1.0 eq	Se, 0.6 eq	8 h	26%	0%	58%
0.1 M	1.0 eq	Se, 0.5 eq	7 h	39%	0%	33%

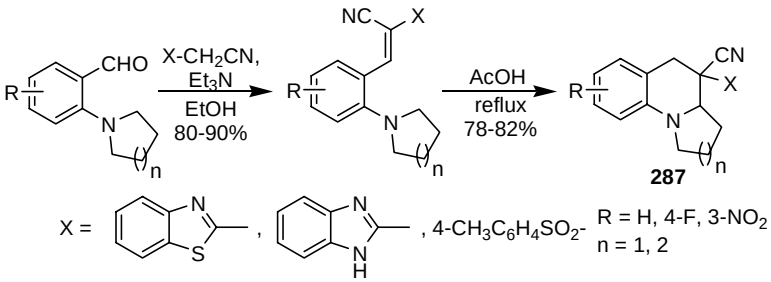
Scheme 169

Vander Eycken and associates [173] reported significant improvement in yields, for the synthesis of pyrido-fused quinolines **(286)** from 2-vinyl *tert* amine when the reaction was performed under solvent free conditions through microwave irradiation (scheme 170).



Scheme 170

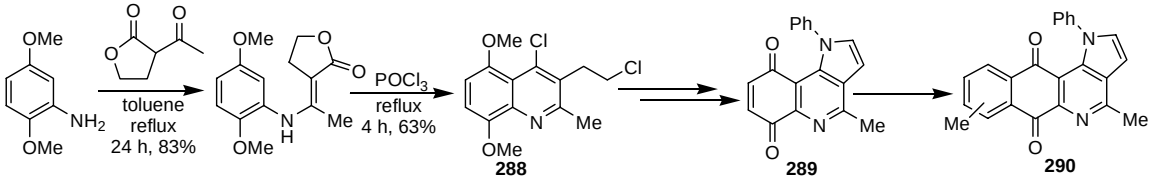
Tverdokhlebov and his group [174] reported the synthesis of hetaryl- and arylsulfonyl-substituted pyrrolo- and pyrido[1,2-*a*]quinolines **(287)** from the reaction of 2-*tert*-aminoaryl aldehydes with substituted acetonitriles followed by proton-assisted cyclization of resulting cinnamonitrile derivatives in AcOH at refluxing temperature as shown in scheme 171.



Scheme 171

5.3 From C-C-N-C-C-C Unit

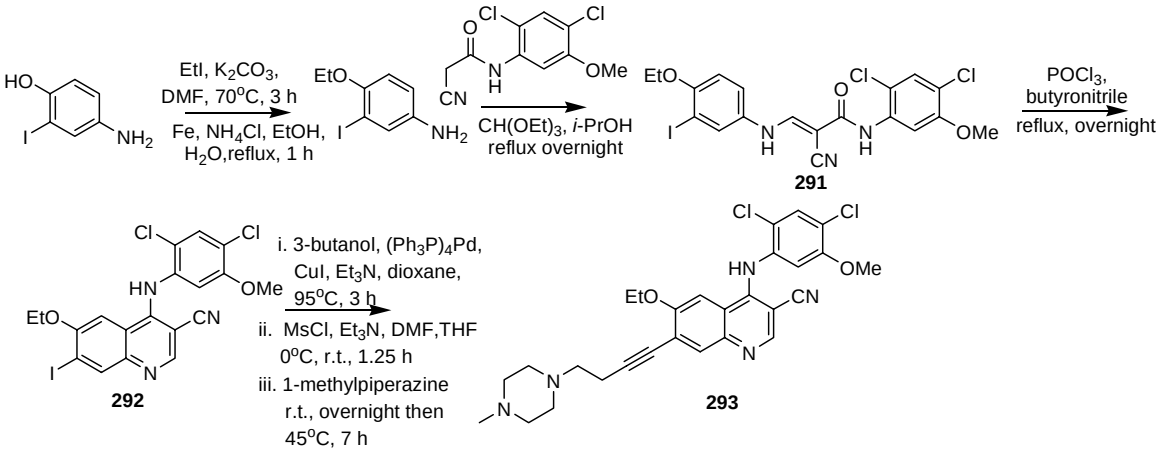
Tapia and co-workers [175] successfully constructed a new class of angular tetracyclic quinolines **(290)** via Diels-Alder reaction between pyrrroloquinolinequinone **(289)** and diene. The starting quinoline **(288)** was obtained from reaction of 3-acetylfuranone with 2,5-dimethyl aniline followed by refluxing in $POCl_3$ as shown in scheme 172.



Scheme 172

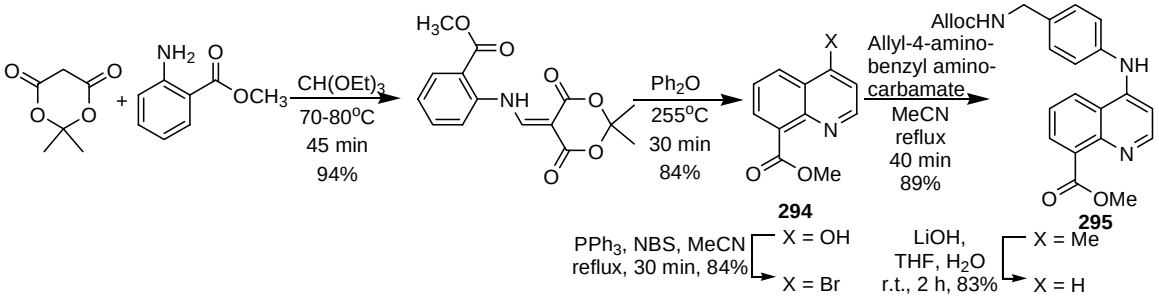
Boschelli and co-workers [176] carried out the synthesis of 7-ethynyl-3-quinolinecarbonitriles and identified the 4-[(2,4-dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile (SKS-927) as a potent Src inhibitor. Their protocol involved the reaction of 4-ethoxy-3-iodoaniline with 2-cyano-*N*-(2,4-dichloro-methoxyphenyl)acetamide and triethylorthoformate to yield

291, which on treatment with $POCl_3$, provided 4-(2,4-dichloro-5-methoxyphenylamino)-6-ethoxy-7-iodoquinoline-3-carbonitrile **(292)**. Reaction of these iodoquinolines **(292)** with 3-butynol followed by mesylation and reaction with 1-methylpiperazine delivered the 4-[(2,4-dichloro-5-methoxyphenyl)-amino]-6-ethoxy-7-[4-(4-methylpiperazin-1-yl)but-1-ynyl]-3-quinolinecarbonitrile **(293)** as shown in scheme 173. Simultaneously they also synthesized 7-ethynyl-3-quinolinecarbonitrile analogs and bioevaluated them for inhibition of Src kinase activity concluding that they were less potent than the SKS-927.



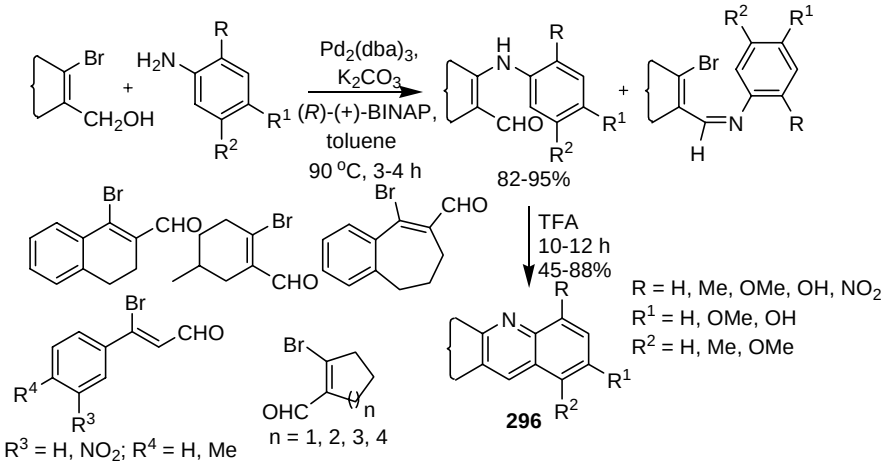
Scheme 173

A high yielding synthesis of methyl-4-(4-methylaminoallyoxycarbamate)anilino-quinoline-8-carboxylate was reported by Beal and co-workers. [177] Their strategy involved condensation of meldrum acid with methylanthranilate and ethyl orthoformate followed by thermal cyclization to furnish the methyl 4-hydroxy quinoline-8-caboxylic acid **(294)** (scheme 174). Hydroxyl quinoline was transformed to bromoquinoline which upon reaction with allyl-4-aminobenzyl aminocarbamate followed by hydrolysis using LiOH afforded the protected amino acid **(295)**. The deprotected 295 was employed as precursor for the synthesis of helix threading peptides (HTPs), which bind to the RNA.



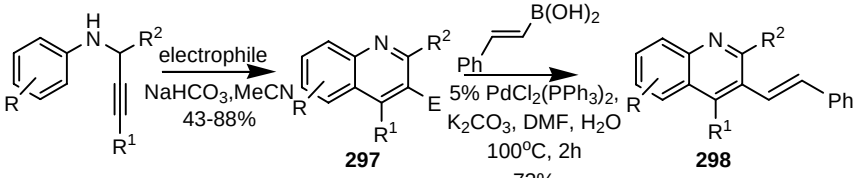
Scheme 174

More recently Some and Ray [178] reported a chemoselective arylamination on β-bromovinylaldehydes with arylamines in the presence of $Pd_2(dba)_3$, K_2CO_3, and *R*-(+)-BINAP in inert atmosphere followed by TFA-mediated cyclization to generate polycyclic quinolines **(296)** as shown in scheme 175.



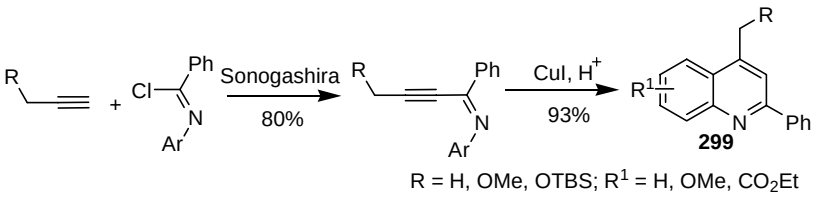
Scheme 175

Larock and his group [179] described the synthesis of quinolines **(297)** substituted at 3-position by an iodo or phenylseleno group in excellent yields from the reaction between propargylic aniline and appropriate electrophiles such as molecular iodine, ICl or PhSeBr. The 3-iodoquinoline compounds **(297)** were subjected to Pd-catalyzed substitution reaction to increase the molecular complexity leading to products **(298)** as shown in scheme 176.



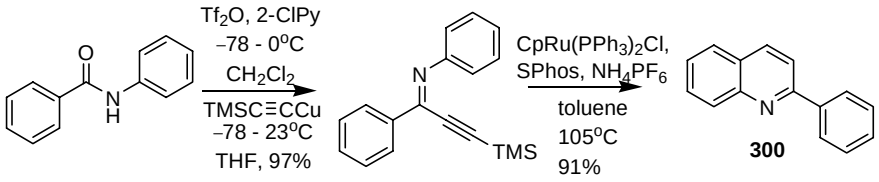
Scheme 176

Gevorgyan and co-workers [180] demonstrated chemodivergent transformation of alkynyl amine cycloisomerization to quinolines **(299)** in the presence of CuI in a mixture of dimethyl acetamide and Et_3N at 110°C (scheme 177).



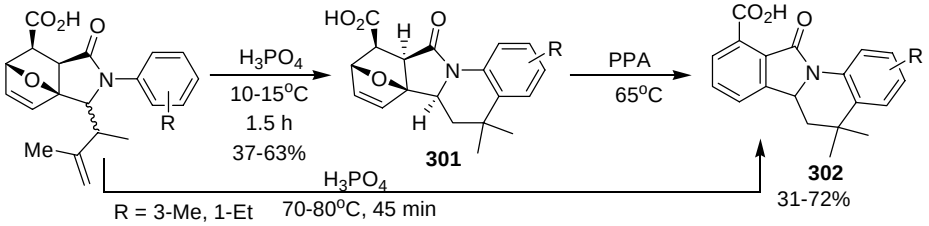
Scheme 177

Hill and Movassaghi [181] disclosed a novel methodology for the synthesis of 2-substituted quinolines **(300)** via protodesilylation and cycloisomerization of trimethyl silyl alkynyl imine in the presence of a Ru-catalyst. The required alkynyl imine was generated from *N*-arylamides in the presence of 2-chloropyridine and Tf_2O (scheme 178).

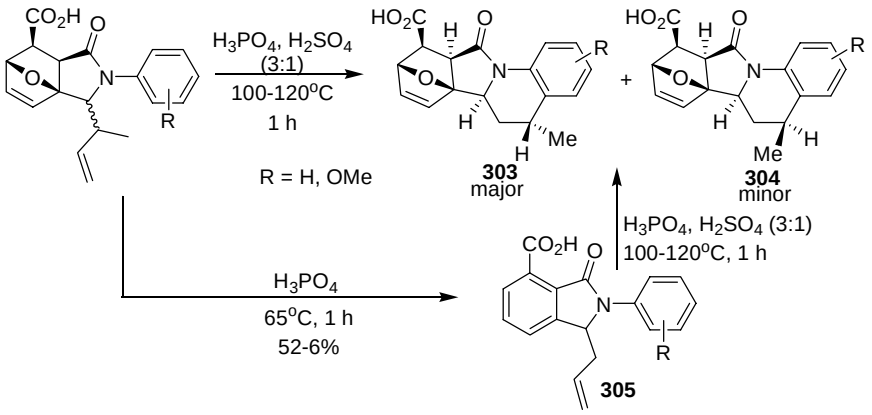


Scheme 178

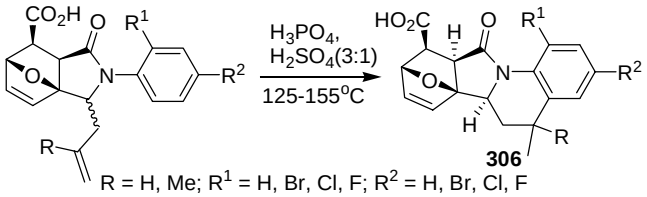
A new synthetic approach to substituted isoindolo[2,1-*a*]quinoline carboxylic acids **(301-304)** via intramolecular Diels-Alder reaction of readily available 4-(*N*-furyl-2)-4 aryl aminobut-1-enes with maleic anhydride in the presence of H_3PO_4 was reported by Zubkov and his group (scheme 179, 180). [182] Simultaneously they described the synthesis of 1- and 3-halo-substituted isoindolo[2,1-*a*]quinolines **(306)** from the same substrate (Scheme 181). [183]



Scheme 179

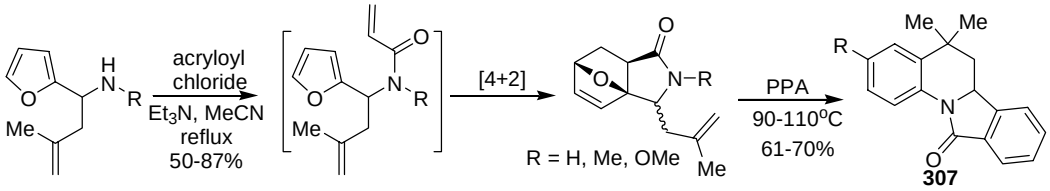


Scheme 180



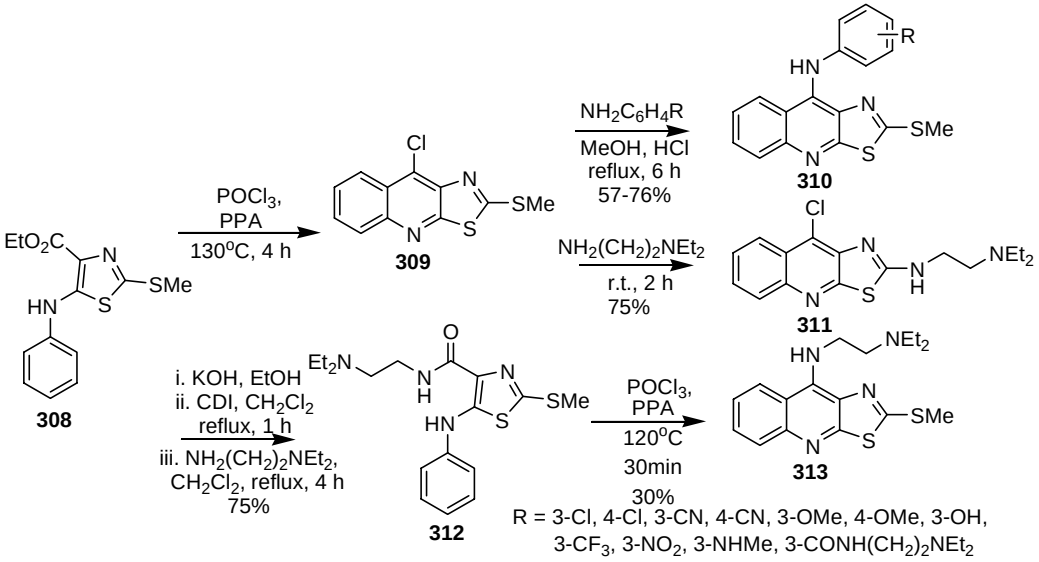
Scheme 181

Further they [184] performed the synthesis of analogous noncarboxyl substituted isoindolo[2,1-*a*]quinolines **(307)**. The acetylation of furyl-substituted homoallylamines with acryloyl chloride and subsequent intramolecular [4+2] cycloaddition in the presence of Et_3N afforded *N*-aryl-3-aza-4-oxo-10-oxatricyclo [5.2.1.$0^{1,5}$]dec-8-enes which on treatment with PPA at 90-110°C, provided the desired products via intramolecular electrophilic substitution reaction as shown in scheme 182.



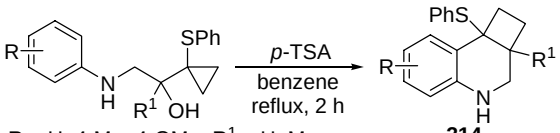
Scheme 182

Very recently Rocha *et al*. [185] have reported the synthesis of several novel anilino thiazolo[5,4-*b*]quinolines **(310)** for evaluation of their cyctotoxic activity. These annulated quinolines **(311 & 313)** were obtained from the thiazole derivative **(308 & 312)** through PPA/ $POCl_3$-promoted cyclization followed by amination of the chloro-derivative **(309)** (Scheme 183).



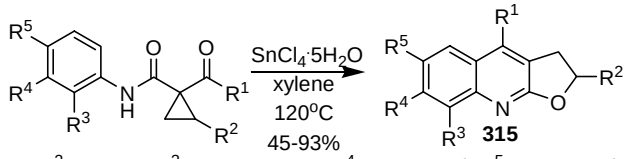
Scheme 183

Alberti *et al*. [186] reported the first example of intramolecular interception of a cyclobutyl thionium ion for the synthesis of hexahydrocyclobutaquinolines **(314)** in the presence of *p*-TSA (scheme 184).



Scheme 184

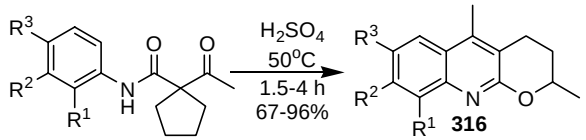
Zhang *et al.* [187] described a highly innovative domino ring opening/ recyclization reaction of doubly activated cyclopropane as a protocol for obtaining the furo-quinolines **(315)** (scheme 185). They observed that, when the reaction was performed with electron donating group containing aryl moiety excellent yields were obtained while the reaction failed to provide the desired products if performed with electron withdrawing groups containing aryl substrates.



Scheme 185

They also reported a new efficient transformation of readily available 1-acetyl-*N*-aryl cyclopentanecarboxamides to pyrano[2,3-*b*]quinolines **(316)** promoted via H_2SO_4

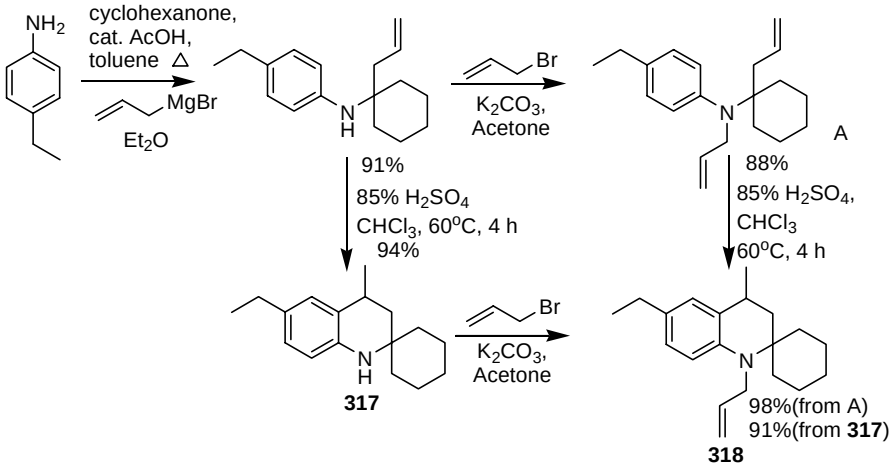
(scheme 186). [188] They proposed that the reaction initiated from H_2SO_4 mediated Combes-type annulation of the starting cyclopentane derivative to afford an alcohol intermediate. This was followed by cyclization/ ring opening/ recyclization reaction of the intermediate.



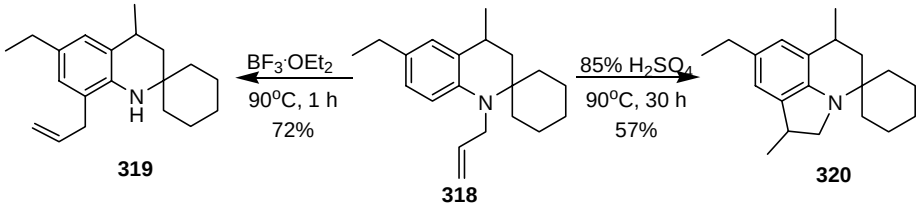
R^1 = H, Cl, Me, OMe; R^2 = H, Cl, Me; R^3 = H, Cl, Me, OMe, NHAc

Scheme 186

Kouznetsov *et al.* [189] reported successful synthesis of new dihydro spiro [1*H*]quinoline-2,1-cyclohexanes **(318)** by the internal alkene alkylation of *N*-(1-allylcyclohexanyl) ethyl phenylamine from corresponding ketone and allyl magnesium bromide as shown in scheme 187. They further demonstrated that the 1-allyl-6-ethyl-4-methyl-3,4-dihydrospiro[1*H*]quinoline-2,1-cyclohexane **(318)** undergoes $BF_3{\cdot}OEt_2$ catalyzed amino-Claisen rearrangement to afford the 8-allyl-6-ethyl-4-methyl substituted spiro quinolines **(319)** (scheme 188). Interestingly a second internal alkylation promoted by H_2SO_4 yielded a novel lilolidine spiro derivative **(320)**.



Scheme 187

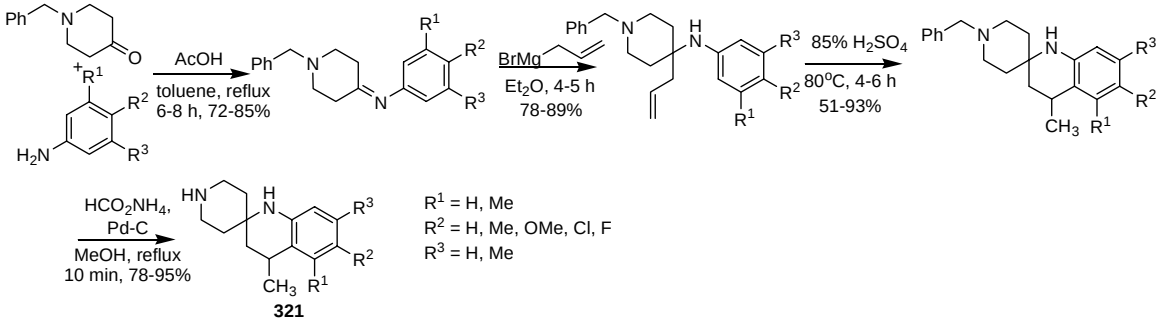


Scheme 188

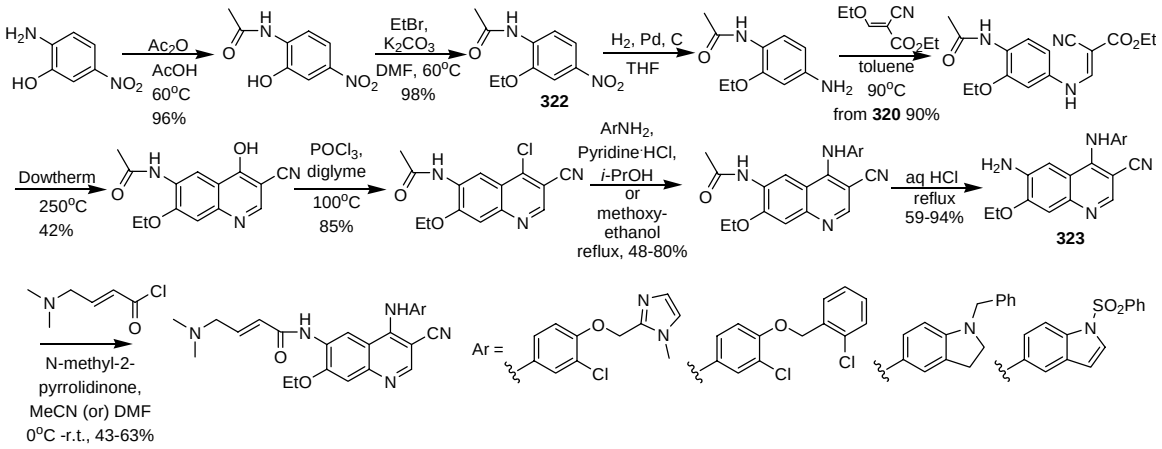
Adopting a similar strategy this group recently demonstrated an efficient synthesis of new 1*H*-4′-methyl-3′,4′dihydro spiro[piperidine-4,2′-(1′*H*)quinolines] **(321)** wherein instead of cyclohexanone, 4-pyrimidone was utilized as the starting material as shown in scheme 189. [190]

Starting from 2-amino-5-nitrophenol, Tsou and co-workers [191] successfully developed the synthesis of new 6,7-disubstituted-4-arylamino quinolin-3-carbonitriles **(323)** which act as irreversable inhibitors for human epidermal grouth factor receptor-2 and epidermal growth factor receptor kinases (scheme 190).

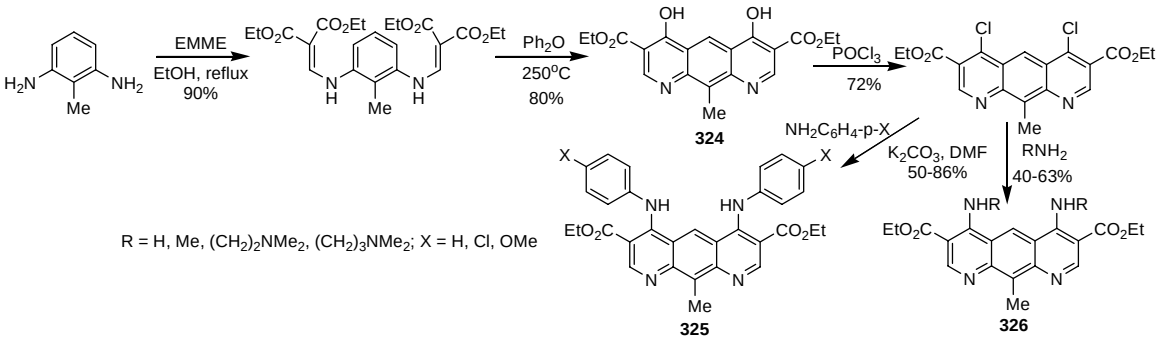
Synthesis of tricyclic pyrido[3,2-*g*]quinoline derivatives **(324)** from the 2,6-diaminotoluene have been reported by Tzeng *et al.* [192] following conventional methodology for quinoline synthesis as shown in scheme 191. They further reported the antiproliferative evaluation of these quinoline derivatives **(325 & 326)**.



Scheme 189

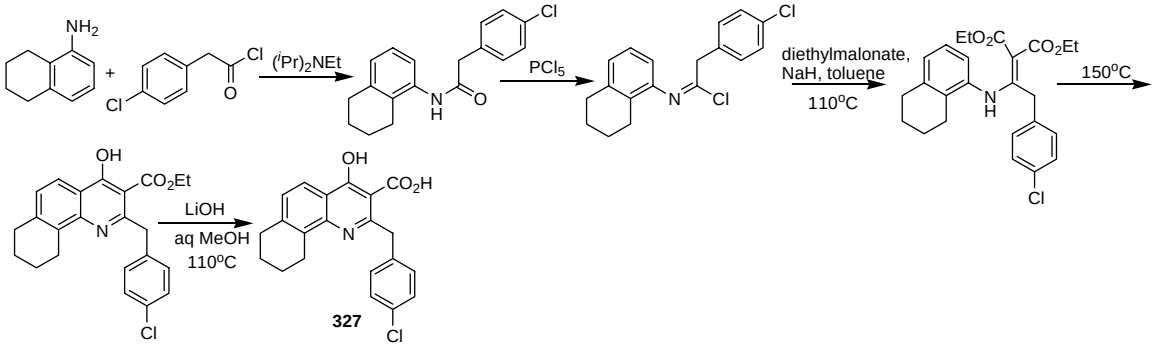


Scheme 190



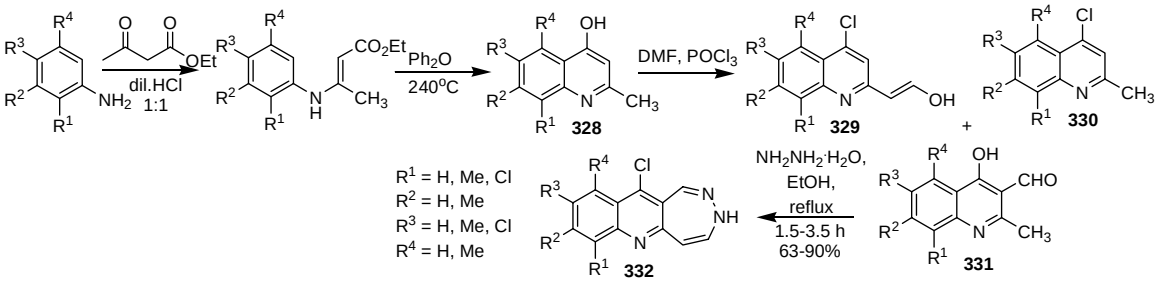
Scheme 191

Kaila *et al*. [90] prepared 2-substituted quinoline salicylic acids from tetrahydronapthylamines as shown in scheme 192. Reaction of an amine with 2-(4-chlorophenyl) acetyl chloride in the presence of DIPEA afforded the amide which on treatment with PCl_5 followed by reaction with diethylmalonate and NaH gave the diester derivative. The diester at 110°C transformed to 2-(4-chlorobenzyl)-4-hydroxy-7,8,9,10-tetrahydrobenzo[*H*]quinoline-3-carboxylic acid **(327)** via thermal cyclization and saponification.



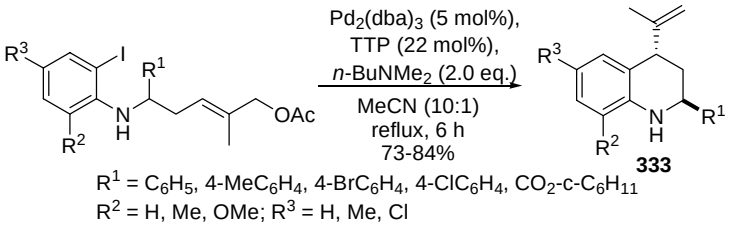
Scheme 192

Nandakumar *et al.* [193] described the synthesis of certain new quinolines **(329-332)** by Vilsmeir-Haack reaction of 4-hydroxyquinolines **(328)** generated using standard methodology of cyclization in diphenyl ether as shown in scheme 193.



Scheme 193

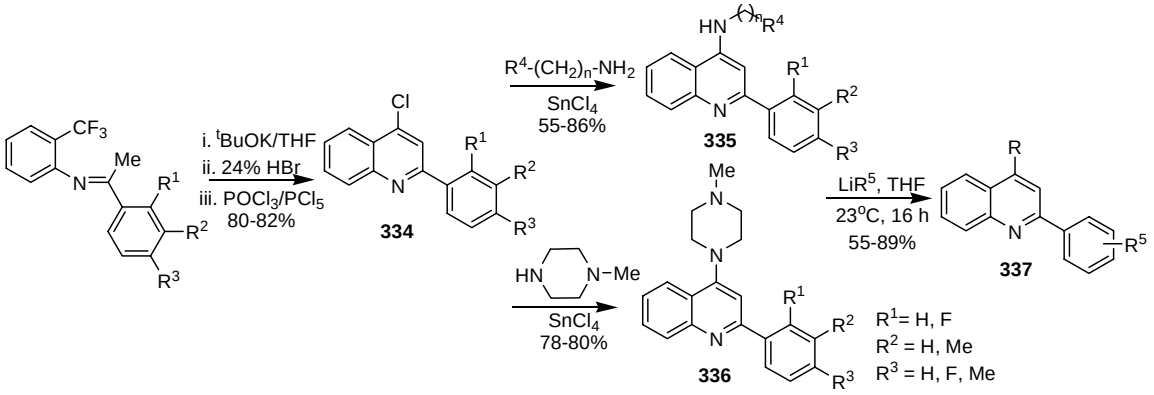
Lautens and co workers [194] reported successful Pd-catalyzed intramolecular cross-coupling reaction between an aryl iodide and an allyl moiety for the generation of trans-isomer of 2,4-disubstituted 1,2,3,4-tetrahydroquinolines **(333)**. Out of the several conditions and catalysts examined it was observed that $Pd_2(dba)_3$ and TTP gave the best yield as shown in scheme 194.



Scheme 194

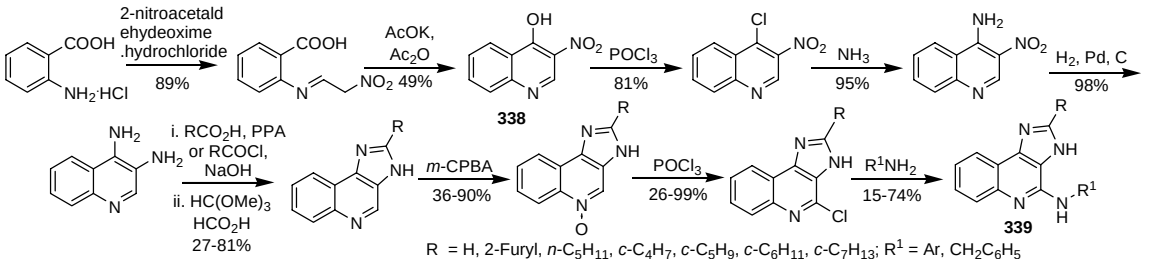
5.4 From C-C-C-N-C-C Unit-

Strekowski and co-workers [195] reported facile synthetic approaches for diverse 2-phenyl-4-aminoquinolines **(335-337)** comprising of an aminoalkyl group at N^4 of the quinolin-4-amine and amino or aminoalkyl groups at the phenyl group (scheme 195). The imine generated from the trifluoromethyl aniline upon reaction with lithiated amino derivatives gave the analogs which were expanded further for the purpose.



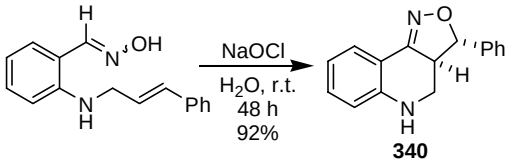
Scheme 195

Goblyos *et al.* [196] reported new 1*H*-imidazo [4,5-*c*]quinolin-4-amine derivatives which were synthesized from anthranillic acid as per the sequence shown in Scheme 196. The 4-hydroxy-3-nitro quinoline **(338)** was generated by the reaction of anthranillic acid with 2-nitroacetaldehyde followed by cyclization in Ac_2O. They developed SAR for new 1*H*-imidazo [4,5-*c*]quinolin-4-amine derivatives **(339)** which were found to be active as allosteric enhancers of the A_3 adenosine receptor.



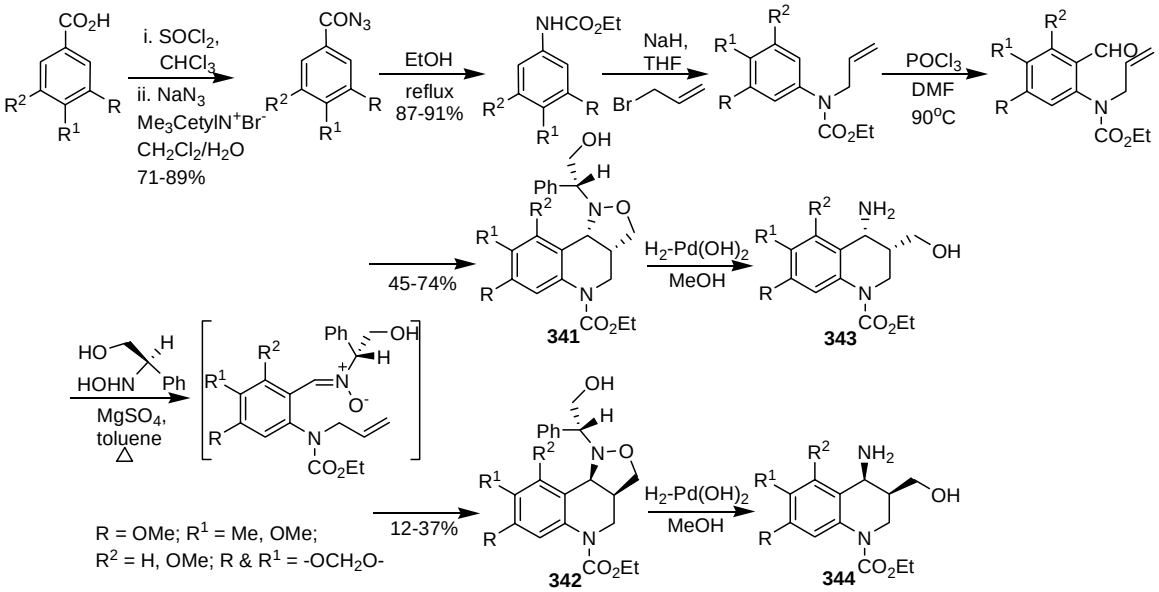
Scheme 196

Bala and Hailes [197] described the preparation of isoxazoloquinolines **(340)** from benzaldoxime using NaOCl in H_2O via 1,3 dipolar cycloaddition of the aldoxime on to the double bond as per the scheme 197.



Scheme 197

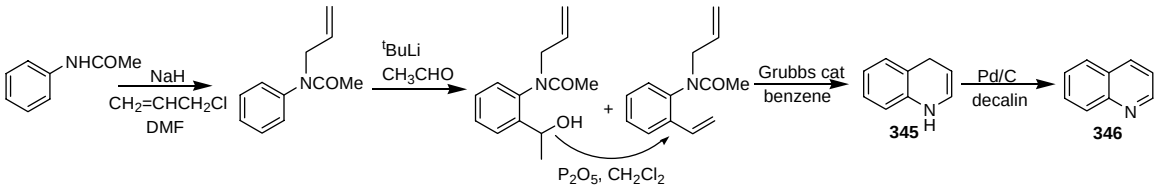
Recently, synthesis of enantiopure 4-amino-3-hydroxymethyl-1,2,3,4 tetrahydroquinoline **(343 & 344)** via intramolecular cycloaddition of chiral nitrones generated from aldehydes and I-α-(hydroxymethyl)-benzylhydroxylamine was described by Broggini and co-workers (scheme 198). [198]



Scheme 198

Ring closing olefin metathesis (RCM) was successfully employed by Sanchez and Pujol [199] for the synthesis of quinoline from a novel diene generated from an acetanilide as shown in scheme 199. The RCM of diene in the presence of dichloro(benzylidene)-

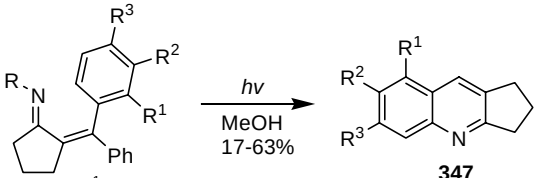
bis(tricyclohexylphosphine)ruthenium (Grubbs catalyst) proceeded via deprotection and isomerization of double bond leading to dihydroquinolines **(345)** which upon treatment with Pd-C in decalin dehydrogenated to quinoline **(346)**.



Scheme 199

5.5 From C-C-C-C-C-N Unit-

Pratt and co-workers [200] reported the synthesis of substituted quinolines **(347)** from 2-benzylidenecyclopentanone *O*-alkyl and *O*-acetyloximes by the photo-irradiation in MeOH (scheme 200). The reaction proceeded through the sequential E to Z-benzylidene group isomerisation and six π-electron cyclization followed by aromatization.

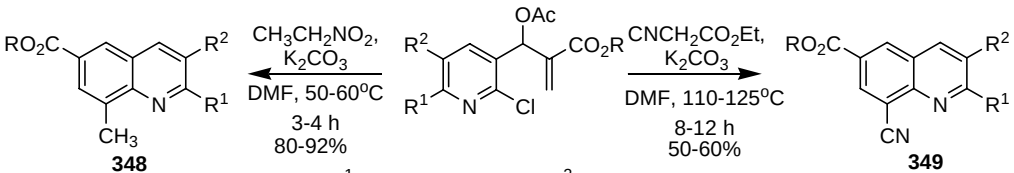


R^1 = H, Me, Cl, F, OMe, NO_2
R^2 = H, Me, t-Bu, Cl, F, OH, OMe, NO_2, NH_2, OAc
R^3 = H, Me, Cl, F, OH, OMe, NO_2, NH_2, NMe_2, OAc

Scheme 200

6.0 Miscellaneous

Rao and co-workers [201] achieved the synthesis of quinolines from substituted 2-chloro-nicotinaldehyde. The Baylis-Hillman acetate of this substrate upon S_N2'-S_NAr reaction sequence with nitro alkane yielded the quinoline **(348)** as the product. Replacing nitro alkane with cyano ethyl acetate gave 8-cyanoquinoline **(349)** as delineated in scheme 201.

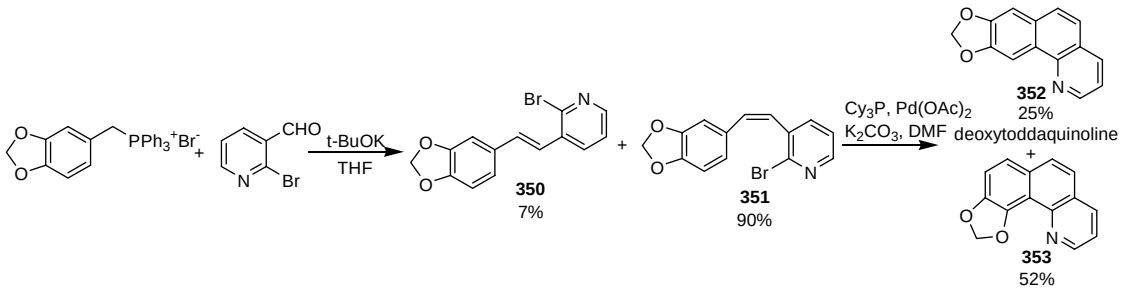


R = Me, Et; R^1 = H, C_6H_5, CO_2Me, R^2 = H, Me, C_6H_5, 4-OMe-C_6H_4,

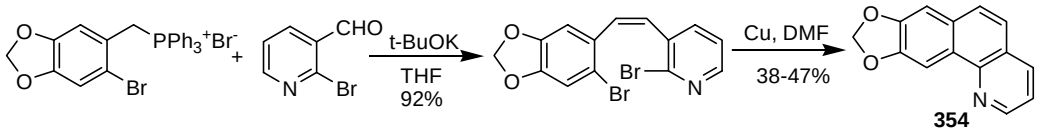
Scheme 201

Serban *et al.* [202] during their studies toward the synthesis of Toddaquinoline demonstrated the synthesis of its tetrahydro core, the

[1,3]dioxolo[4′,5′:4,5]benzo[*h*]quinoline. The Wittig reaction of phosphonium salt of piperonylalcohol with 2-bromo pyridine-3-aldehyde in the presence of ^{t}BuOK yielded the mixture of *trans* and *cis* bromo alkene (1:15) **350 & 351**. The *cis* biaryl compound was converted to deoxytoddaquinolines **(352 & 353)** in the presence of Pd-catalyst (scheme 202), whereas the biaryl coupling reaction of dibromides via Ullman reaction in the presence of Cu gave the desired products **(354)** in 38-47% yields (scheme 203).

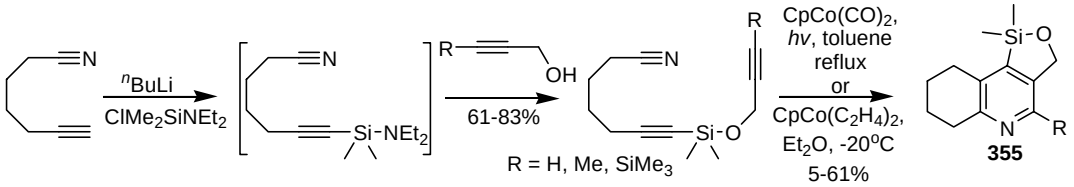


Scheme 202



Scheme 203

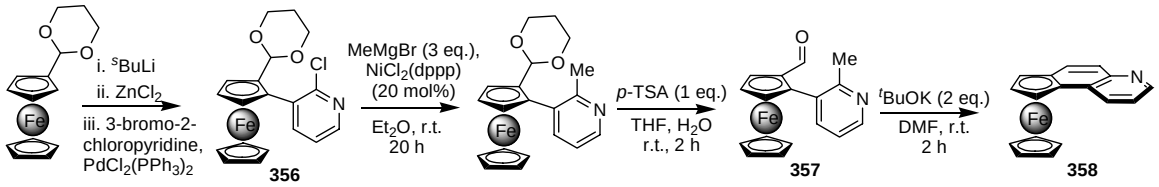
Groth *et al*. [203] reported a regioselective synthesis of tetrahydroquinolines **(355)** starting from silyl containing diynenitriles precursors in the presence of a Co-complex (scheme 204). These diynenitriles were in turn obtained by sequential treatment of heptynenitrile with BuLi, $ClMe_2SiNEt_2$ and various propynyl alcohols.



Scheme 204

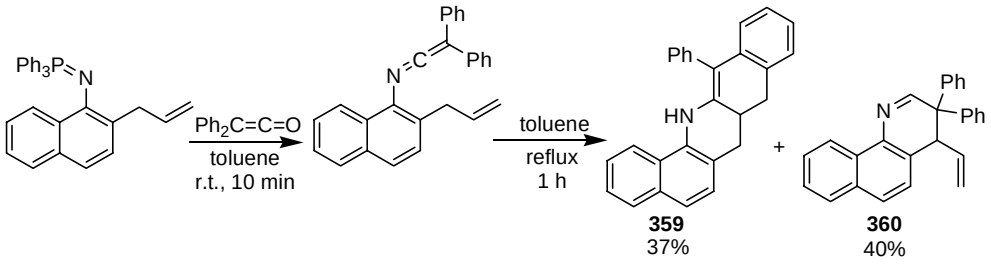
Mamane and Fort [204] have disclosed an efficient method for accessing the chiral ferrocenoquinolines. Their methodology involved the Negishi coupling of ferrocenyl zinc 3-acetals (obtained from the reaction of ferrocenyl acetal with *sec*-BuLi and $ZnCl_2$) with 3-bromo-2-chloro pyridines in the presence of $PdCl_2(PPh_3)_2$ catalyst to afford the chloro pyridine derivative **(356)**. Treatment with MeMgBr in the presence of $NiCl_2$(dppp) catalyst by means of Kumuda coupling followed by deprotection of acetal afforded the

aldehyde derivatives **(357)** (scheme 205). These aldehydes were transformed to ferrocenoquinolines **(358)** by the reaction with 2.0 eq. of ^{t}BuOK in DMF at room temperature.

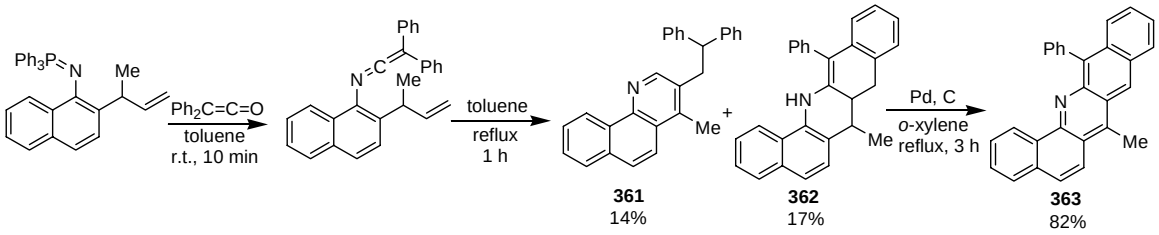


Scheme 205

Alajarin *et al.* [205] described the synthesis of dibenzacridine **(359, 362 & 363)** and benzquinoline **(360 & 361)** by refluxing *N*-[2-(2-propenyl)-1-napthyl] ketenimine which was obtained via aza-Wittig reaction of triphenylphosphazene with diphenylketene (scheme 206 & 207). The transformation proceeded through intramolecular Diels-Alder reaction and [1,5]-hydrogen migration followed by 6π electron cyclization. The tetrahydrodibenz[*b,h*]acridines **(362)** were oxidized to dibenz[*b,h*]acridines **(363)** by refluxing in Pd-C in *o*-xylene (scheme 207).

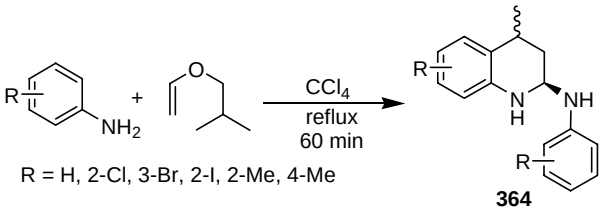


Scheme 206



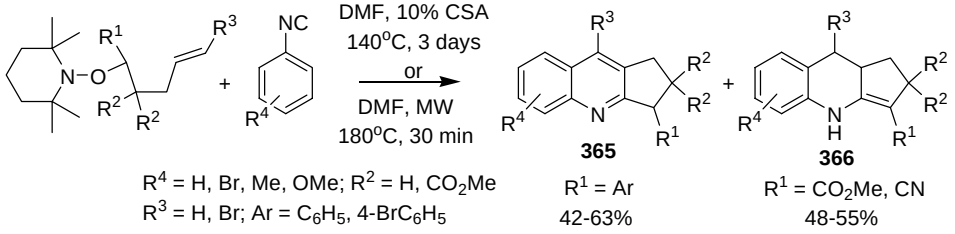
Scheme 207

Piri *et al*. [206] reported the mild and efficient protocol for the preparation of *N*-(4-methyl-1,2,3,4-tetrahydro-2-quinolinyl)-*N*-aryl amines **(364)** from the reaction of isobutyl vinyl ether and aryl amines in refluxing CCl_4 (scheme 208).



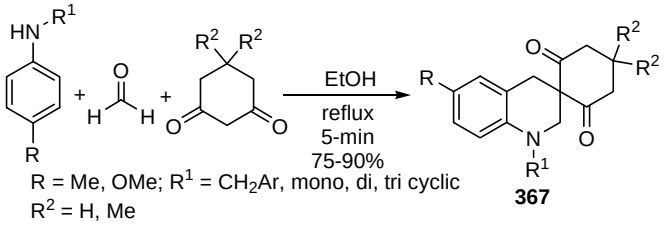
Scheme 208

Janza and Studer [207] demonstrated a highly efficient tandem radical process comprising a thermal alkoxyamine homolysis, an isonitrile trapping reaction, a 5-exo-trig cyclization and homolytic aromatic substitution to generate substituted dihydroquinolines **(366)**. The readily available alkoxyamines with CSA under heating or microwave irradiation underwent homolytic cleavage followed by reaction with isonitrile and subsequent 5-exo-trig and homolytic aromatic substitution (scheme 209).



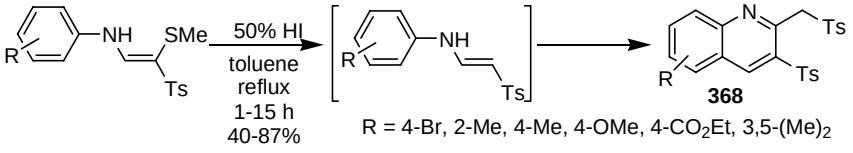
Scheme 209

Kadutskii and Kozlov [208] obtained high yields of 3-spirosubstituted 1,2,3,4-tetrahydroquinolines **(367)** containing different substituents at the *N*-atom by conducting the reaction between β-diketones, formaldehyde and substituted anilines in EtOH at refluxing temperature (scheme 210).



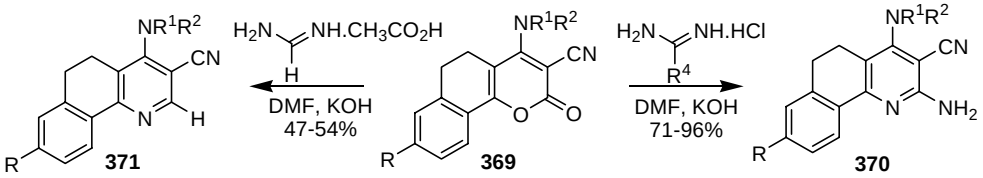
Scheme 210

Matsumoto, and Okura [209] demonstrated that when 2-(arylamino)-1-(methylthio)-1-tosylethene was refluxed with HI, elimination of thiomethyl functionality followed by dimeric cyclization resulted in the formation of quinolines **(368)** (scheme 211).



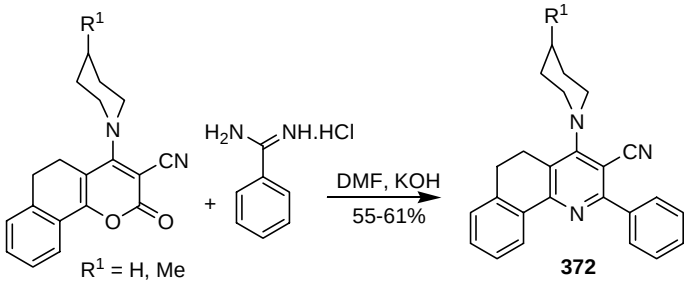
Scheme 211

Pratap and Ram [210] reported the synthesis of highly functionalized benzo[*h*]quinolines from corresponding chromenes. Reaction of 2-oxo-dihydrobenzo[*h*]chromenes **(369)** with S-methylthiourea sulfate or 1-carboxamidine pyrazole hydrochloride in the presence of KOH in DMF afforded the 2-amino-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]quinoline-3-carbonitriles **(370)** (Scheme 212). Replacing the reactants to formamidine acetate or benzamidine hydrochloride yielded 4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]quinoline-3-carbonitriles **(371)** and 2-phenyl-4-*sec*-amino-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **(372)** respectively, by the elimination of ammonia (scheme 213).



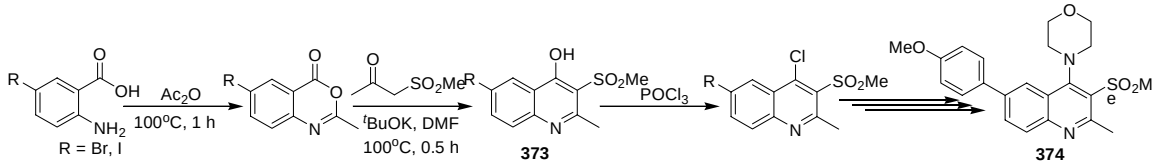
R = H, OMe; NR^1R^2 = piperidin-1-yl, 4-Me-piperidin-1-yl, 4-Benzyl-piperidin-1-yl, 4-Morpholin-1-yl, tetrahydroisoquinolin-1-yl

Scheme 212



Scheme 213

Atechian *et al.* [61] developed new methodology for the synthesis of 3-(methylsulfonyl)quinolines from the reaction of anthranilic acid with Ac_2O at 100°C to produce the 2-methyl-4*H*-3,4-benzoxazin-4-ones, which on further treatment with methane sulfonyl acetone in the presence of ^{t}BuOK in DMF at 100°C for 0.5 h to afforded substituted 3-methanesulfonyl-4-hydtroxy quinolines **(373)**. Subsequent treatment with $POCl_3$ followed by reaction with different secondary amines produced the corresponding 4-aminoquinolines **(374)** (scheme 214).

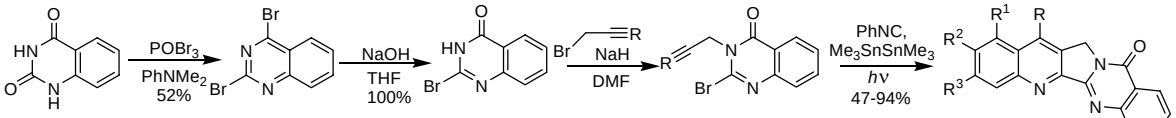


Scheme 214

7.0 Natural product synthesis

Quinoline subunit is present in several natural products too. The examples in the literature which described the synthesis of quinoline during the construction of natural product are being included here.

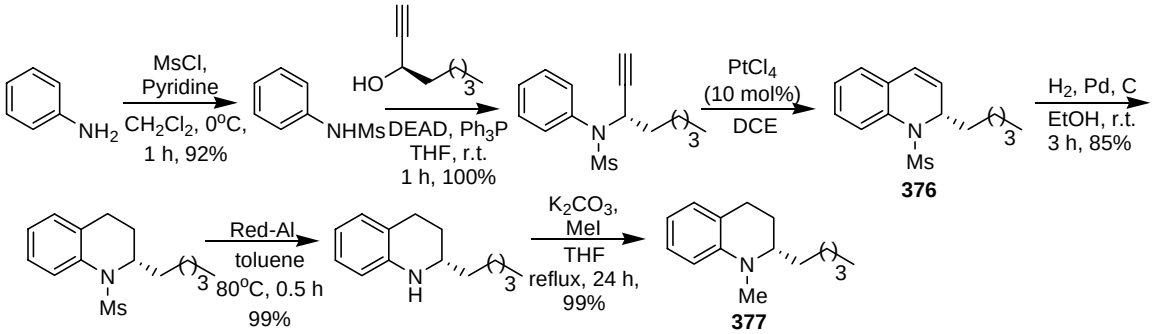
The total synthesis of Luotonin A from benzoylene urea was described by Curran and co-workers. [211] The bromination of benzoylene urea using $POBr_3$ followed by hydrolysis yielded the bromoquinazolone which on sequential propargylation with propargyl bromide and photoirradiation with substituted phenyl isonitriles in the presence of Me_3Sn-$SnMe_3$ afforded the luotonin **(375)** and its analogs (scheme 215). The prepared compounds exhibited activity in a topoisomerase I DNA cleavage assay.



R = H, Et, CH_2CH_2TMS; R^1 = H; R^2 = H, F, Me, CF_3, OMe, OAc, NHBoc; R^3 = H; R^1 = R^2 = -OCH_2O- **375**

Scheme 215

Ryu [212] demonstrated hydroarylation strategy for the synthesis of tetrahydroquinoline **(376)** which involved Mitsunobu reaction of a chiral propargyl alcohol to aniline followed by intramolecular cyclization in the presence of $PtCl_4$. Although he examined gold and mercury catslysts too, $PtCl_4$ was found to yield the product in better yields. This synthetic outcome was applied for the concise total synthesis of (+)-(S)-angustureine **(377),** which is a quinoline base of alkaloid isolated from *G. officinalis* (scheme 216).

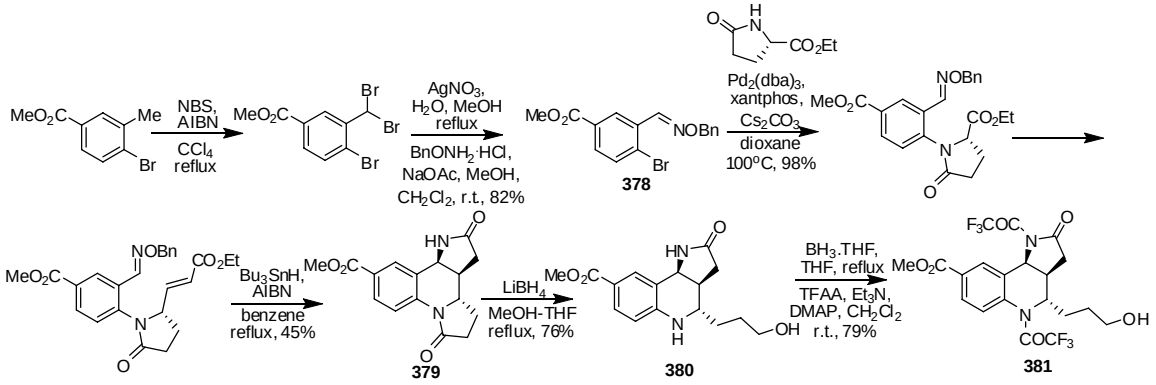


376 **377**

Scheme 216

The asymmetric synthesis of (-)-matrinellic acid via dipyrroloquinoline as a key intermediate was reported by Miyata and his group. [213] The treatment of methyl 4-bromo-3-methylbenzoate with NBS led to the dibromo derivative which on treatment with $AgNO_3$ yieided the aldehyde. The aldehyde was transformed to *O*-benzyloxime

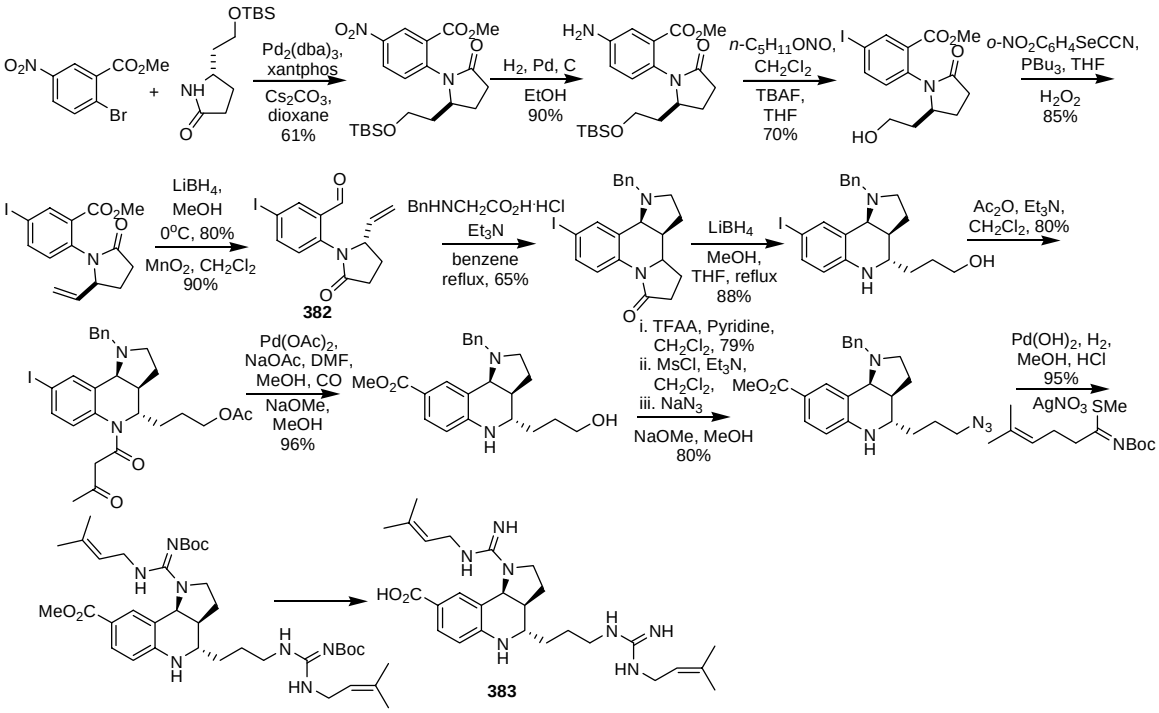
ether **(378)** followed by coupling reaction with L-pyroglutamic acid ethyl ester to afford the *N*-arylpyrrole derivative. *N*-arylpyrrole derivative was converted to α,β-unsaturated ester by sequential reduction oxidation and Wittig reaction. Treatment of α,β-unsaturated ester with Bu_3SnH in the presence of AIBN afforded the desired 3a*R*,3b*S*,11b*S*-dipyrroloquinoline **(379)** via radical addition cyclization and elimination. Chemoselective reduction of dipyrroloquinoline **(379)** with $LiBH_4$ under the influence of MeOH in THF furnished the aminoalcohol **(380)** which was converted to trifluoroacetamide **(381)** by reduction of lactam and acylation with TFAA as shown in the scheme 217.



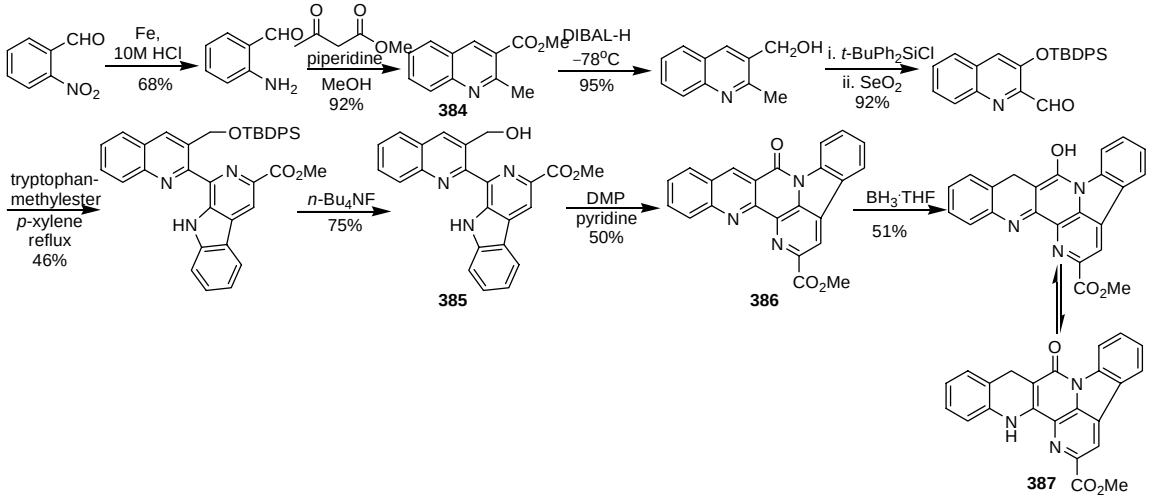
Scheme 217

More recently Badarinarayana and Lovely [214] also reported the total synthesis of (-)-matrinellic acid **(383)**. The key steps involved in their strategy were a Pd-catalyzed aryl amidation reaction of a pyroglutamate derivative **(382)** followed an intramolecular azomethine ylide-alkene cycloaddition that proceeded without recemization and reductive ring opening reaction as shown in scheme 218.

Nourry *et al.* [215] obtained Lavendamycin analogs using Friedlander annulation and Pictet-Spengler reaction. Condensation of 2-aminobenzaldehyde with methylacetoacetate in the presence of piperidine yielded 2-methyl-quinoline-3-carboxylic acid methyl ester **(384)** (scheme 219). Reduction of the ester followed by protection with the silyl group and oxidation with SeO_2 afforded the aldehyde. Pictet-Spengler reaction of the resulting aldehyde with tryptophan methyl ester in *p*-xylene on reflux and subsequent desilylation furnished the desired hydroxylester **(385)**. Compound **385** upon treatment with DMP in pyridine furnished the product **386** via oxidation and intramolecular cyclization. Their attempt to prepare the deoxygenated compound through reduction with BH_3·THF, resulted in **387**.

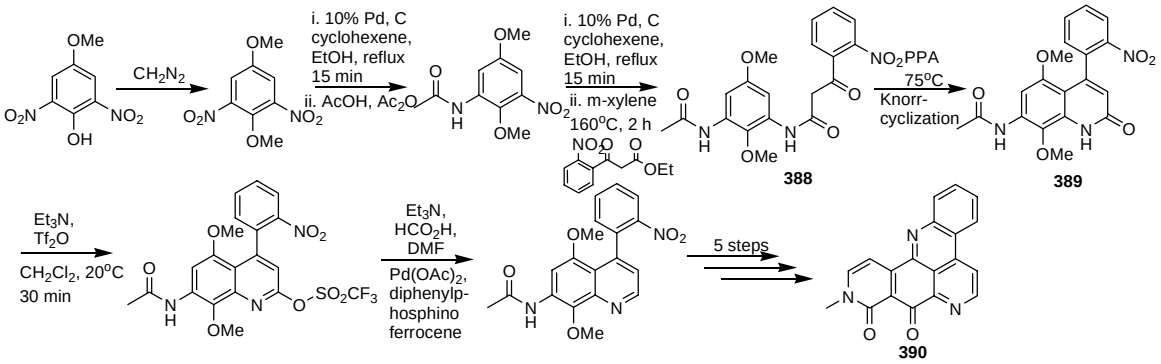


Scheme 218



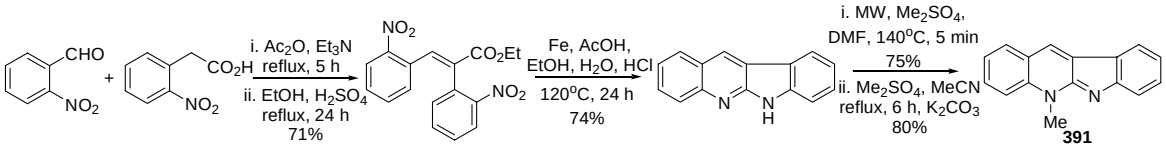
Scheme 219

Ireland and his group [216] demonstrated the first total synthesis of Neoamphimedine **(390)** that comprises of a quinoline unit as shown in scheme 220. The key quinoline intermediate was generated from 2-quinolone **(389)** which in turn was obtained via Knorr cyclization of **388**.



Scheme 220

Parvatkar *et al*. [217] reported a new and efficient three-step synthesis of indoloquinoline alkaloid cryptotackieine (neocryptolepine) from 2-nitrobenzaldehyde and 2-nitrophenyl acetic acid. A Perkin reaction followed by a 'one-pot' double reduction, double cyclization and isomerization furnished the final product **(391)** in excellent yield (scheme 221).



Scheme 221

8.0 Conclusion

It is evident from the literature assimilated in the preceding text that the synthesis of quinoline nucleus is a subject of great interest for several research groups. As a result impressive spectrum of novel strategies have evolved providing the opportunity to construct quinoline and quinoline annulated derivatives decorated with choicest of substitutions. This has assisted the discovery of new properties in quinoline-based compounds in particular the biological activities associated with them. Although the work towards synthesis of quinoline and quinoline annulated ring systems has come a long way, we believe this area of research will continue of evolve with discovery of newer application s of new catalysts and reagents.

9.0 Abbreviations*

hv	=	ultraviolet irradiation
^{o}C	=	degree celsius
AIBN	=	azobisisobutyronitrile
BHT	=	2,6-bis(1,1-dimethylethyl)-4-methylphenol

BINAP	=	2,2'-bis(diphenylphosphino)-1,1'-binapthyl
BINOL	=	1,1'-bi(2-naphthol)
Boc	=	*tert*-butoxy carbonyl
Boc_2O	=	di-*tert*-butyl dicarbonate
BOP-Cl	=	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
CAN	=	ceric ammonium nitrate
CDI	=	N,N'-carbonyl diimidazole
CSA	=	camphor-10-sulphonic acid
Cy_3P	=	tricymene phosphine
m-CPBA	=	*meta*-chloroperbenzoic acid
DBU	=	deoxyribonucleic acid
DABCO	=	1,4-diazabicyclo[2.2.2]octane
DCC	=	N,N'-dicyclohexylcarbodiimide
DCE	=	1,2-dichloroethane
DDQ	=	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	=	diethyl azodicarboxylate
DIBAL-H	=	diisobutyl aluminium hydride
DIPEA	=	diisopropyl ethylamine
DMAP	=	4-*N*,*N*-dimethylamino pyridine
DMC	=	dimethyl carbonate
DME	=	1,2-dimethoxy ethane
DMF	=	*N*,*N*-dimethyl formamide
DMP	=	dess martin periodnane
DMSO	=	dimethylsulfoxide
DPP	=	diphenyl phosphate
EMME	=	diethyl ethoxy methylene malonate
HATU	=	2-(1H-7-Azabenzotriazol-1-yl)—1,1,3,3-tetramethyl ulfona hexafluorophosphate Methanaminium
NBS	=	*N*-bromo succinimide
PPA	=	polyphosphoric acid

PQSP	=	Polyquinoline containing spirobifluorene and phenathiazine
TBAB	=	tetrabutyl ammonium bromide
TBAF	=	tetra-n-butylammonium fluoride
TBPA	=	tris(4-bromophenyl)ammonium
TCT	=	2,4,6-trichloro-1,3,5-triazine
TDAE	=	tetrakis (dimethyl-1-amino)ethylene
TEATFB	=	tetraethylammonium tetrafluoroborate
TEAP	=	tetraethylammonium perchlorate
Tf	=	trifluoromethane sulfonyl
Tf_2NH	=	*N,N*- bis (trifluoromethane sulfonamide)
Tf_2NPh	=	*N*-phenyl bis (trifluoromethane sulfonamide)
TFA	=	trifluoroacetic acid
TFAA	=	trifluoroacetic anhydride
TFAE	=	trifluoroacetaldehyde ethyl hemiacetal
TFE	=	trifluoroethanol
THF	=	tetrahydrofuran
TFMSA	=	trifluoromethyl sulfonic acid
TMEDA	=	N,N,N',N'-tetramethylethylenediamine
TMSCl	=	trimethylsilylchloride
TTP	=	tri(o-tolyl)phosphine
p-TSA	=	*para*-toluene sulfonic acid

*Abbreviations for reagents which have been expressed by chemical formula are not provided

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10.0 References

CDRI Communication no. 7428

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