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# ADVANCES ON CATALYTIC APPROACHES TOWARDS THE SYNTHESIS OF QUINOLINE DERIVATIVES USING POVAROV REACTION

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**Abstract** – The aza-Diels-Alder reaction is a [4+2] cycloaddition, involving the insertion of nitrogen atom into dienes or dienophiles. A series of biologically and pharmaceutically active essential heterocycles have been developed as a result of this approach. This method witnessed as a powerful tool for the construction of a diverse range of biological active quinoline scaffolds and other nitrogen containing heterocyclic compounds due to its operational modesty, high atom economy, regio- and stereoselectivity. The present report focuses on the advancement of aza-Diels-Alder reaction for the synthesis of optically active and inactive quinoline derivatives.

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## 1. INTRODUCTION

Quinoline can be considered to be a pervasive nitrogen containing heterocyclic aromatic compound having a high potential for medicinal as well as industrial application. It has a molecular formula of $C_9H_7N$ and having double ring heterocyclic structure containing a benzene ring along with pyridine scaffolds.[1] It has weak basic character and forms salts in the presence of acids as well as participates in electrophilic and nucleophilic substitution reaction like benzene or pyridine kind of moieties.[2] Quinoline or benzo[*b*]pyridine is one of the most affluent *N*-containing heterocyclic moieties which is found in considerable amounts in various important natural products, pharmacologically active synthetic substances. Pyranoquinoline system is basic skeleton of a number of valuable alkaloids like Cinchona alkaloids.[3] Quinoline scaffolds are basically an important chemical moiety for synthesizing various potential drug candidates. Most importantly it is non-toxic to human immune system.[2] 1-Azanaphthalene or quinoline acquires broad scope of pharmaceutical activities (Figure 1) like antimalarial, antibacterial, antioxidant, anticancer, anti-inflammatory, antifungal, antiasthmatic, antipsychotic, antiglaucoma, antileishmanial, anthelmintic and cardiotonic, antiprotozoal, local anaesthetic, etc.[4] A wide number of anti-viral drugs like indinavir, saquinavir have been approved, but have their limitations as well regarding cytotoxicity, drug resistance, etc. Amodiaquine, mefloquine, piperquine, primaquine were developed as analogous to chloroquine to avoid resistance against malaria.[5] Fluoroquinolone antibiotics like ciprofloxacin, norfloxacin, moxifloxacin were also synthesized.[6] Apart from this, pitavastatin (lowering cholesterol level), tipifarnib (farnesyl transferase inhibitor for leukemia), bedaquiline (anti-TB), Lenvatinib (kinase inhibitor for cancer) were developed which contains functionalized quinolines as core moiety.[7] Finafloxacin is a fluoroquinolone antibiotic used for the treatment of otitis externa and this drug is marketed by Novartis, approved by FDA in 2014.[8] First approved remedy by FDA in 2012 for metastatic medullary thyroid cancer is Cabozantinib a non-specific tyrosine kinase inhibitor.[9]

Considering their several crucial biological activities, extensive research has been carried out and still ongoing towards the efficient and atom-economic synthesis of quinolines and their functionalized derivatives. Friedländer[10] synthesis starting from *o*-aminobenzaldehyde and ketones, Skraup[11] synthesis utilizing anilines and acrolein, Combes quinoline synthesis that aims to combine 1,3-diketones and anilines are worth mentioning. Apart from these methods, Gould-Jacobs,[12] Pfitzinger,[13] Doebner-von Miller,[14] Conrad-Limpach[15] synthesis of quinolines are the classical reaction methodologies which are

utilized as well. Transition metal-free catalytic methods, ultrasound irradiated reactions, microwave assisted catalytic reactions, and greener protocols are being investigated in order to discover more efficient chemical routes to synthesize this noble quinoline derivatives.[16,17] Hence considering its immense importance, we have made an attempt in this report to describe various chemical methodologies being investigated by various research groups which are important building blocks for making quinolines and its derivatives.

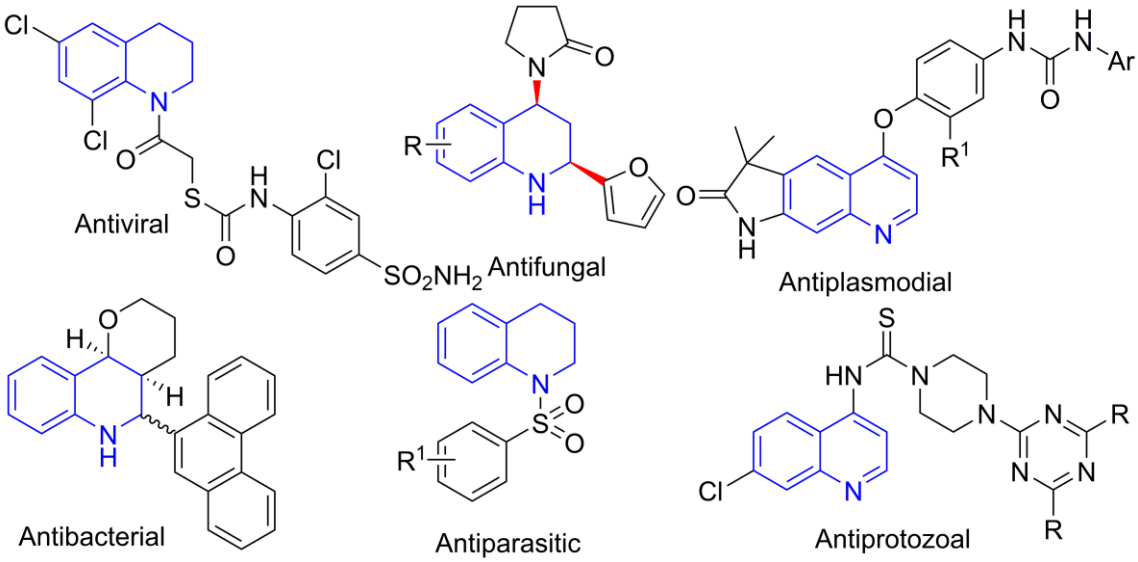



**Figure 1.** Biologically important quinoline and tetrahydroquinoline derivatives[7b,7c]

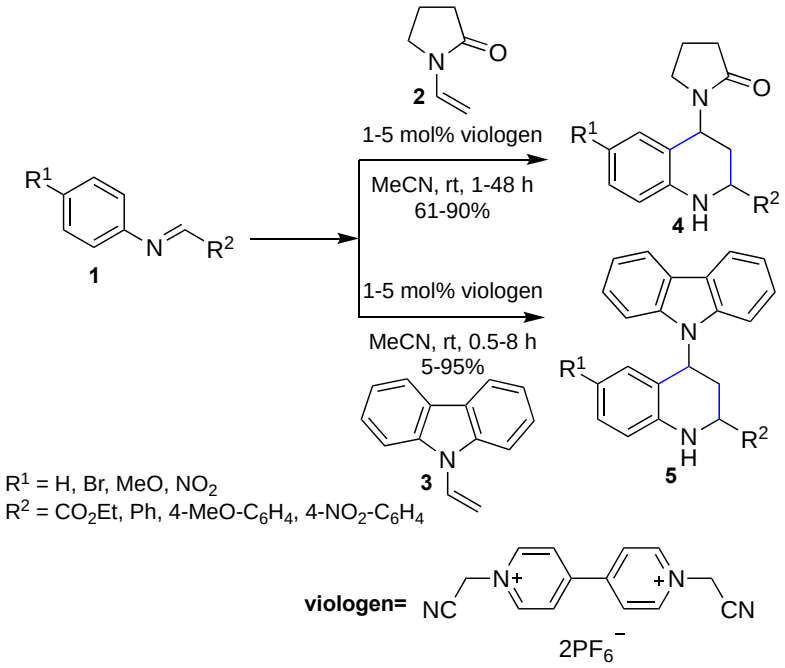
## 2. SYNTHESIS OF QUINOLINE AND TETRAHYDROQUINOLINE DERIVATIVES USING POVAROV REACTION

### 2.1 INTERMOLECULAR POVAROV REACTION

In this section, we have described the synthesis of quinoline and tetrahydroquinoline derivatives by utilizing alkenes and alkynes as dienophile *via* intermolecular aza-Diels-Alder reaction involving generation of two new bonds.

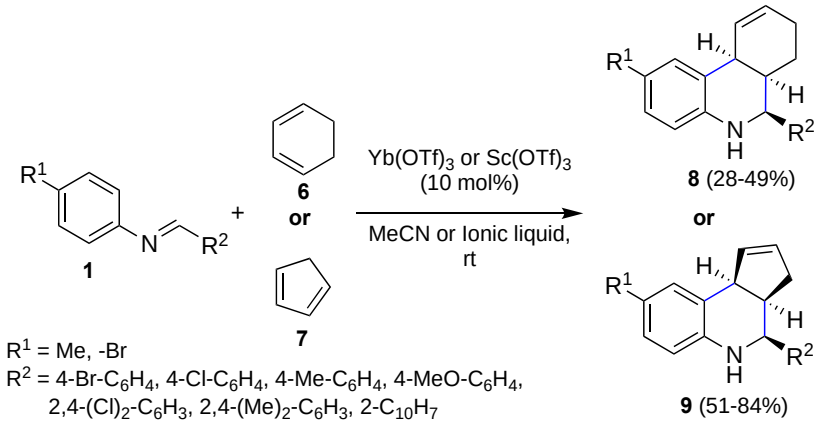
#### 2.1.1 ALKENE AS DIENOPHILE

Mayer and co-workers[18] demonstrated that, when the viologen (*N*,*N*′-dicyanomethyl-4,4′-bipyridinium•2$PF_6$) with low catalytic loadings was used as catalyst, it has readily produced 1,2,3,4-tetrahydroquinolines **4** and **5** that gave appreciable *cis*:*trans* selectivity and yields (Scheme 1).



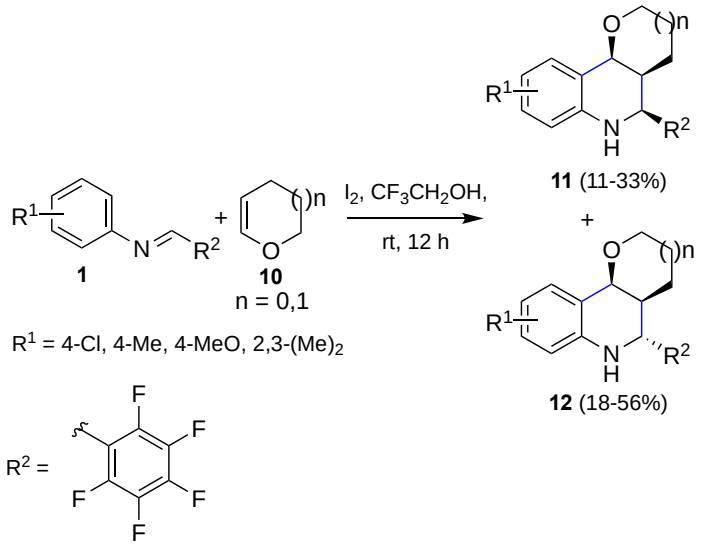

**Scheme 1.** Synthesis of C-2 and C-4 substituted 1,2,3,4-tetrahydroquinolines

Turgut and coworkers[19] attempted to discover stereospecific synthesis that is efficient for preparation of quinoline **9** and phenanthridine derivatives **8** in the presence of Lewis acid catalysts such as $Sc(OTf)_3$ or $Yb(OTf)_3$ in MeCN. Additionally, it was also shown that the reaction can be performed using reusable ionic liquid derived from DBU as demonstrated in (Scheme 2).



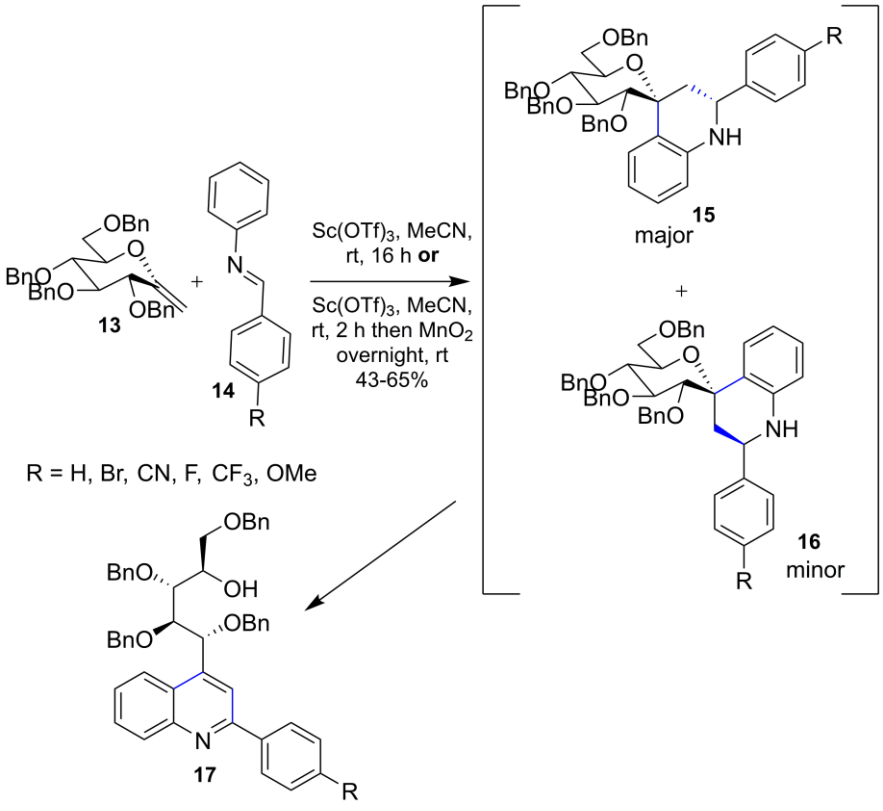

**Scheme 2.** Stereospecific synthesis of derivatives of quinoline and phenanthridine

Zhang and group[20] have reported the synthesis of tetrahydroquinolines using the concept of iodine catalyzed aza-Diels-Alder reaction linking enol ethers (DHP/DHF) and pentafluorobenzylideneaniline under mild conditions. Reaction proceeds in one-pot operation in polar solvent to yield a mixture of *cis*/*trans* stereoisomers of the correspåonding tetrahydroquinolines derivatives **11** and **12** in moderate yields. It was found that the polarity of solvent plays a vital role, due to increased coordination ability of the iodine leading to better yields of the targated substances (Scheme 3).



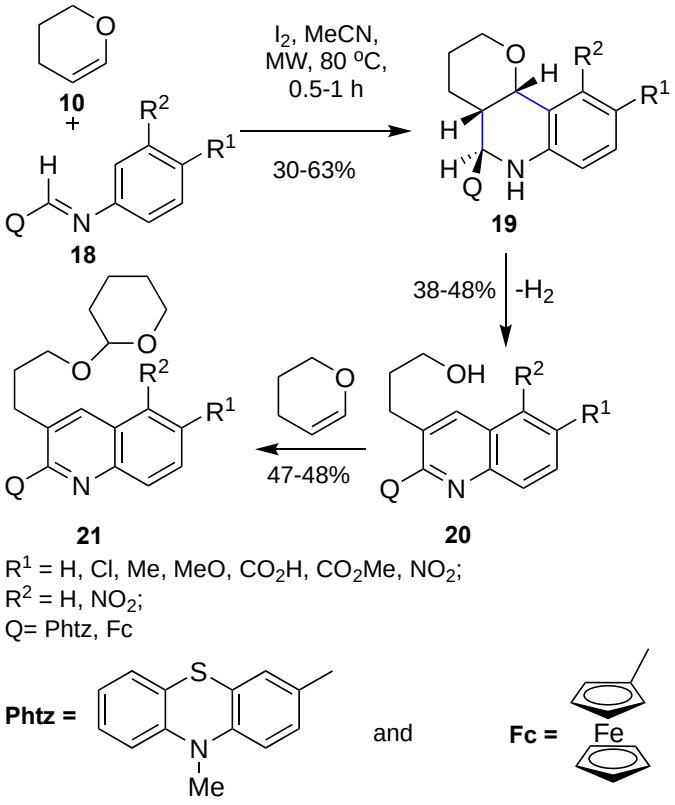

**Scheme 3.** $I_2$-Catalysed aza-Diels-Alder reaction for the synthesis of 1,2,3,4-tetrahydroquinolines

One-pot Lewis acid-catalyzed Povarov reaction was also employed by Dobbelaar and Marzabadi[21] towards the synthesis of novel open-ring glycosylidene-derived quinoline **17** *via* the formation of spiroanellated tetrahydroquinoline **15** and **16** as depicted in Scheme 4. Experimental follow-up of the reaction concluded that the products **15** and **16** can be obtained using only $Sc(OTf)_3$ as catalyst. Interestingly, the ring opening product **17** can be formed exclusively if $MnO_2$ is added in the same reaction mixture.



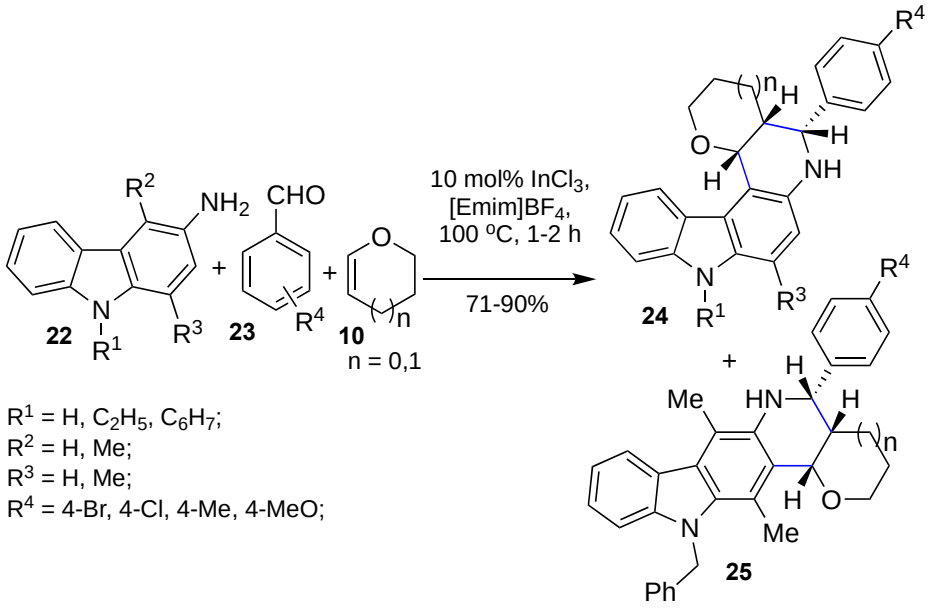

**Scheme 4.** Synthesis of glycosylidene-derived quinolines

Csampai and co-workers[22] studied the scope of inverse electron demand aza-Diels-Alder cycloaddition that is represented by iodine-catalysis and MW irradiation using deactivated Schiff's bases of *C*-phenothiazinyl-along with ferrocenyl-substituents that are electron donating with 3,4-dihydropyran (DHP) as donor component (Scheme 5). It was investigated that 2*H*-pyrano[3,2-*c*]quinolines **19** or 3-(3-hydroxypropyl)quinolines **20** were produced during reaction of phenothiazine-containing imines and the process depends on the *N*-phenyl group substitution. However, it was found that quinolines **21** were formed directly from ferrocene-based imines that are less reactive and it doesn't depend on the *N*-phenyl substituent's electronic nature. Moreover, stepwise reaction pathways were suggested for the cycloaddition procedure of intermediate iodoiminium ions when analysis was done by DFT calculation based on B3LYP/DGZVP.



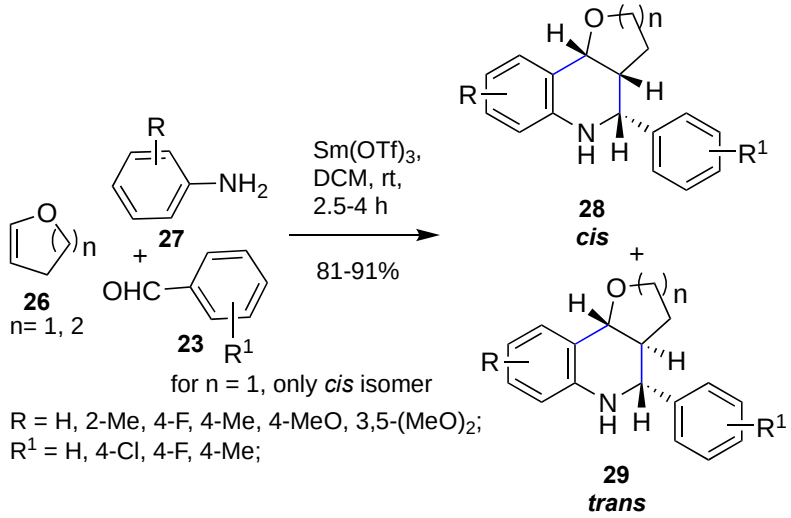

**Scheme 5.** $I_2$-Catalyzed aza-Diels-Alder cycloaddition using deactivated Schiff's base

A novel, practical and scalable process for the preparation of isomeric ellipticine derivatives **24** and **25** *via* diastereoselective synthesis was described by Gaddam and Nagarajan[23] using an intermolecular imino-Diels-Alder process. The transformation was accomplished by the reaction of electron-rich alkenes such as DHP, DHF and ethyl vinyl ether with substituted benzaldehydes and 3-aminocarbazoles in the presence of ionic liquid as reaction medium and catalytic amounts of $InCl_3$ (Scheme 6).



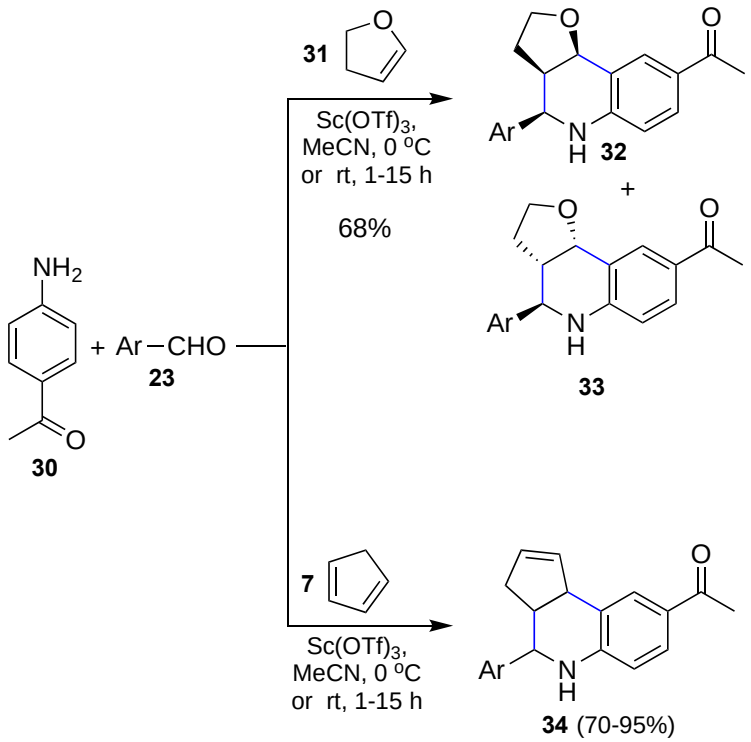

**Scheme 6.** Synthesis of isomeric ellipticine derivatives using aza-Diels-Alder reaction

The synthesis of pyrano **28** and furanoquinolines **29** was reported by Narsaiah and co-workers[24] using mild Lewis acid samarium triflate as a catalyst that provides optimal yields along with *endo*-selectivity with the help of three component coupling reaction of cyclic enol ethers, amines and aldehydes. Interestingly, the reaction with DHF afforded exclusively the *cis*-isomer, while by using DHP the corresponding *trans*-isomer was also obtained as minor product (Scheme 7).



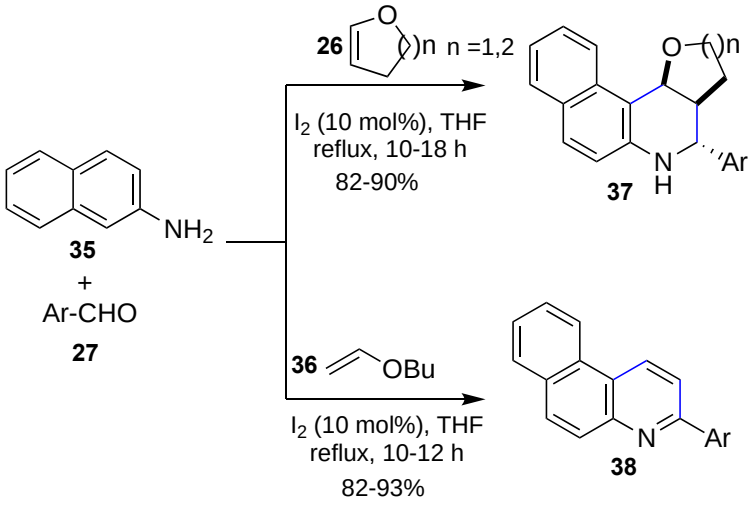

**Scheme 7.** $Sm(OTf)_3$-Catalyzed three-component coupling reaction

An excellent, diastereoselective synthesis of tetrahydroquinolines **32**, **33** and **34** was developed by Arterburn and co-workers[25] as GPR30 agonist by using multicomponent or stepwise aza-Diels-Alder cyclization in presence of $Sc(OTf)_3$ catalyst in catalytic amounts (Scheme 8).




**Scheme 8.** Diastereoselective synthesis of tetrahydroquinoline

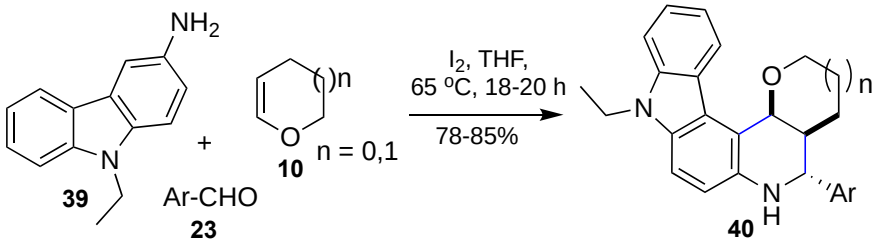
Recently, Wang and co-workers[26] contributed a selective three-component reaction for pyranoquinoline and furoquinoline derivatives **37** using 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran, anthracen-2-amine or naphthalen-2-amine **35** and aromatic aldehydes **23** as starting materials for multicomponent Povarov reaction in the presence of catalytic amounts of iodine. However, in this method the reaction favours high selectivity for *exo*-isomer. Apart from the high yields of the product formed, surprisingly they have observed that the butoxy group encounters an unexpected loss in 3-arylbenzo(naphtha)[*f*]quinolines **38** when *n*-butyl vinyl ether was utilized as starting material (Scheme 9).




Ar = Ph, 3-Br-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 3,4-$(MeO)_2$-$C_6H_3$, 3,4-$OCH_2O$-$C_6H_3$, 2-thienyl

**Scheme 9.** Synthesis of 3-arylbenzo(naphtha)[*f*]quinolines

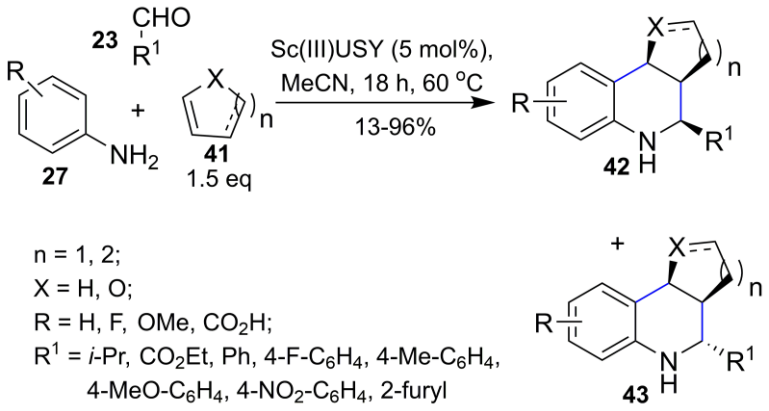
Wang *et al.* demonstrated a stereoselective synthetic approach that is efficient and mild for cryptotaciene derivatives **40** *via* three-component reaction of electron rich alkene, aromatic aldehyde and 3-amino-9-ethylcarbazole in the presence of iodine as catalyst (Scheme 10).[27]




Ar= 3-Cl-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2,4-$Cl_2$-$C_6H_3$, 3,4-$Cl_2$-$C_6H_3$, 3,5-$(MeO)_2C_6H_3$

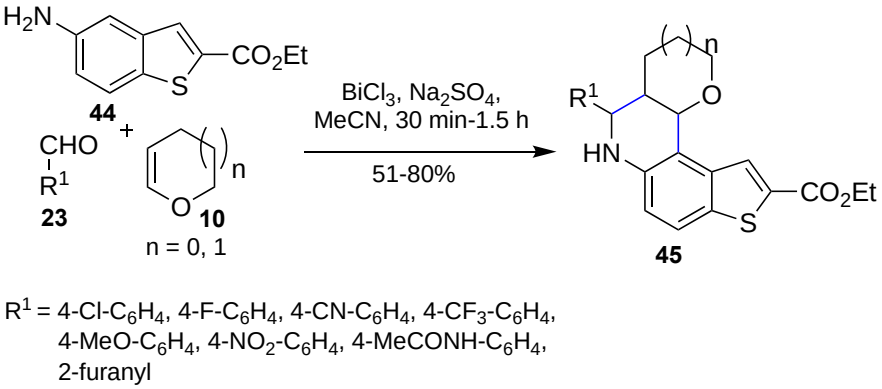
**Scheme 10.** Iodine-catalyzed stereoselective synthesis of cryptotaciene derivatives

Pale *et al*. reported the *in situ* formation of imines for the [4+2] cyclocondensation of alkenes, aldehydes and amines utilizing heterogenous ligand-free catalyst scandium(III)-exchanged zeolite to synthesize tetrahydroquinoline derivatives **42** and **43**. This scheme follows a high regio- and stereoselectivity. The catalyst showed broad substrate scope and effortless to use, and reusable up to three times and could be isolated by simple filtration (Scheme 11).[28]



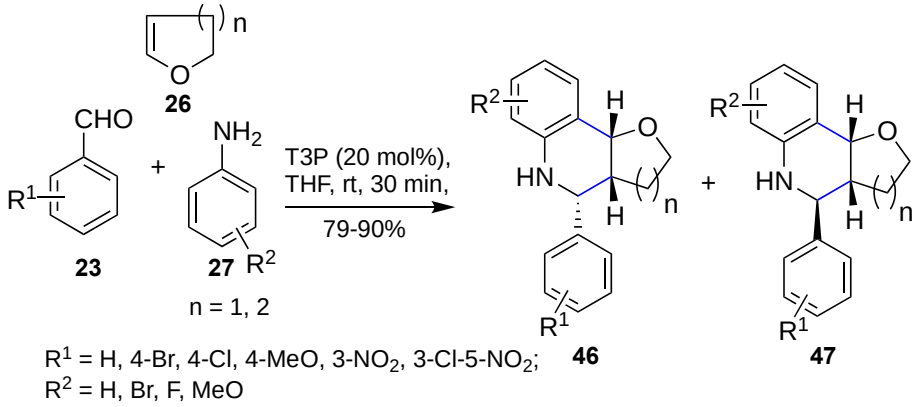

**Scheme 11.** Synthesis of regio- and stereoselective tetrahydroquinolines

For the preparation of tetrahydrothieno[3,2-*f*]quinolines **45** an effective one-pot method is established utilizing the imino Diels-Alder reaction between cyclic enol ethers **10**, aromatic aldehydes **23** and ethyl-5-aminobenzothiophene-2-carboxylate **44**. In addition, the synthesis of hydroxyalkyl-substituted tetrahydrothieno[3,2-*f*]quinolines was achieved with optimal yields, by exhibiting an aldehyde free, similar imino-Diels-Alder reaction. The reaction of *o*-(allyloxy)benzaldehyde with 5-aminobenzothiophene was also performed *via* intramolecular aza-Diels-Alder reaction that results in the formation of thienoquinoline derivatives (Scheme 12).[29]



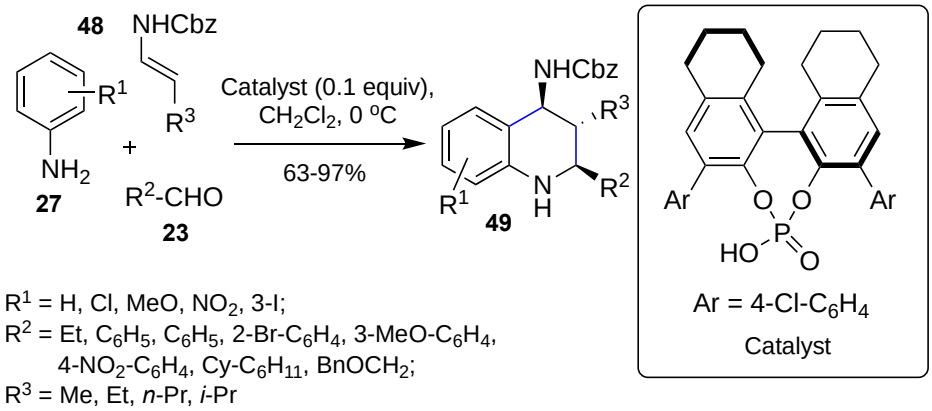

**Scheme 12.** Synthesis of tetrahydrothieno[3,2-*f*]quinolines

In regards to the aza-Diels-Alder reactions of aldimines with dihydrofuran or dihydropyran, T3P was seen to be an effective catalyst in order to produce pyrano- and furo[3,2-*c*]quinolines **46** and **47** in a short period of time with high diastereoselectivity and in high yields (Scheme 13).[30]



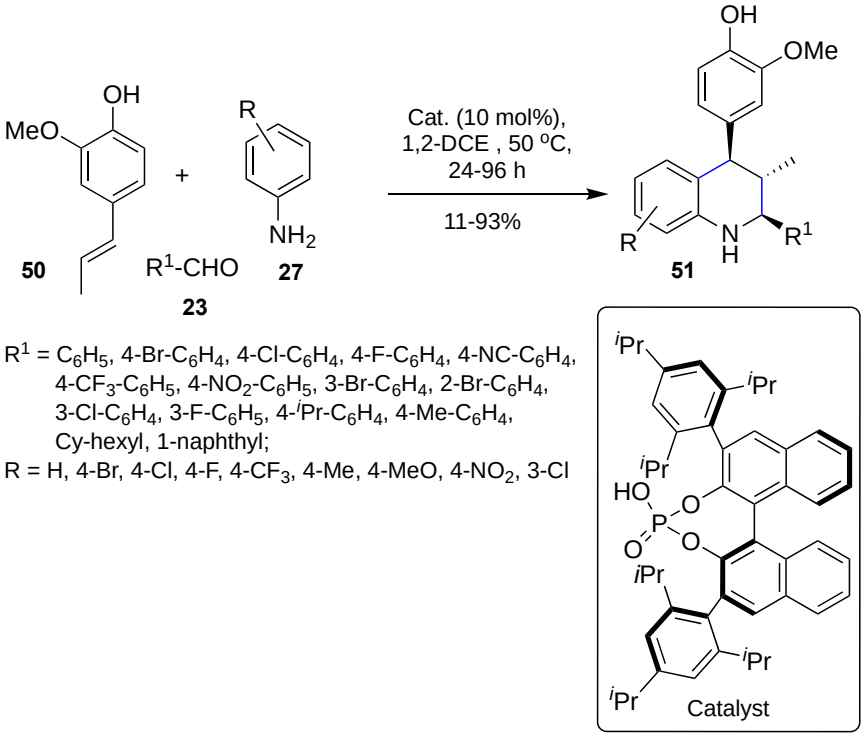

**Scheme 13.** Synthesis of pyrano- and furo[3,2-*c*]quinolines

High yields of *cis*-4-amino-2-aryl(alkyl)-1,2,3,4-tetrahydroquinolines **49** with almost completed enantioselectivities (up to > 99% ee) and very good diastereoselectivities (>95%) were obtained from a three-component Povarov reaction of enecarbamates **48**, anilines **27**, and aldehydes **23** under the influences of chiral phosphoric acid as catalyst. For the first time, in the enantioselective Povarov reaction, aliphatic aldehydes could be utilized and reaction conditions tolerate wide variety of anilines containing electron-withdrawing (such as $NO_2$, $CF_3$, Cl), and electron-donating (OMe) groups (Scheme 14). The 1,2,3,4-tetrahydroquinolines that are 2,3,4-trisubstituted having three neighbouring stereogenic centers were synthesized with outstanding enantio- and diastereoselectivities (87 to > 99% ee) using β-substituted acyclic enecarbamates. Catalyst loading was decreased from 10% to 0.5% after a thorough investigation of the active catalytic species without degrading enantiomeric excess. Additionally, having performed the mechanistic studies, it could be stated with absolute certainty that a stepwise mechanism was followed by the Povarov reaction using the enecarbamate as dienophile. It was shown that the free NH group of the enecarbamate played a crucial part for achieving this transformation. Additionally, documented NMR experiments showed a linear relationship between the product ee's and the catalyst as well as the catalyst-substrate interaction.[31]



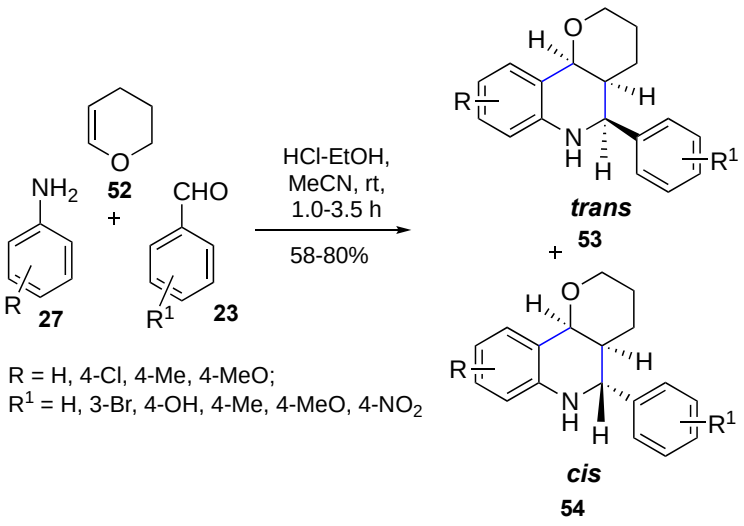

**Scheme 14.** Acid-catalyzed synthesis of tetrahydroquinolines

Masson *et al*. documented a multicomponent aza-Diels-Alder reaction catalyzed by chiral phosphoric acid having isoeugenol derivative **50**, anilines, aldehydes, for the systematic one-pot synthesis of 2,3,4-trisubstituted 4-aryl-tetrahydroquinolines **51** with excellent stereoselectivities (up to >99% ee and >95:5 dr ) maintaining good yields (Scheme 15).[32]



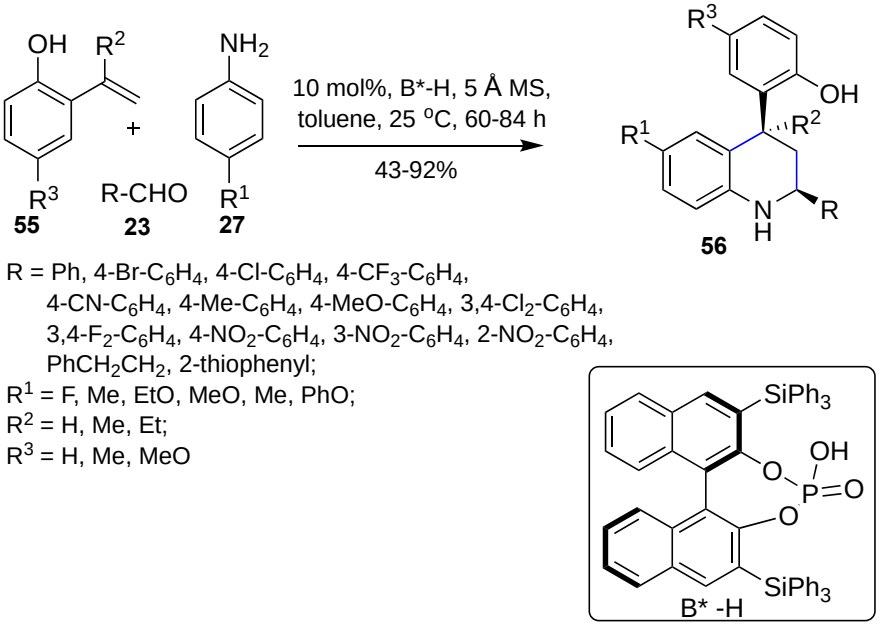

**Scheme 15.** The aza-Diels-Alder reaction catalyzed by a chiral phosphoric acid

One-pot synthesis of pyrano[3,2-*c*]quinoline catalyzed by HCl-ethanol using anilines, benzaldehydes, dienophiles was reported by Liu and co-workers with the observation of good to high yield and excellent diastereoselectivity *via* Povarov reaction (Scheme 16).[33]



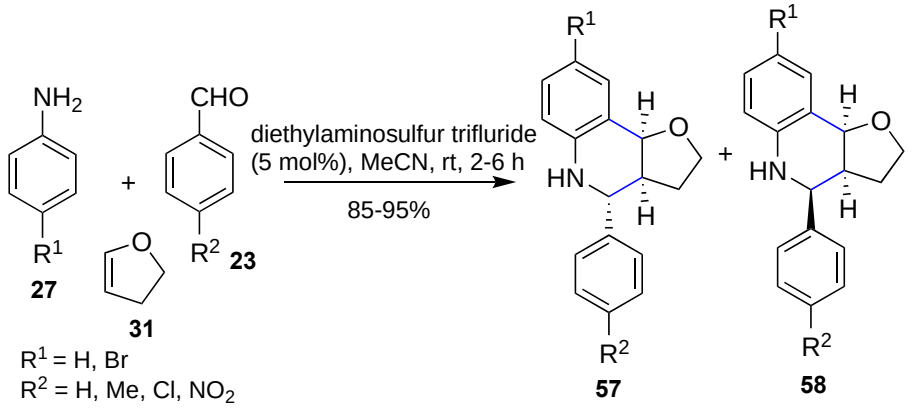

**Scheme 16.** Synthesis of pyrano[3,2-*c*]quinolines using Povarov reaction

A systematic method was demonstrated by Shi and co-workers to produce *cis*-disubstituted tetrahydroquinolines **56** that are structurally diverse with excellent stereoselectivities of up to 97% ee and >99:1 dr involving three component organocatalytic asymmetric Povarov reaction that includes 2-hydroxystyrenes as substrates. Involvement of the substrates α-alkyl-2-hydroxystyrenes produced **56** with chiral quaternary stereocenters. The Povarov reaction went through an intramolecular Friedel-Crafts reaction and a vinylogous sequential Mannich reaction. Both the 2-hydroxystyrene and aldimine were simultaneously activated by the bifunctional phosphoric acid catalyst (Scheme 17).[34]



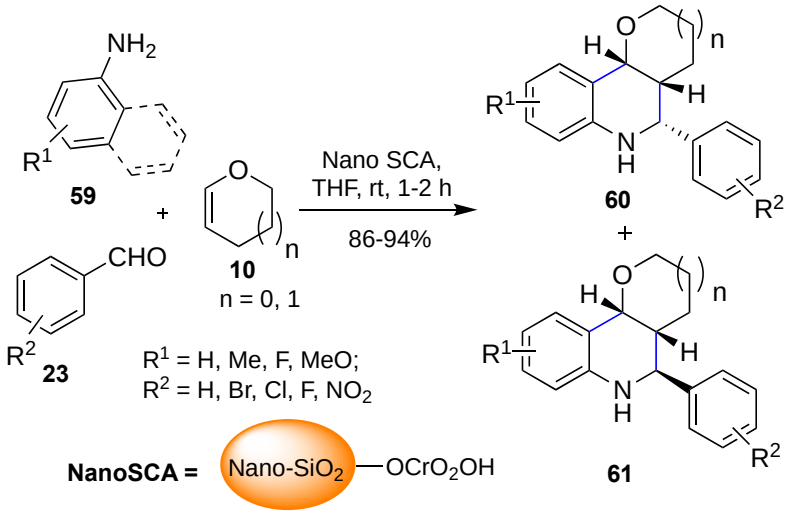

**Scheme 17.** Phosphoric acid catalyzed synthesis of tetrahydroquinolines

The synthesis of furanotetrahydroquinolines reported by Dhanapal and co-workers *via* Diels-Alder reaction of substituted anilines, aldehydes, dihydrofuran in acetonitrile as solvent in the presence of diethylaminosulfur trifluoride as catalyst at room temperature afforded **57** and **58** in 80-95% isolated yields (Scheme 18).[35]



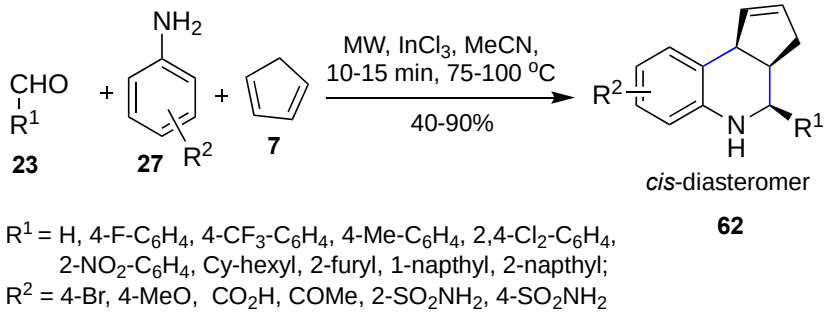

**Scheme 18.** Synthesis of substituted furanoquinolines

Gharib and coworkers have introduced the synthesis of pyrano- and furanoquinolines **60** and **61** by utilizing nano-silica chromic acid (nano-SCA) as catalyst and precursors like cyclic enol ethers, amines and aldehydes considering 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran utilizing mild reaction conditions. This multicomponent coupling reaction delivers excellent yields as well as high endoselectivity. It is noteworthy to mention that the 2,3-dihydrofuran produced *endo*-products very selectively with no change in the reaction conditions. The supremacy of reported protocol is less reaction time, heterogenous conditions, high yield and facile reaction procedure (Scheme 19).[36]



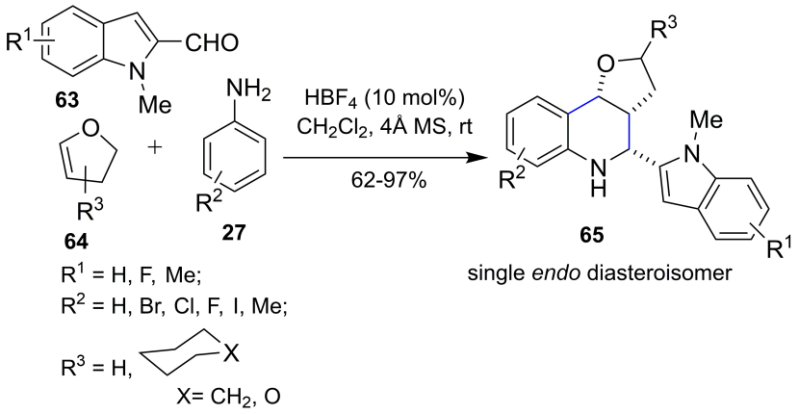

**Scheme 19.** Nano-silica chromic acid catalyzed three-component reaction

Thakur *et al*. established a microwave assisted protocol for synthesizing cyclopentadiene ring-fused tetrahydroquinolines **62** by utilizing three component Povarov reaction. The described indium(III) chloride catalyzed reaction has high yield (90%) with a shorter reaction time period of 10-15 minutes and is appropriate in regards to parallel library synthesis. It is noteworthy that the microwave assisted protocol provided better yields over the conventional methods favoring *cis*-diastereomeric products (Scheme 20).[37]



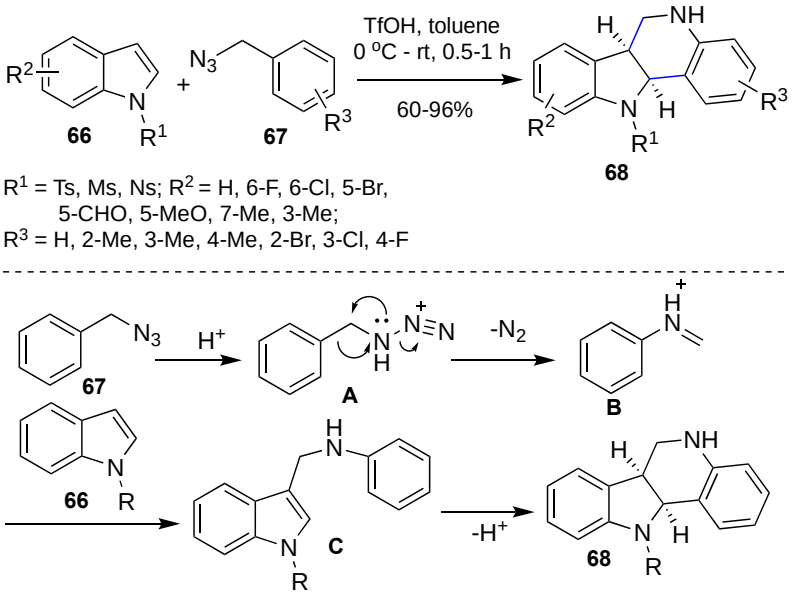

**Scheme 20.** Synthesis of cyclopentadiene ring-fused tetrahydroquinolines

Stereoselective synthesis of cyclopenta[*b*]indoles was reported by Rodriguez *et al*. starting from electron rich alkenes, anilines, indole-2-carboxaldehydes **63** *via* [3+2] carbocyclization and is believed to be different from the traditional Povarov reaction i.e. formal [4+2] cycloaddition consisting of tetrahydroquinolines **65**. It is interesting to account that this multicomponent coupling reaction could be converted into the Povarov method by altering Bronsted acid catalyst to produce cyclopenta[*b*]indoles along side *via* the formation of corresponding *anti*-Povarov pathways (Scheme 21).[38]



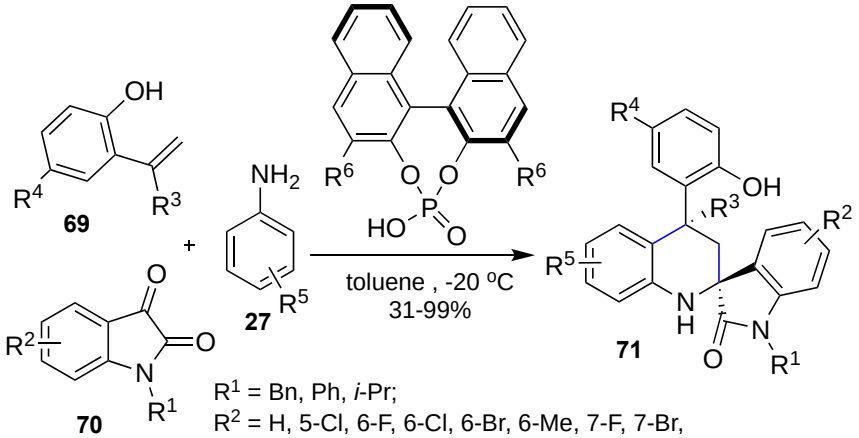

**Scheme 21.** Synthesis of tetrahydroquinolines substituted indoles

Song *et al*. established a protocol for synthesizing tetrahydro-5*H*-indolo[3,2-*c*]quinolines **68** *via* [4+2] cycloaddition. A novel one-step mechanism starting from indoles **66** and benzyl azides **67** has been proposed. The reaction mechanism includes an iminium rearrangement of benzyl azide **67** and a cascade reaction sequence preceded by two Pictet-Spengler processes to produce quinolines **68** in moderate to excellent yields. This method own a broad scope and significant potential in the formation of quaternary and/or tertiary carbon centers containing polycyclic indolines (Scheme 22).[39]




**Scheme 22.** Synthesis of optically active tetrahydroquinolines

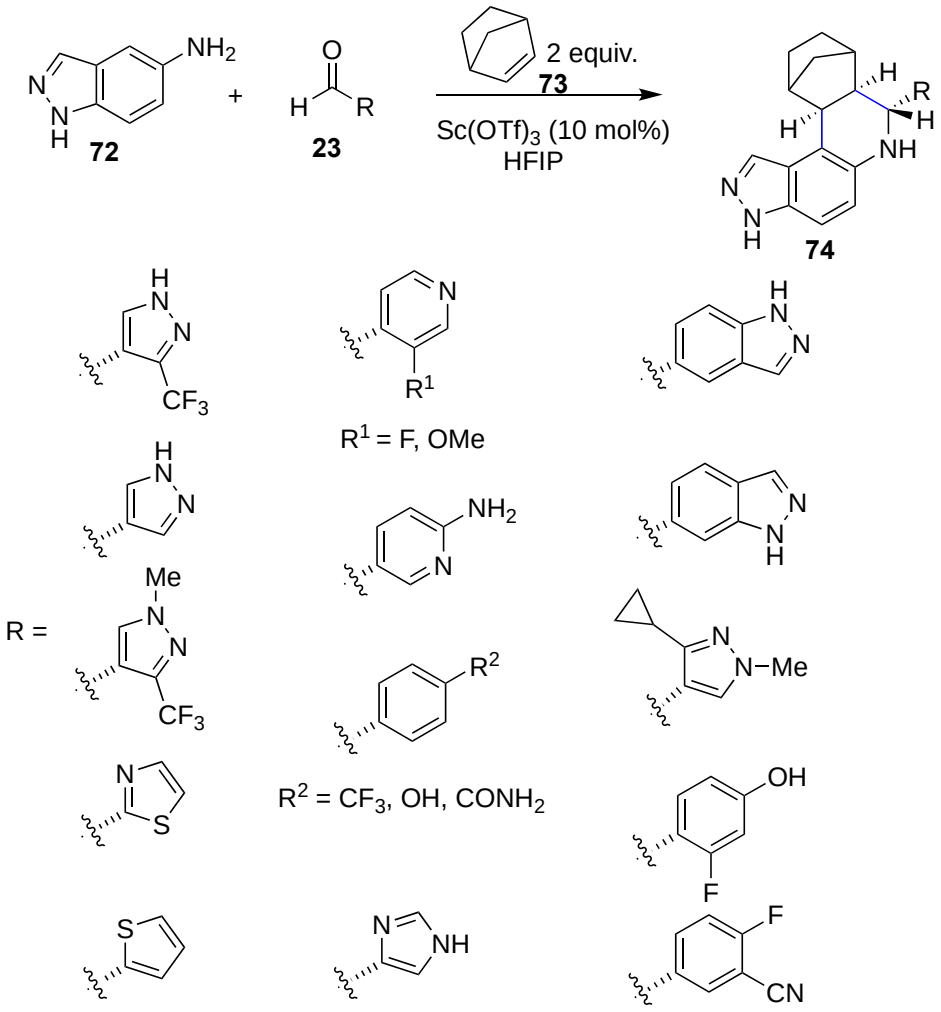
The first catalytic asymmetric Povarov reaction was reported by Shi *et al*. utilizing isatin based starting material (Scheme 23). This reaction gives the access of enantio enriched two quaternary stereogenic centres containing spiro[indoline-3,2`-quinoline] moiety **71** in excellent stereoselectivities (up to 97% ee, all >99:1 dr) with high yields.[40]




$R^1$ = Bn, Ph, *i*-Pr;
$R^2$ = H, 5-Cl, 6-F, 6-Cl, 6-Br, 6-Me, 7-F, 7-Br, 7-$CF_3$, 7-Me, 5,6-$F_2$;
$R^3$ = Me, Et;
$R^4$ = H, Me, MeO;
$R^5$ = 4-MeO, 4-EtO, 4-PhO, 4-F
$R^6$ = 2,4,6-($^i$Pr)$_3$C$_6$H$_2$

**Scheme 23.** Chiral phosphoric acid catalyzed Povarov reaction using isatin based starting material

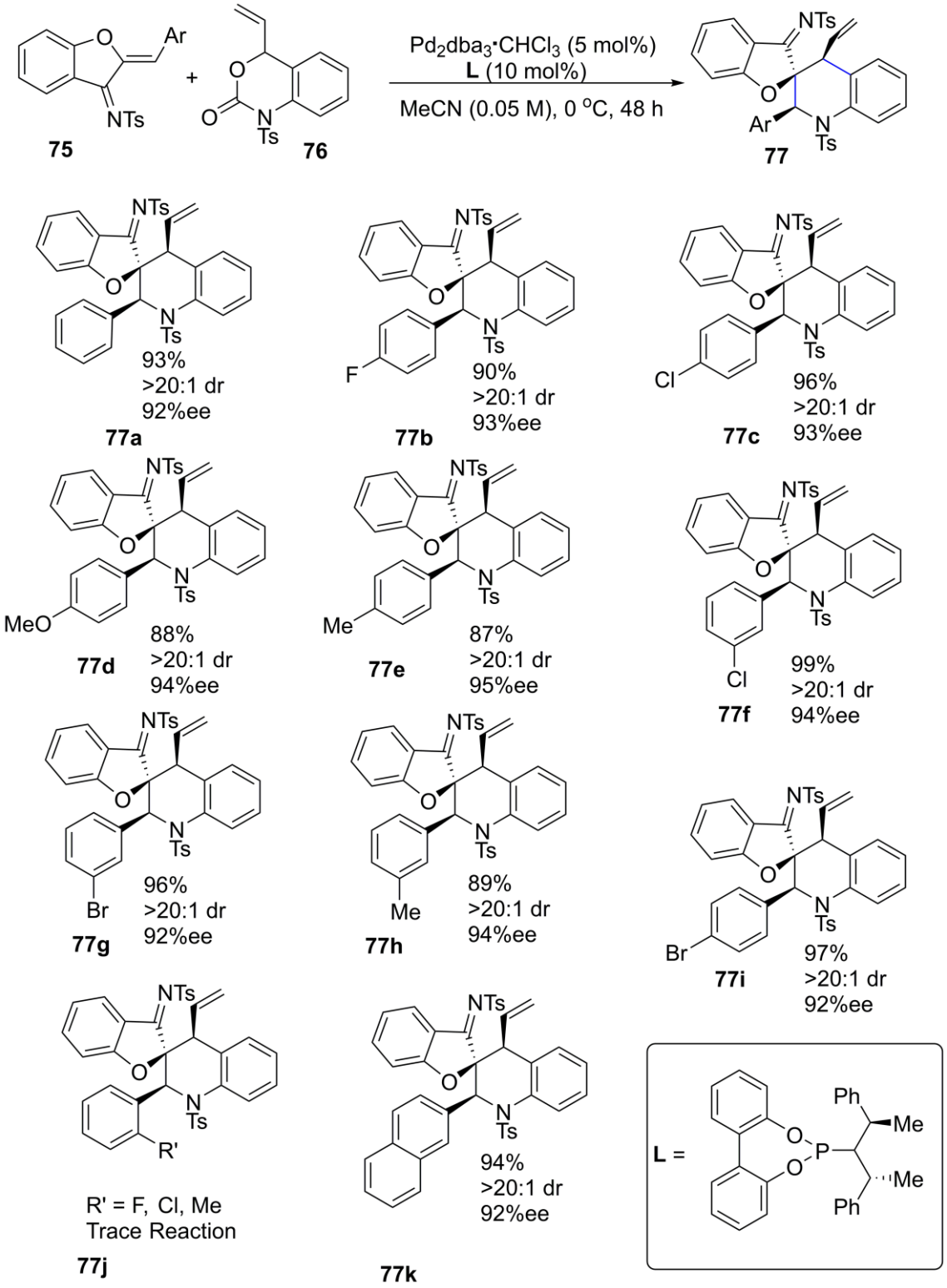
Sintim and coworkers prepared a library of tetrahydro-3*H*-pyrazolo[4,3-*f*]quinoline moiety which were having quite considerable potential to inhibit NCI-60 cancer cell lines. These compounds are promising even at sub-micromolar concentrations. This task has been achieved by uniting elite 5-aminoindazole **72**, norbornene **73** i.e. an activated alkene and corresponding aldehydes **23** in one pot to offer tetrahydro-3*H*-pyrazolo[4,3-*f*]quinolines **74**. The goal has been achieved *via* 10 mol% of scandium triflate as Lewis catalyst and HFIP as a potential solvent due to the insolubility of starting materials in traditional solvents. The standard reaction mixture has been stirred at room temperature for 8-12 hours giving the desired products in 33-66% yields (Scheme 24).[41]




**Scheme 24.** Lewis acid catalyzed synthesis of tetrahydroquinoline derivatives **74**

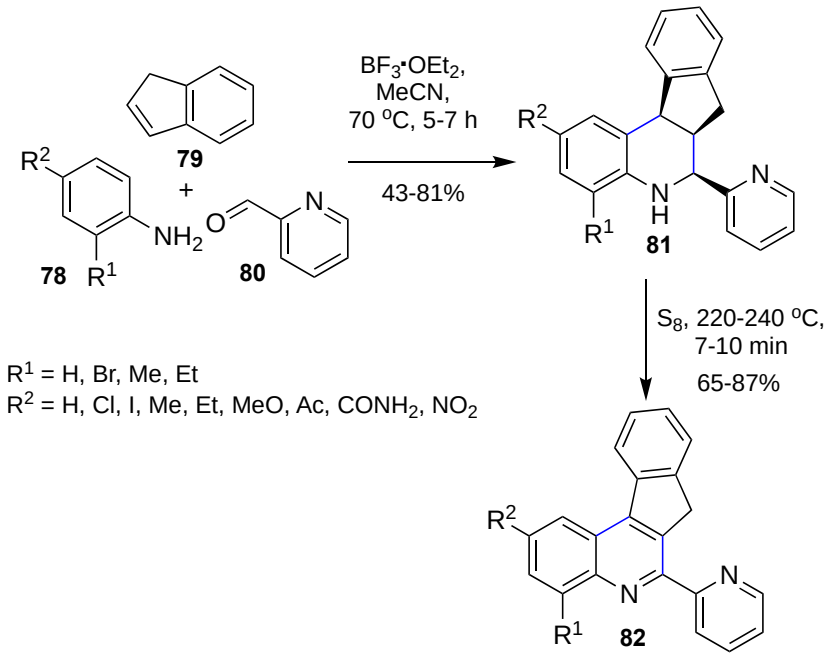
In addition to being highly prevalent in natural products and biologically active compounds, the spirocyclic motifs are becoming more and more significant in drug discovery. Including spirocycles, in order to create hetero- and carbocycles of various sizes, Zhao and his team previously incorporated dipoles of varied numbered of synthons by employing azadienes in cycloadditions. Novel spirocyclic compounds with a tetrahydroquinolines **77** core that is pharmaceutically useful have been created using fused *N*-Ts azadienes **75** and a highly enantio- and diastereoselective [4+2] cycloaddition of vinyl-benzoxazinanone **76**. Three contiguous stereocenters containing unique spirocyclic tetrahydroquinoline scaffold as a single diastereomer was created using a chiral secondary amine containing phosphoramidite ligand with a straightforward biphenyl backbone in high enantioselectivity. The effectiveness of the reaction depends heavily upon the electronics and steric factors of azadiene. The *para* and *meta*-positions were well received by neutral and electron-withdrawing groups, such as methyl groups and halogens, producing outstanding yields, dr, and ee. As a result of their reduced reactivity with these substrates,

azadienes with electron-donating groups like the sterically bulky naphthalene and methoxy group required longer reaction time (Scheme 25).[42]




**Scheme 25.** Spirocyclic tetrahydroquinolines **77** synthesis by Zhao group

Kouznestov and team[43] demonstrated the stereoselective production of a series of 2-pyridyl-substituted indeno[2,1-*c*]quinoline derivatives **82**. An imino-Diels-Alder cycloaddition that is three-component is the first and most important step involved in the formation of asymmetric tetrahydroquinoline **81** and further oxidation with sulfur yields the corresponding analogues of DNA-topoisomerase inhibitors TAS-103, indeno[2,1-*c*]quinoline derivatives **82** (Scheme 26).



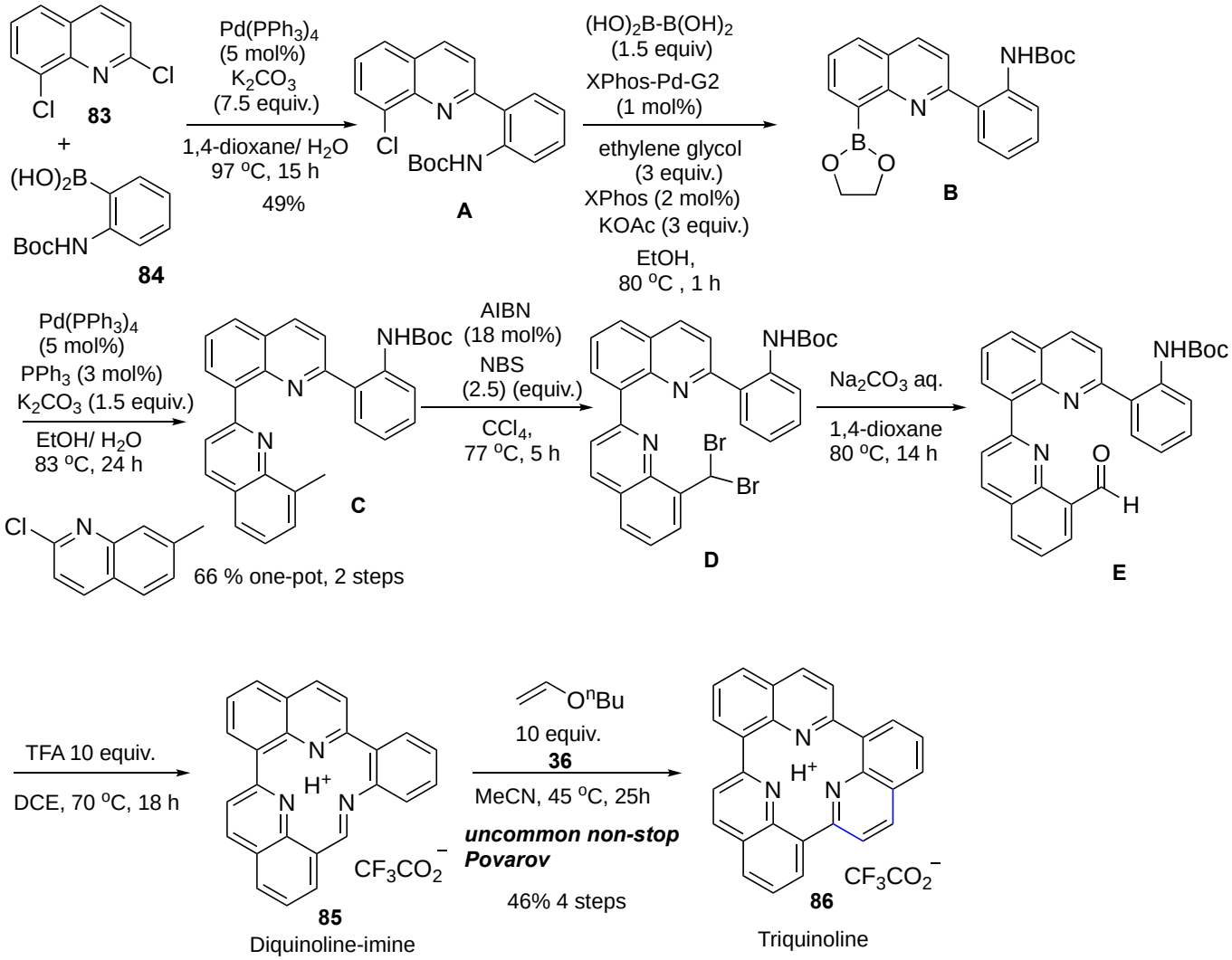

**Scheme 26.** Stereoselective synthesis of 2-pyridyl-substituted indeno[2,1-*c*]quinolines

In recent years, the development of polyaromatic hydrocarbons and graphitic materials is emerging as a new era in addition to the modifications in the synthetic procedures and defects to find out numerous physiochemical features of graphitic materials.

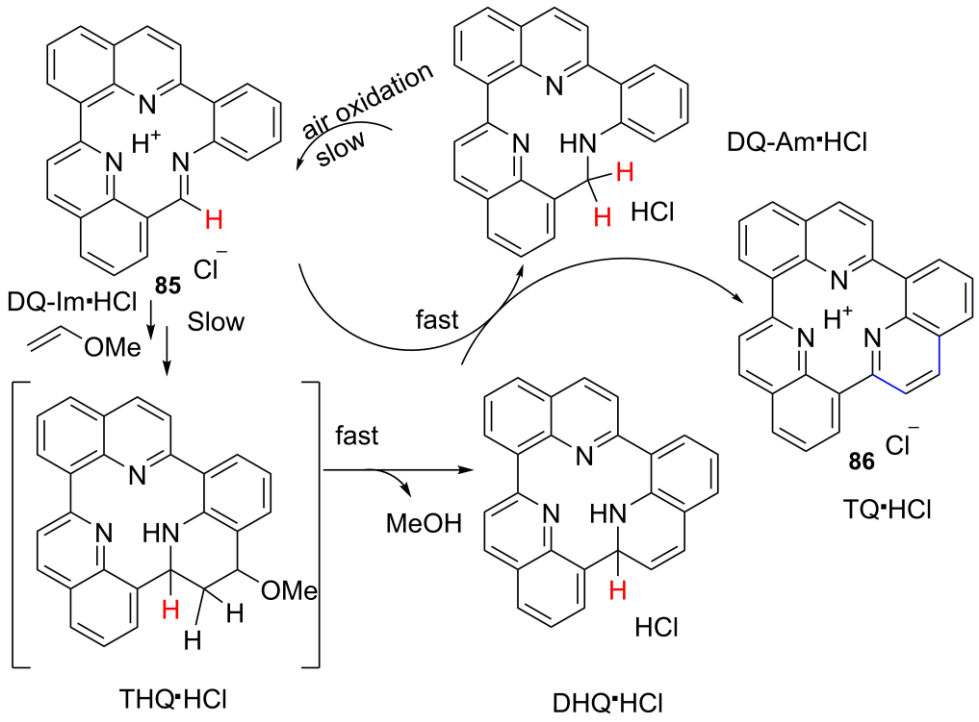
Triquinoline is an affixed system of three quinoline moieties which gathered significant attention in the field of organic synthesis due to its versatile and unique properties including utilization in OLEDs, optoelectronics and its luminescence properties.

Adachi and co-workers[44] in 2019 reported a multistep synthesis of triquinoline moiety **86** for utilizing as a model defect having three nitrogen sites in graphitic structure. Triquinoline was synthesized *via* multistep organic transformations commenced from 2,8-dichloroquinoline **83** in the presence of *N*-Boc protected phenylboronic acid **84** and consecutively the final step involves di-quinoline **85** along with enol ethers **36** to afford triquinoline **86** by utilizing the concept of Povarov reaction (Scheme 27). It is noteworthy to mention that an abnormal trend was observed in triquinoline synthesis from diquinoline where non-stop Povarov reaction was found to occur along with a fast hydride transfer reaction (Scheme 27a). The unique 2D structures having atomic void surrounded by pyridinic nitrogen atoms were reported for this

uncommon behavior which has also been verified by DFT study. The atomic-sized void in the two-dimensional structure of triquinoline has been reported to show the prominent proton affinity which provokes the molecule for complexation with another graphitic scaffolds *via* pi-pi and CH-pi interactions. It has been observed that the proton captured triquinoline moiety is a valuable resource for DNA intercalators which includes the inhibition of topoisomerase I enzyme activity. Besides that, the high proton affinity facilitates the formation of supramolecular scaffolds *via* edge to plane and plane to plane contract modes. Formation of binary and ternary complexes have also been reported and verified using NMR studies.

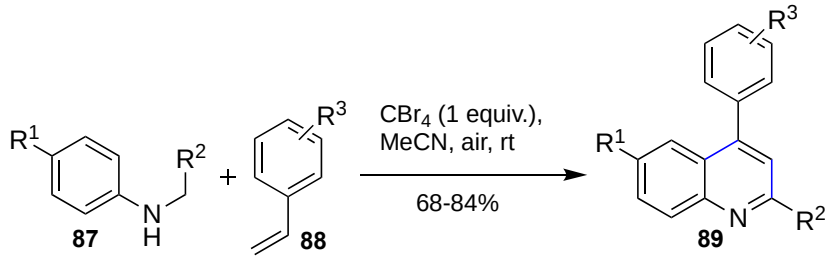



**Scheme 27.** Multistep synthesis of triquinoline *via* unusual Povarov reaction




**Scheme 27a.** Proposed reaction mechanism for the synthesis of triquinoline

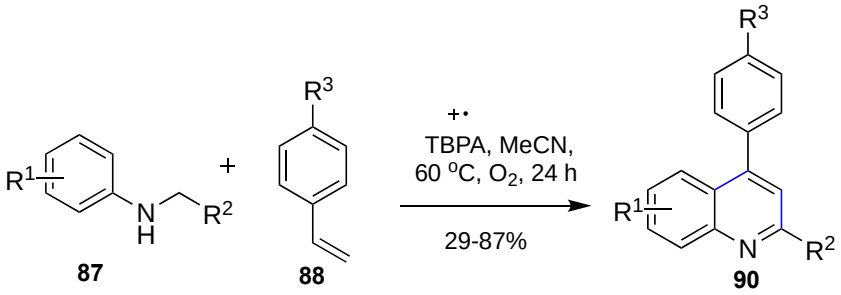
Quinoline derivatives **89** were synthesized by reacting alkenes with glycine derivatives *via* tandem reaction of aromatization and dehydrogenative Povarov reaction, which is shown in scheme 28. The operation was undertaken using $CBr_4$ in acetonitrile medium which is dehydrogenative C-H functionalization process. It is believed that the procedure undergoes a radical process.[45]




$R^1$ = Me, OMe;
$R^2$ = $CO_2$Me, $CO_2$Et, $CO_2$nBu, $CO_2{}^t$Bu, $CO_2$Allyl, C(O)NHMe, C(O)NHEt, C(O)NHnBu, C(O)NH$^t$Bu, C(O)NHBn;
$R^3$ = H, Me, MeO, $^t$Bu, Cl

**Scheme 28.** $CBr_4$-Mediated CDC reaction of alkenes with glycine derivatives

*N*-Benzylanilines **87** were explored as precursors to synthesize quinoline derivatives as illustrated in Scheme 29. The transformations have been accomplished using the concept of Povarov reaction making use of radical cation salt assisted catalytic environment. The reaction conditions have shown maximum efficacy and high yields for the synthesis of quinolines **90**. The mechanistic studies show that in the catalytic oxidation, a radical intermediate was involved.[46]

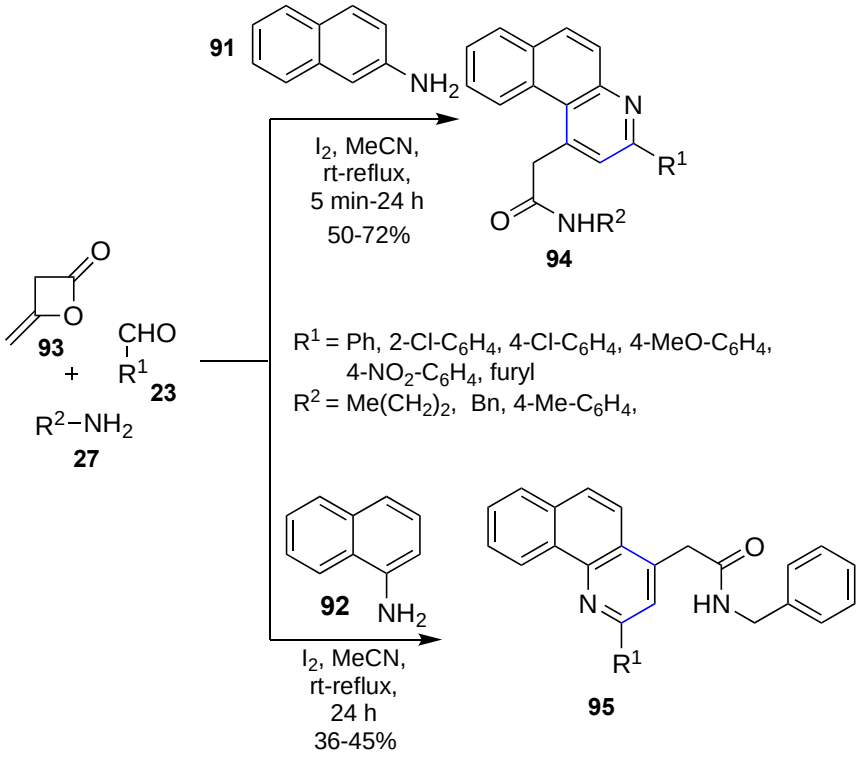



TBPA = tris(4-bromophenyl)aminium hexachloroantimonate

$R^1$ = H, Me, Br, Cl, F, OH, MeO, $NO_2$;
$R^2$ = Ph, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-Me-$C_6H_4$, 4-MeO-$C_6H_4$, 4-$NO_2$-$C_6H_4$, Cy, 2-thiophene;
$R^3$ = Me, Br, MeO, OCOMe

**Scheme 29.** Synthesis of quinoline derivatives from *N*-benzylanilines

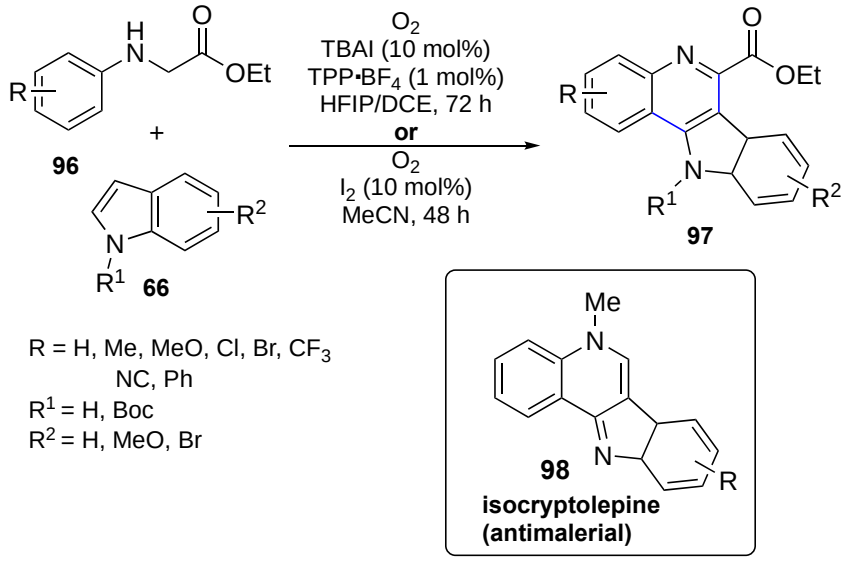
Zeng and Cai developed a fascinating domino reaction between naphthalenamine **91**, **92**, aromatic aldehydes **23**, amines **27** and diketene **93** in the presence of iodine as catalyst that leads to the formation of benzo[*f*]quinolinyl **94** and benzo[*h*]quinolinyl acetamides **95** under mild conditions (Scheme 30).[47]




**Scheme 30.** Iodine-catalysed Povarov reaction

In 2019, Brasholz and team showcased an efficient photo-induced aerobic protocol for synthesizing tetracyclic 11*H*-indolo[3,2-*c*]quinolines **97** *via* a tandem amine dehydrogenation/Povarov cyclization/aromatization reactions of indoles **66** and *N*-arylglycine esters **96** (Scheme 31).[48] A metal free

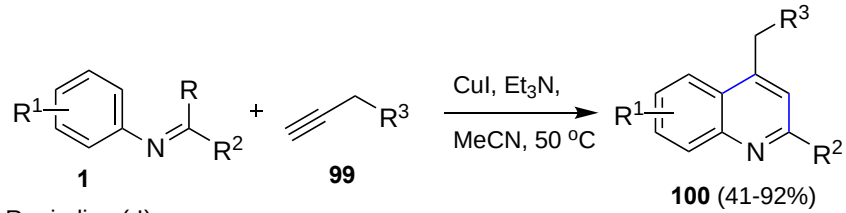
visible light mediated approach comprising of [4+2] cycloaddition reaction of an imine intermediate and indole derivatives rendered a series of new analogs of the antimalarial natural alkaloid isocryptolepine **98** in high yields and selectivity. Two different aerobic conditions have been elicited, one with iodine as catalyst i.e. photocatalyst free protocol and another with photoredox catalyst assisted by halide ion.




**Scheme 31.** Visible light-mediated synthesis of tetracyclic 11*H*-indolo[3,2-*c*]quinolines

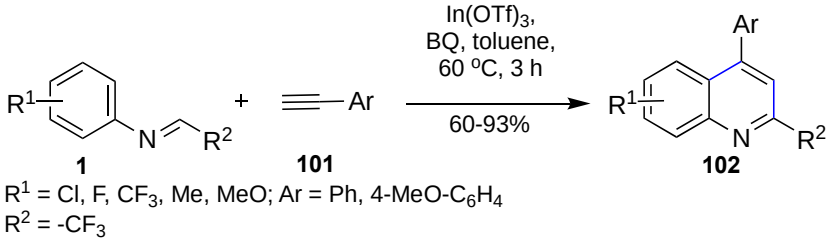
### 2.1.2 ALKYNE AS DIENOPHILE

An efficient and convenient approach was developed by Wu and team[49] for the preparation of fluorinated quinolines **100** in one-pot by reaction of terminal alkynes with *N*-aryl-fluorinated imidoyl iodides in optimal percentage under the influences of CuI as a catalyst (Scheme 32).



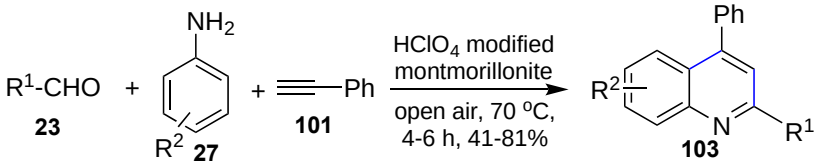

**Scheme 32.** One-pot synthesis of fluorinated quinolines

An effortless and well organized method for the production of quinoline **102** was revealed by Wu and co-workers[50] from alkynes and 2-trifluoromethylimine in presence of $In(OTf)_3$ and *para*-benzoquinone (BQ) in catalytic amount as an oxidant (Scheme 33). On the account of deuterium labeling research it was confirmed that the Diels-Alder mechanism is the way through which the reaction proceeds.



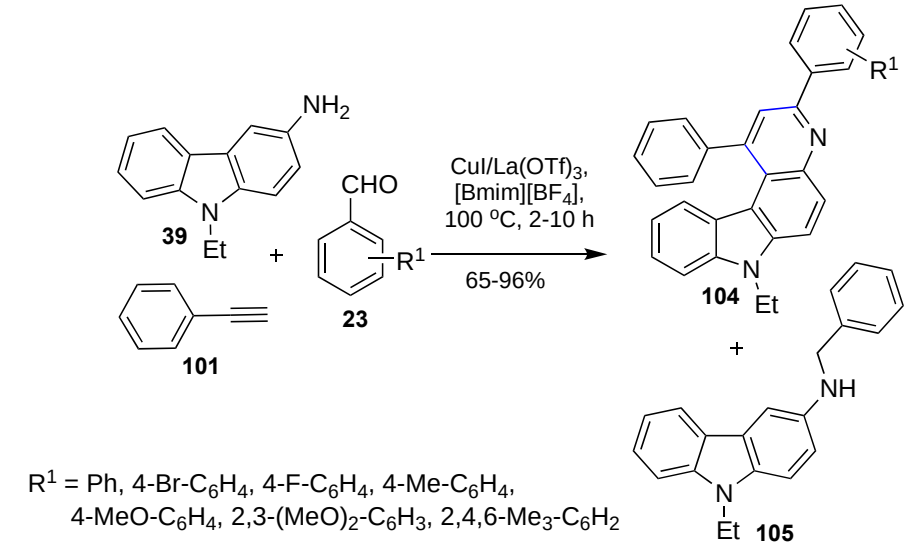

**Scheme 33.** In(OTf)$_3$-Catalyzed synthesis of 2-trifluoromethyl-4-arylquinolines

A multicomponent Povarov reaction was reported by Guchhait *et al.*[51] for the synthesis of substituted quinolines **103** which are crucial precursors in the development of antimalarial drugs, using $HClO_4$ modified montmorillonite as catalyst with legitimate yield. Furthermore, $HClO_4$ modified montmorillonite catalyst could be useful for multicomponent hetero Diels-Alder reaction and heterocyclic scaffolds (Scheme 34).



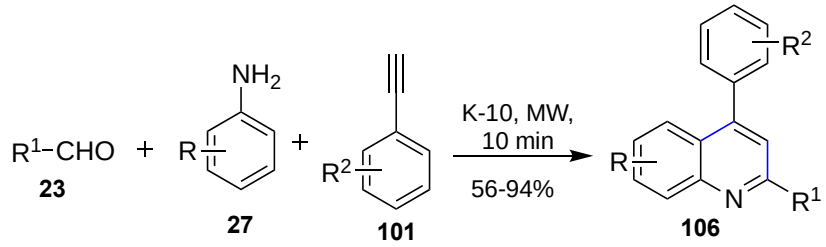

**Scheme 34.** Montmorillonite-promoted multicomponent Povarov reaction

Gaddam and co-workers developed a strategy presented in Scheme 35, towards the sequential intermolecular cyclization of imines with substituted alkynes using CuI/La(OTf)$_3$ catalyst for the production of isomeric ellipticine derivatives **104** and **105** *via* one-pot synthesis.[52]




**Scheme 35.** CuI/La(OTf)$_3$-Catalyzed sequential intermolecular cyclization of substituted alkynes with imines

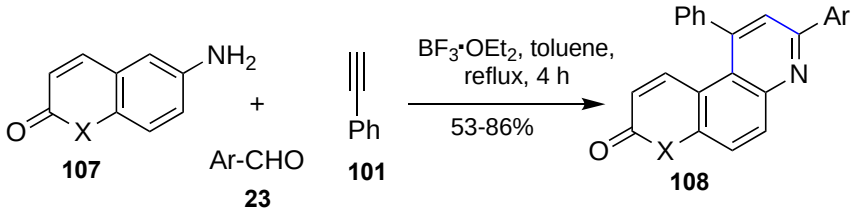
The synthesis of substituted quinolines **106** was reported by Kulkarni and co-workers using montmorillonite K-10 as catalyst under microwave irradiation. This multicomponent domino reaction that includes terminal alkynes, aldehydes, anilines was reported to proceed *via* imine formation and intermolecular addition of imine to an alkyne. The 90% atom economy was achieved in few minutes with high yield. In addition this solid acid catalyzed, microwave irradiated, multicomponent domino reaction has high selectivity with high yield along with less energy consumption. Overall, a very good example of environment friendly synthesis has been described (Scheme 36).[53]




R = H, 4-Cl
$R^1$ = 2-Br-$C_6H_4$, 4-F-$C_6H_4$, 4-CN-$C_6H_4$, 4-Me-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 3,4-$Cl_2$-$C_6H_4$, COPh, Cy-hex;
$R^2$ = 4-F-$C_6H_4$, 4-Me-$C_6H_4$

**Scheme 36.** Synthesis of quinolines using domino reaction

Majumder *et al*. demonstrated a multicomponent aza-Diels-Alder domino reaction of terminal alkynes, aldehydes, heterocyclic amines, utilizing Lewis acid catalyst $BF_3$•$OEt_2$ for the synthesis of pyrano[3,2-*g*]quinoline and pyrano[3,2-*f*]quinoline **108** (Scheme 37) featuring mild reaction conditions and operational simplicity.[54]

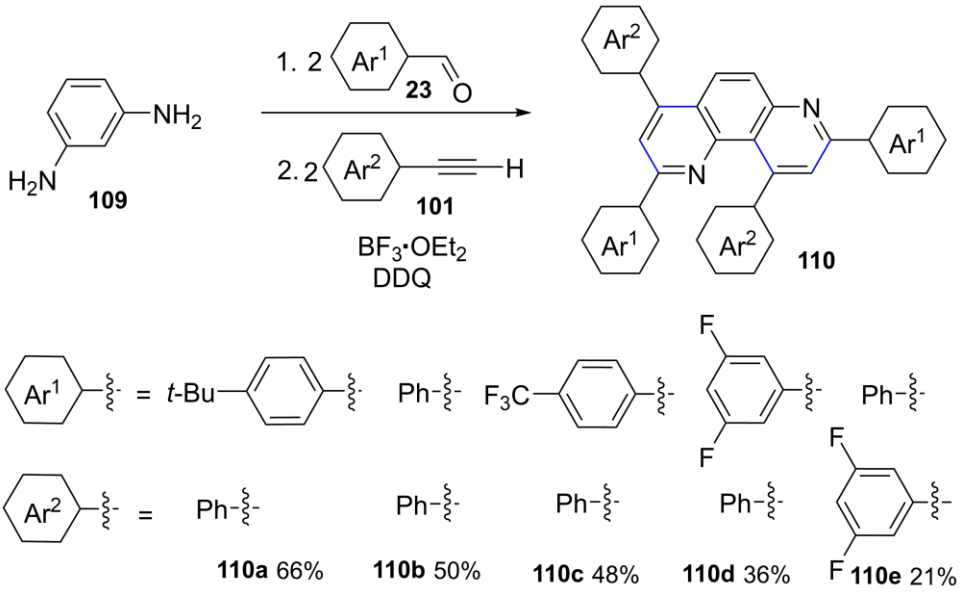



X = O, *N*-Me, *N*-Et;
Ar = Ph, 4-Me-$C_6H_4$, 2-Cl-$C_6H_4$, 3-Cl-$C_6H_4$, 4-Cl-$C_6H_4$, 4-MeO-$C_6H_4$, 2-Py, 2-furyl, 2-thiophene

**Scheme 37.** Three-component domino reaction for the synthesis of pyrano[3,2-*f*]quinoline

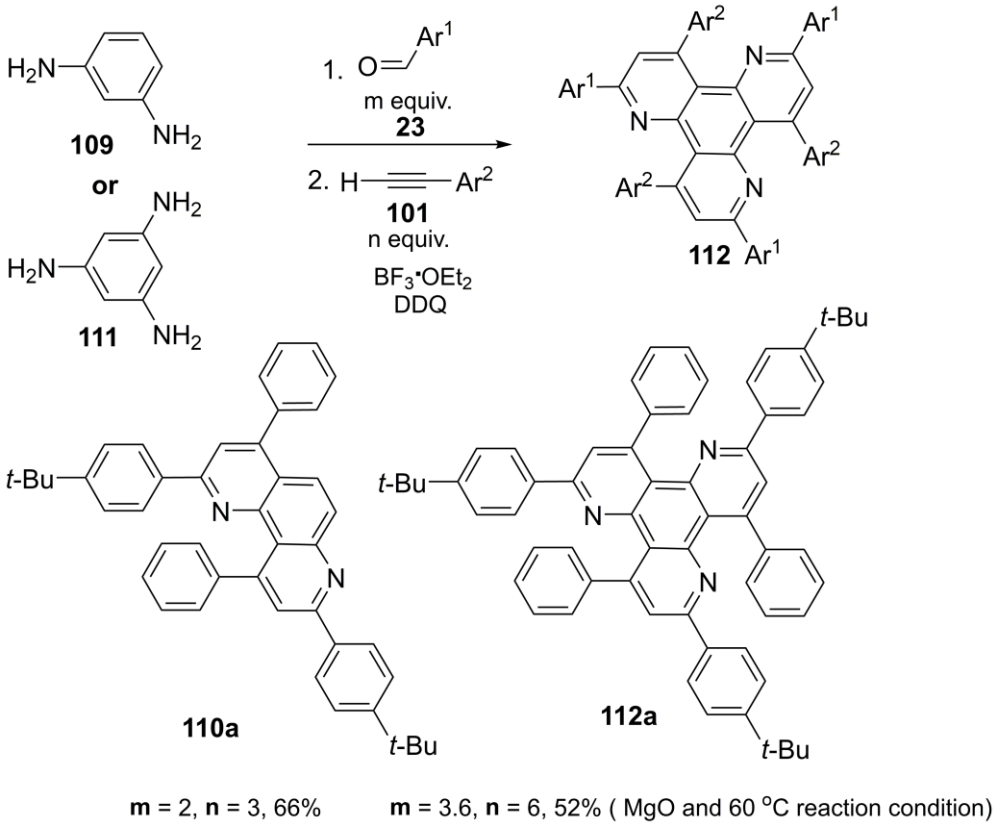
Phenanthroline derivatives and their chemical properties are well known in the application of Diodes, especially in OLEDs that constitutes of those derivatives for which these have been utilized as a hole blocking as well as electron-carriers in modern days. Usually 1,10-phenanthrolines have been well explored compared to the other derivatives. In early 2022, Kuwabara *et al*. reported[55] aza-Diels-Alder reaction based synthetic procedure for 1,7-phenanthroline and its derivatives. They have been explored the correlation of substituents on the 1,7-phenanthroline derivatives and their materialistic properties can

be properly utilized in OLEDs. One-pot synthetic procedure involving starting materials **109**, **23** and **101** have been considered in the presence of $BF_3$•$OEt_2$ and DDQ to produce five 1,7-phenanthroline derivatives **110** (Scheme 38). Synthesis in the presence of electron donating substituents was reported to produce high yields for which trouble free electrophilic cyclization steps are reasonable to consider. From the XRD data it was revealed that the more planar structure is relevant with less sterically hindrance in between the adjacent cores of 1,7-phenanthroline derivatives, less is the HOMO-LUMO gap and hence, better for the utilization as a hole blocking and electron carrier materials in the OLEDs.



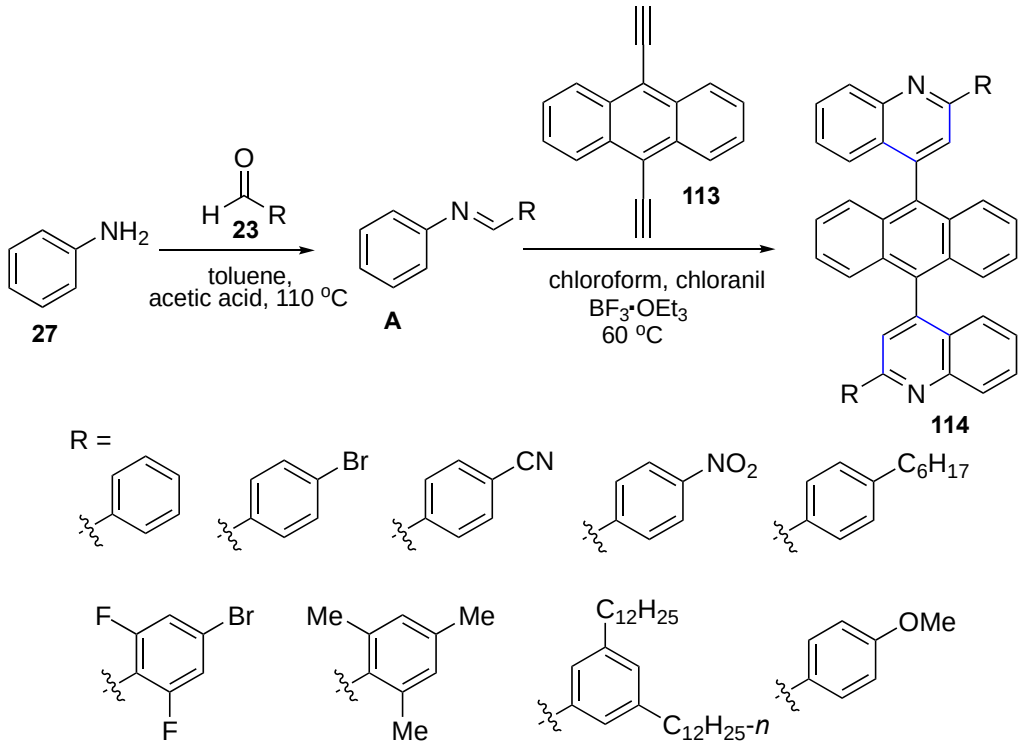

**Scheme 38.** Organic transformation for synthesizing 1,7-phenanthroline derivatives

Considering the importance of conjugated pi-extended systems like phenanthroline and its derivatives as the prominent molecules in the development of hole blocking materials in OLEDs, the preparation of these molecules were reported by Kuwabara *et al*.[56] in 2021 by employing an efficient one-pot organic transformation. This strategy afforded the useful compounds 1,5,9-triazatriphenylene **112** starting from 1,3,5-triaminobenzene **111**, arylaldehyde **23** and phenylacetylene **101** as starting materials in the presence of Lewis acid such as $BF_3$•$OEt_2$ and DDQ as an oxidant *via* consecutive three Povarov reactions (Scheme 39). The basic idea behind the synthesis was based on the one-pot Povarov reaction of aromatic amines, aldehydes and alkynes to form aza-polycyclic compounds. During the synthesis of phenanthroline derivatives using consecutive Povarov reactions, it was also realized that the selectivity of the reaction is independent of steric hindrance in the product and dependent on the HOMO distribution of the intermediate. It is noteworthy to mention that the HOMO energy level of triazatriphenylene moiety **112a** was found to be sufficiently low (-6.33 eV) and form a thin film because of which it could be utilized as the hole blocking material in OLEDs.

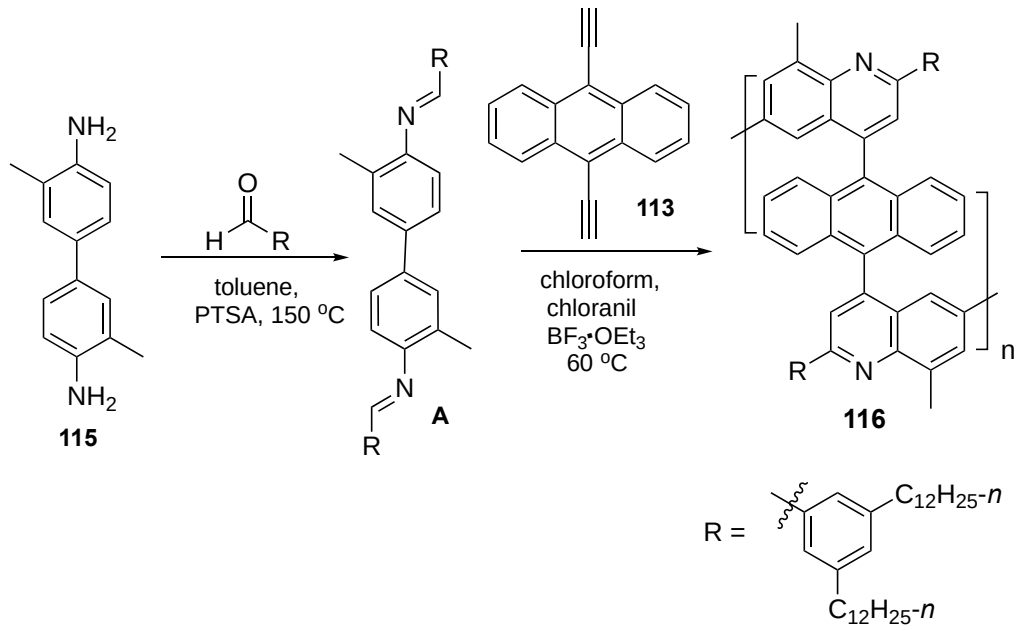



**Scheme 39.** Povarov reaction of substituted anilines to synthesize aza-polycyclic compounds

Recently, a series of studies have attracted attention towards the preparation of acene's molecular structure in order to improve the properties of materials, especially related to the performance of devices.[57-59] In order to synthesize both diquinolineanthracenes **114** and polydiquinolineanthracenes **116**, Dibble and colleagues have developed a generic method, which is highlighted in Scheme 40 and 40a.[60] They have contributed the synthesis of a number of diquinolineanthracenes that are substituted with symmetrical quinolines and have functionalities at their 2-positions that are electron-withdrawing, electron-donating, and sterically congested. Then, by employing an AA/BB-type polymerization procedure, they synthesized polydiquinolineanthracenes under the same reaction conditions by using commercially available AA-type diimine and BB-type diethynylanthracene monomers.



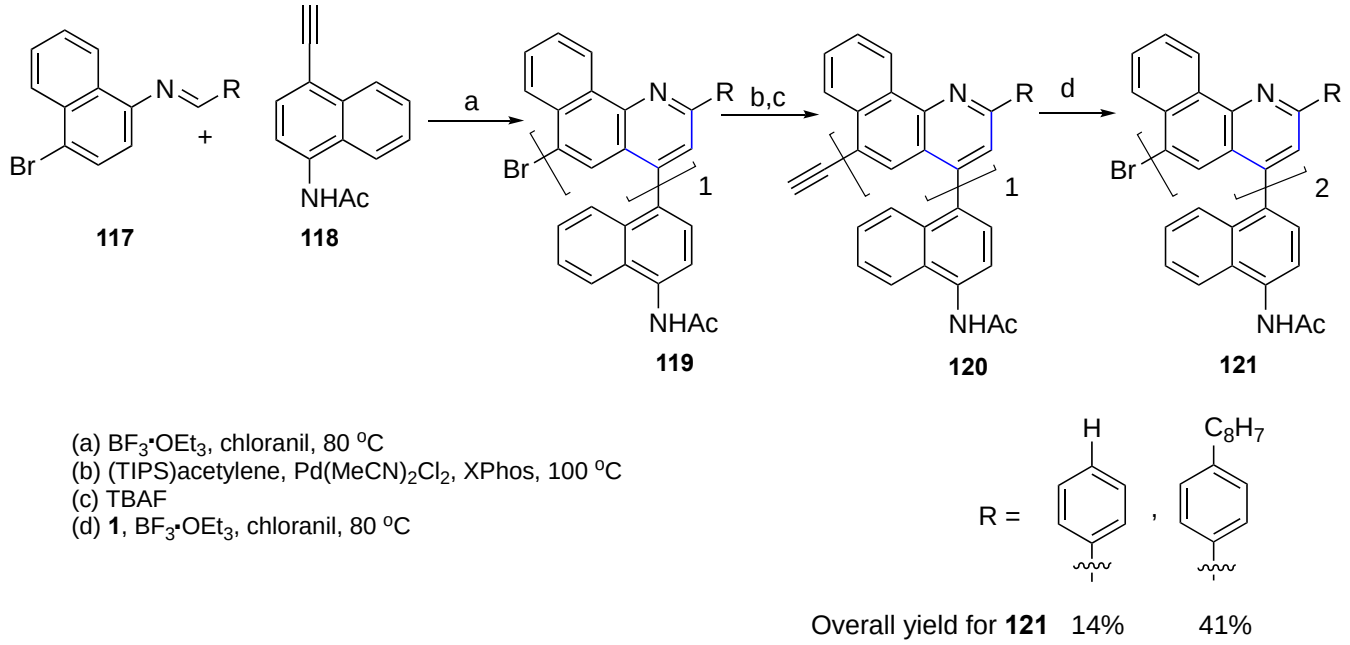

**Scheme 40.** Synthesis of 9,10-diquinolineanthracenes




**Scheme 40a.** Synthesis of polydiquinolineanthracene

The preparation of graphene nanoribbons has received immense attention, since it represents a promising class of materials for the upcoming semiconductor devices.[61-64] To synthesize a number of benzoquinoline model compounds, Dibble and colleagues initially employed a general aza-Diels-Alder reaction conditions.[65] Then, by using the verified conditions for the model compounds, they synthesized

an AB-type bifunctional monomer and utilized it to prepare a congested polybenzoquinoline **121** *via* a Diels-Alder type polymerization reaction (Scheme 41). After synthesized polybenzoquinolines of varied sizes with diverse peripheral substituents, they in turn showed the range and adaptability of their methodology.



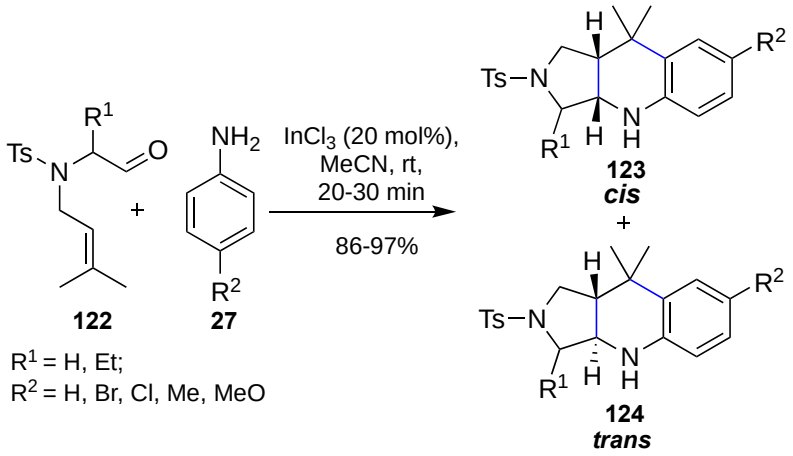

**Scheme 41.** Synthesis of benzoquinoline model compounds

## 2.2 INTRAMOLECULAR POVAROV REACTION

In addition to the intermolecular aza-Diels-Alder reactions discussed in the previous section, we have described here the considerable number of protocols for the synthesis of quinoline and tetrahydroquinoline derivatives *via* intramolecular aza-Diels-Alder reaction involving generation of one and two new bonds by employing alkenes and alkynes as dienophile.

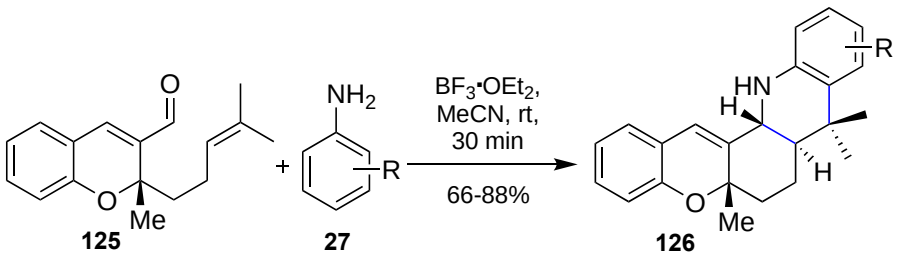
### 2.2.1 ALKENE AS DIENOPHILE

In 2009, Raghunathan and co-workers have developed an indium(III) chloride catalyzed methodology in order to synthesize a sequence of hexahydropyrrolo[3,4-*b*]quinolines **123** and **124** with an optimal yields by utilizing aldimines procured from *N*-phenylated aliphatic aldehydes and aromatic amines (Scheme 42).[66]



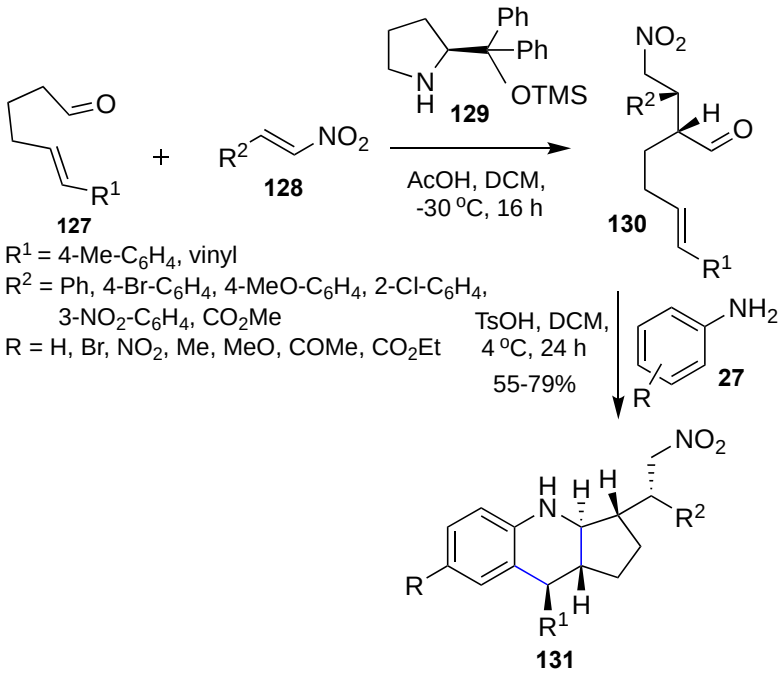

**Scheme 42.** $InCl_3$-Catalyzed synthesis of hexahydropyrrolo[3,4-*b*]quinolines

In 2010, Reddy *et al*. reported a protocol for the synthesis of a sequence of unique 5*H*-chromeno[2,3-*c*]acridine derivatives **126** *via* the combination of chromene-3-carboxaldehyde **125** that are alkene-tethered with different aromatic amines. The reaction delivers a combination of *cis*- and *trans*-diastereomer, where the formation of *trans*-isomer was found in higher yield (Scheme 43).[67]



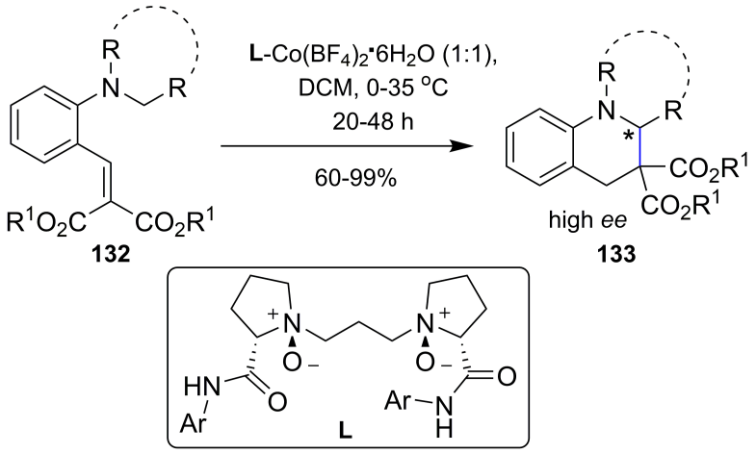

**Scheme 43.** Synthesis of novel 5*H*-chromeno[2,3-*c*]acridine derivatives

An effective organocatalytic one-pot process that supplies five stereogenic centers containing polycyclic hexahydrocyclopenta[*b*]quinoline derivatives **131** has been investigated by Jensen *et al*. The different nitroalkenes, anilines, and aldehydes were nicely tolerated by the reaction conditions. High yields of the products were obtained with excellent enantio- and diastereo-selectivities (Scheme 44).[68]




**Scheme 44.** Synthesis of polycyclic hexahydrocyclopenta[*b*]quinoline derivatives

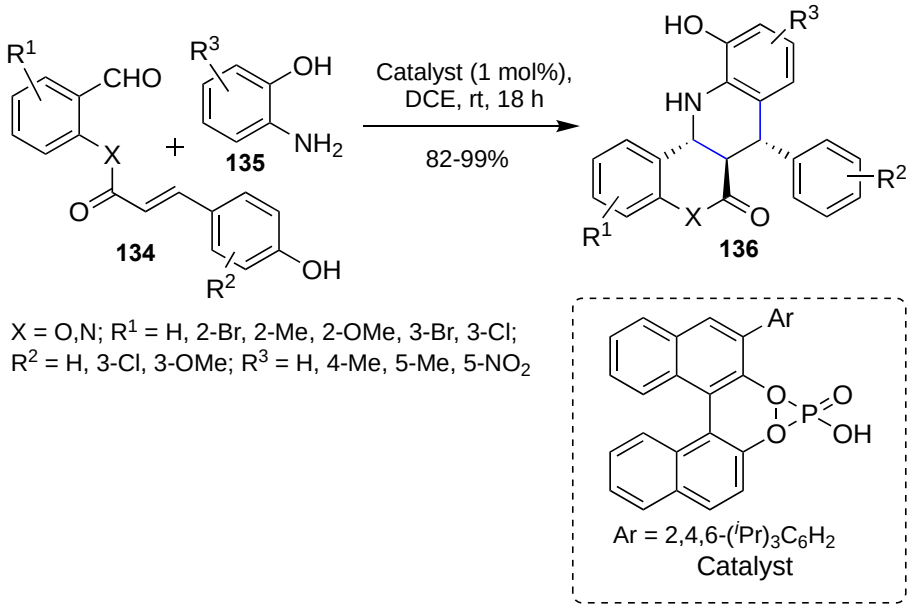
Cao *et al.* demonstrated that *o*-dialkylamino-substituted alkylidenemalonates undergoes an intramolecular cyclization/1,5-hydride transfer process that is highly enantioselective by using $Co(BF_4)_2$•$6H_2O$ and *N*,*N*'-dioxide which is a chiral catalyst that facilitated the asymmetric synthesis of biologically interesting tetrahydroquinolines **133** in good yields when performed in ambient conditions (Scheme 45). In order to explain the starting point of asymmetric induction and activation, a transition-state model was proposed, in view of the product's absolute configuration.[69]




**Scheme 45.** Synthesis of optically active tetrahydroquinolines

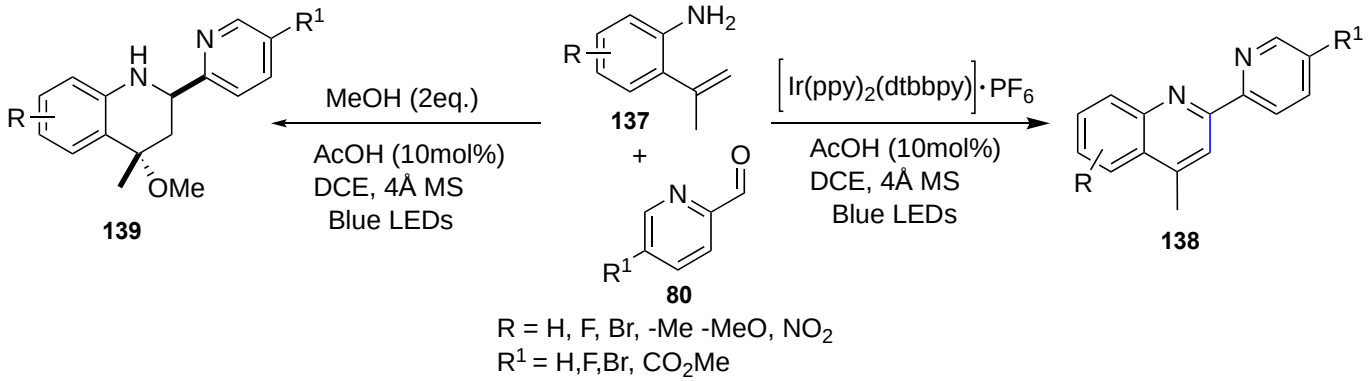
Masson *et al*. in 2017 developed[70] a highly competent enantioselective intramolecular cycloaddition reaction i.e. Povarov reaction using chiral phosphoric acids as an organocatalyst with low catalyst loading.

The 2-azadiene precursors were provided by primary anilines and extended numbers of fused azacycles **136** in excellent yields with high diastereoselectivity and enantioselectivity (>99:1 dr and up to 99:1 er) avoiding column chromatography purification. Furthermore, the obtained cycloadducts could be the valuable precursors for preparing chemically diverse heterocycles moiety *via* well-reported catalytic reactions (Scheme 46).




**Scheme 46.** Synthesis of quinoline derivatives *via* intramolecular Povarov reaction

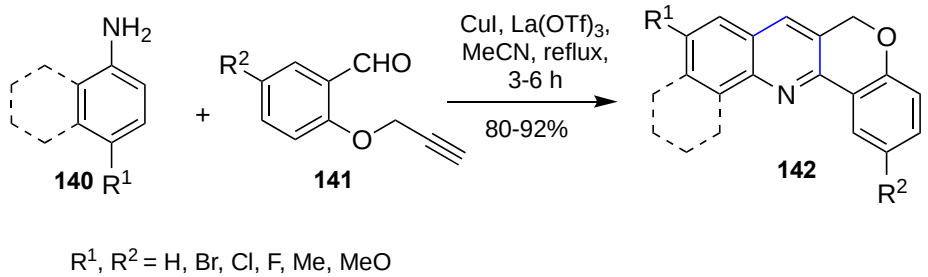
Recently in 2023, Fallan and coworkers, considering the application of quinolines in both agro and medicinal chemistry, explored the photocatalyst mediated cyclization of 2-vinylanilines **137** and aryl-aldehydes **80** to afford quinolines **138** and tetrahydroquinolines **139** moiety. In order to accomplish the synthetic process, the solution of 1 mol% of phtotcatalyst $[Ir(ppy)_2(dtbbpy)]\bullet PF_6$, 10 mol% of acetic acid and all the precursors i.e. 2-vinylaniline and suitable aryaldehydes in DCM was exposed to 450 nm light source for 8 hours which leading to the desired product quinolines **138** in NMR yields up to 73%. The other observation is by taking methanol as substitute of the concerned photocatalyst leads to the formation of privileged 1,2,3,4-tetrahydroquinolines **139** (Scheme 47).[71]



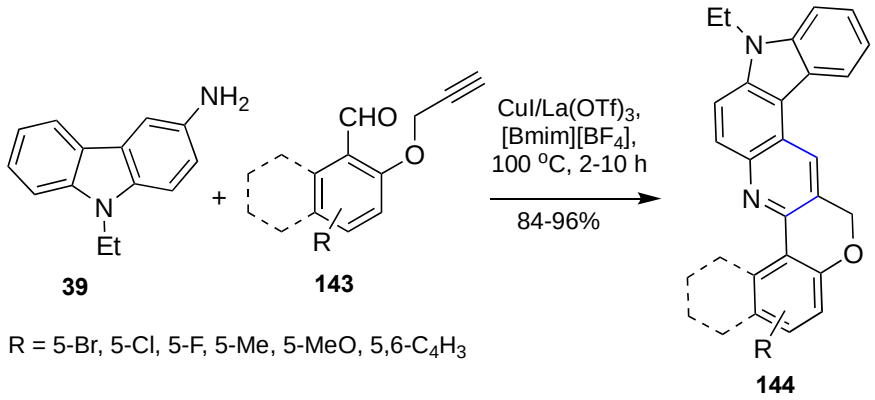

**Scheme 47.** Visible light-promoted synthesis of quinolines **138** and tetrahydroquinolines **139**

### 2.2.2 ALKYNE AS DIENOPHILE

A broad range of chromenoquinolines **142** can be synthesized by the reactions of various substituted anilines or naphthylamines with *O*-propargylated salicylaldehydes in presence of combined catalytic system such as CuI/La(OTf)$_3$ (Scheme 48a).[72] Employing same catalytic system, authors have investigated the production of isomeric ellipticine derivatives with unique one-pot synthesis of **144** (Scheme 48b).[52]

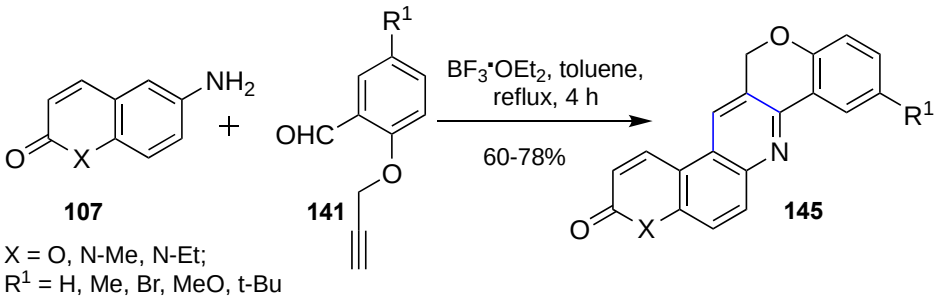



**Scheme 48a.** Lewis acid catalysed synthesis of chromenoquinolines derivatives



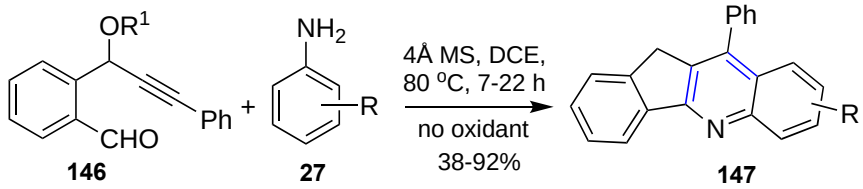

**Scheme 48b.** CuI/La(OTf)$_3$-Catalysed synthesis of ellipticine derivatives

The aza-Diels-Alder reaction of *o*-propargylated salicylaldehyde **141** was investigated to synthesize chromeno[4,3-*b*]pyrano[3,2-*f*]quinolin-3(13*H*)-one derivatives **145** with 6-aminoquinolones and 6-aminocoumarin respectively (Scheme 49). A single-step approach provides high yields of polycyclic heterocycles that are potentially bioactive.[73]



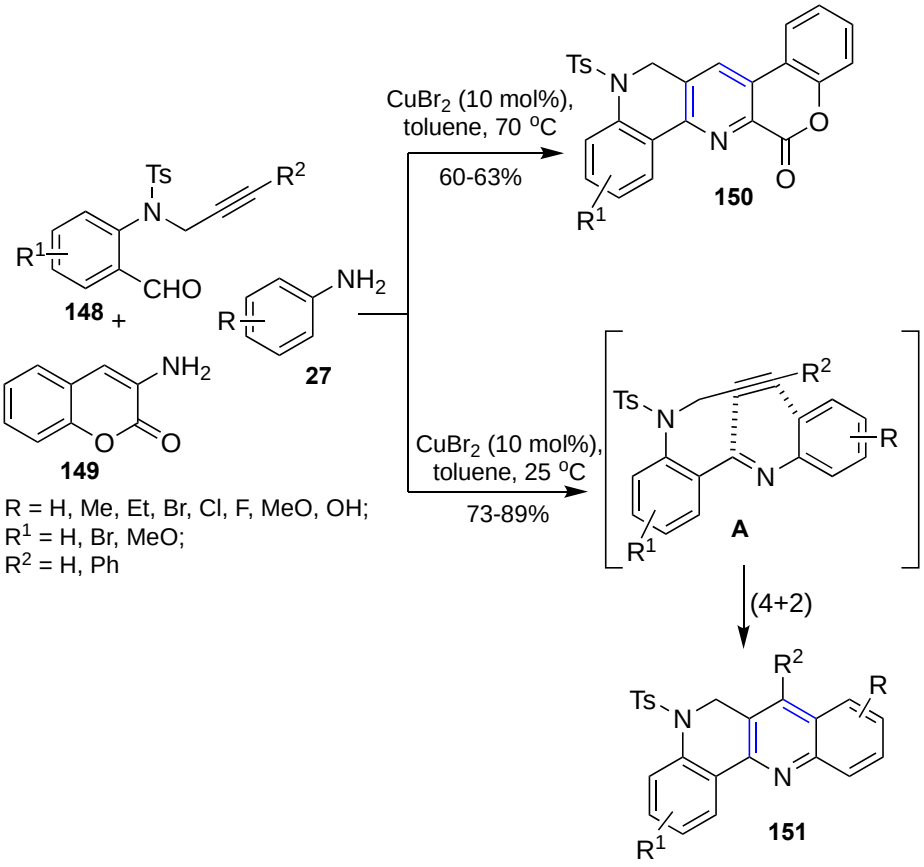

**Scheme 49.** Synthesis of bioactive polycyclic heterocycles *via* aza-Diels-Alder reaction

Indeno[1,2-*b*]quinolines **147** was produced *via* a new synthetic route on the basis of intramolecular aza-Diels-Alder (Povarov) reaction that includes reactions of *N*-arylamines with *O*-propargyl benzaldehydes **146**. Several advantages are offered by this method such as a wide reaction scope, high efficiency and no necessity for an oxidant (Scheme 50).[74]



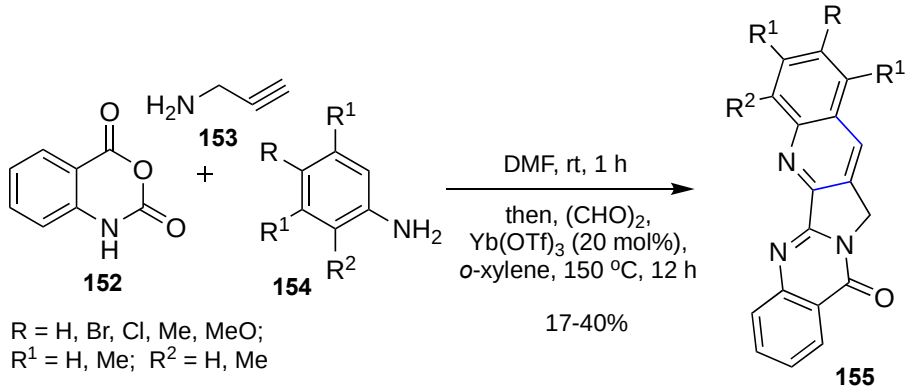

**Scheme 50.** Synthesis of indeno[1,2-*b*]quinolines using Povarov reaction

A novel intramolecular inverse electron-demand hetero Diels-Alder reaction (IEDDA) has been reported by the reaction of aryl amines and 2-(*N*-propargylamino)benzaldehydes. The transformation was achieved *via in situ* generated electron-deficient hetero-dienes tethered with alkyne in the presence of $CuBr_2$ catalyst. The present method delivered the functionalized quinolines **150** and **151** selectivity under mild conditions and in high yields (Scheme 51).[75]




**Scheme 51.** $CuBr_2$-Catalyzed preparation of functionalized quinolines

Tseng *et al.* proposed an economically and efficient synthesis of luotonin A and its analogues **155** (Scheme 52). This method is the shortest method for the preparation of luotonin A. It was observed that among the compound prepared, few of them showed inhibitory activity that is more potent than luotonin A for human topoisomerase I enzyme.[76]

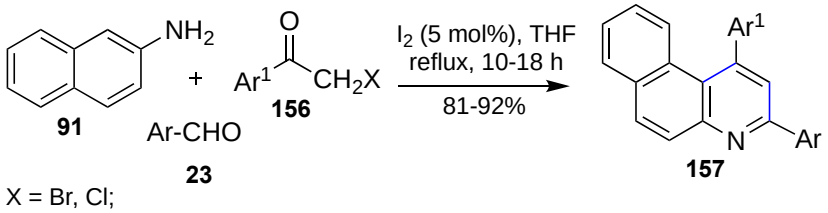



**Scheme 52.** Lewis acid catalyzed synthesis of luotonin A and its analogues

## 3. MISCELLANEOUS

In this section, we have described those protocols in which the dienophiles are *in situ* generated to accomplish the aza-Diels-Alder reaction.

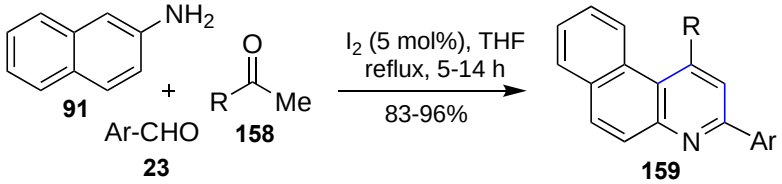
Wang and co-workers demonstrated the synthesis of 1,3-diarylbenzo[*f*]quinolines **157** involving the multicomponent reaction of 2-halogenated acetophenone **156**, naphthalen-2-amine **91**, aromatic aldehyde **23**, with 5 mol% iodine as catalyst in THF. The formation of unexpected product was explained by Cram's rule. (Scheme 53).[77]




X = Br, Cl;
Ar = 3-Br-$C_6H_4$, 3-$NO_2$-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2,3-$Cl_2$-$C_6H_3$, 2,4-$Cl_2$-$C_6H_3$,3,4-$Cl_2$-$C_6H_3$, 3,4-$Me_2$-$C_6H_3$, 3,4-$(MeO)_2$-$C_6H_3$, 3,5-$(MeO)_2$-$C_6H_3$, 2-thienyl;
$Ar^1$ = Ph, 3-Cl-$C_6H_4$, 3-$NO_2$-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-$NO_2$-$C_6H_4$

**Scheme 53.** Unexpected synthetic routes for 1,3-diarylbenzo[*f*]quinolines

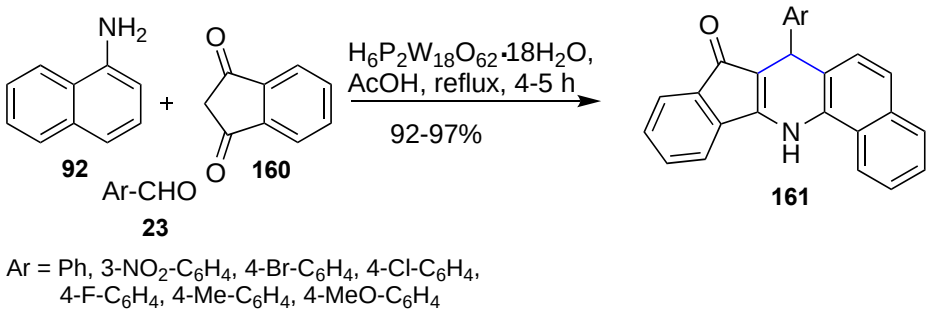
The production of benzo[*f*]quinoline derivatives **159** was reported by Wang *et al*. using 5 mol% iodine as catalyst through multicomponent reaction involving naphthalen-2-amine **91**, arylaldehyde **23**, and acetophenone or acetone **158** with high yield (Scheme 54).[78] It is worth mentioning that protocol own mild reaction conditions and operational simplicity.




Ar = 2-$NO_2$-$C_6H_4$, 3-Br-$C_6H_4$, 3-Cl-$C_6H_4$, 3-$NO_2$-$C_6H_4$, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 2,3-$Cl_2$-$C_6H_3$, 2,4-$Cl_2$-$C_6H_3$, 3,4-$Cl_2$-$C_6H_3$, 3,4-$Me_2$-$C_6H_3$, 3,4-$(MeO)_2$-$C_6H_3$, 3,5-$(MeO)_2$-$C_6H_3$, 2-thienyl;
R = Me, Ph, 4-Br-$C_6H_4$, 4-Cl-$C_6H_4$, 4-F-$C_6H_4$, 4-$NO_2$-$C_6H_4$, 4-Me-$C_6H_4$

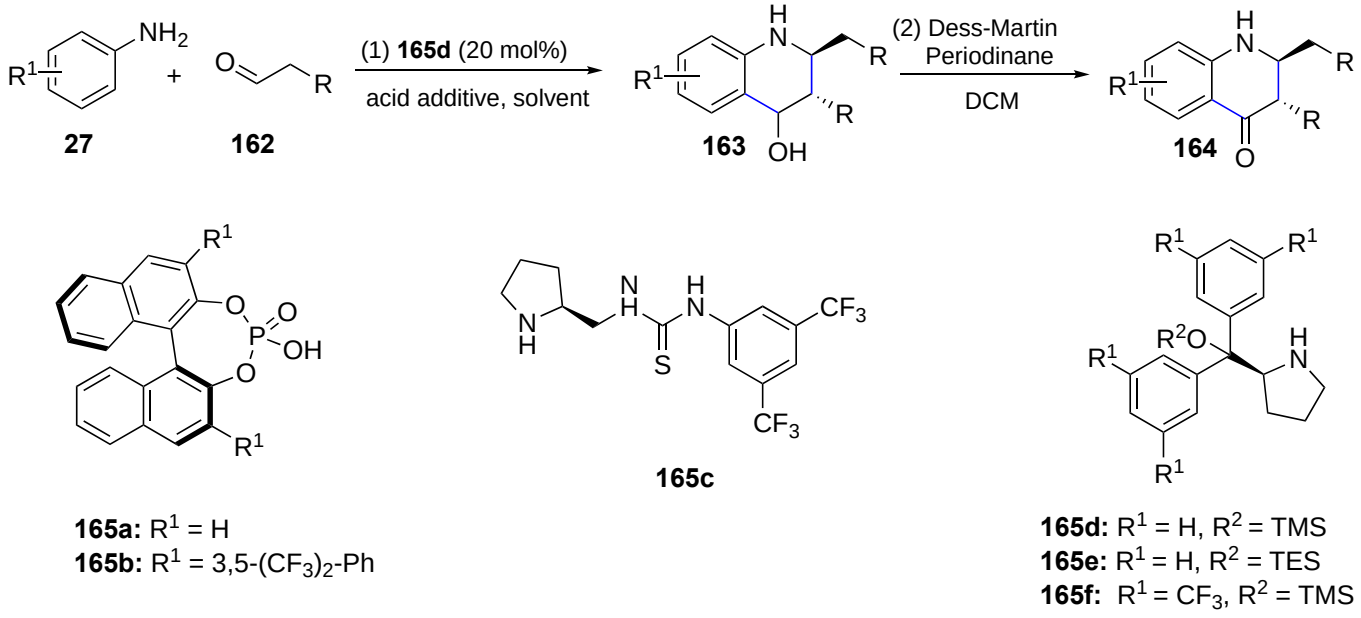
**Scheme 54.** Synthesis of benzo[*f*]quinoline using three-component reaction

Heravi *et al*. established the preparation of indeno[1,2-*b*]quinolin-7-one derivatives **161** *via* one-pot synthesis from the precursors 1,3-indanedione **160**, 1-naphthylamine **92** and various aldehydes **23** in the assistance of a reusable and green catalyst $H_6P_2W_{18}O_{62}$•$18H_2O$ under reflux conditions in AcOH (Scheme 55). This method was rapid and efficient for the preparation of these scaffolds.[79]




**Scheme 55.** $H_6P_2W_{18}O_{62}$•$18H_2O$ Catalyzed synthesis of quinoline

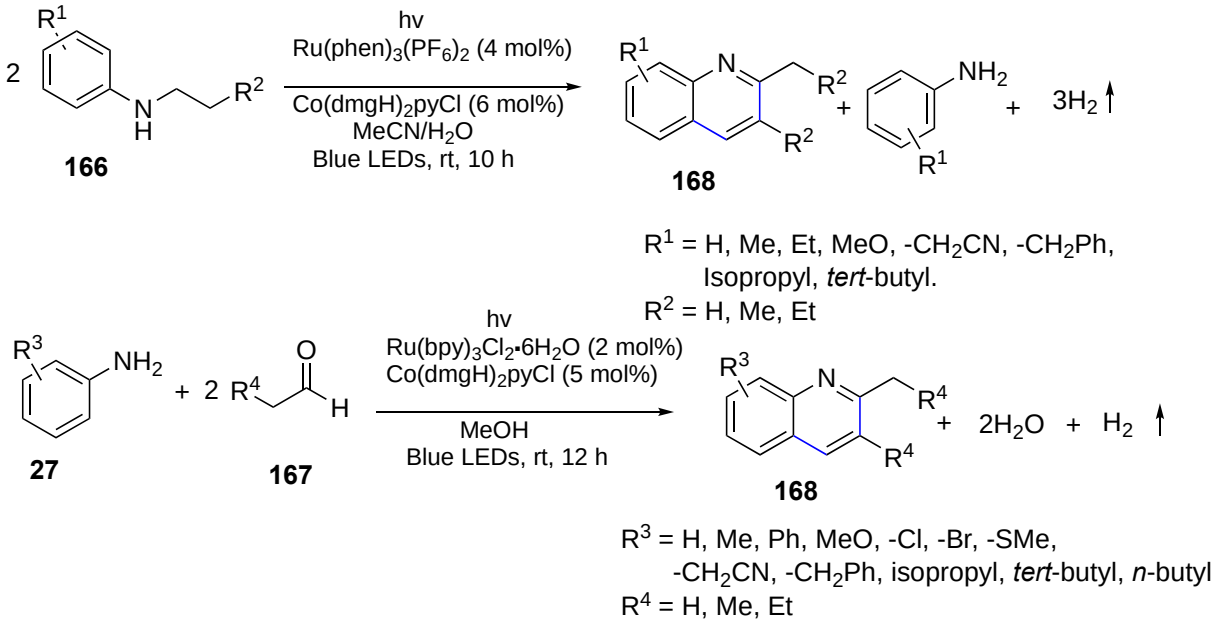
Xiong and group contributed the enantio- and diastereoselective synthetic route of chiral tetrahydroquinolines **163**, **164** using organocatalyst such as chiral secondary amine catalyst (Scheme 56). Being the first asymmetric Povarov reaction the whole route has been produced through cyclization between anilines **27** and aliphatic as well as aromatic aldehydes **162**.[80]




**Scheme 56.** Organocatalyzed synthesis of chiral tetrahydroquinolines **163** by Xiong *et al*.

Numerous biologically active molecules contain the quinoline scaffold, which has a wide range of applications. One method used to prepare the quinoline nucleus is the Povarov reaction, which is preceded by oxidation. Su and colleagues have created a dual-catalyst system made up of a proton reduction co-catalyst and a photocatalyst for the Povarov reaction, followed by oxidation, to produce quinolines **168** from anilines **27** and aldehydes **167** or from *N*-alkylanilines **166**. While the latter catalyst produces $H_2$ by reducing the protons removed from the substrates by capturing electrons from the reaction intermediates and substrates, the former catalyst assists in the transformation by utilizing light energy as the means of propulsion. The yield of the products from the *ortho*-substituted *N*-alkylanilines was

relatively lower. The *para*-substituted *N*-alkylanilines produced majority of quinolines in good to outstanding yields (Scheme 57).[81]




**Scheme 57.** Tetrahydroquinolines synthesis by utilizing *N*-alkylanilines **166** and anilines **27** and aldehydes **167**

## 4. CONCLUSION

In conclusion, quinoline and its derivatives take part in major development of medicinal chemistry and organic synthesis. Preparation of these derivatives has been performed by using various transition metal-free and transition metal-catalyzed reactions, microwave assisted synthetic transformations, different pericyclic reactions, and multicomponent one pot synthesis. Many of these methods are greener in nature like eco-friendly, atom-economic, metal-free, solvent-free and involving aqueous medium. The quinoline derivatives are crucial in developing many drug candidates to show antiviral, antibacterial, antifungal, anti-cancer activities. This review has highlighted numerous methods for the preparation of these scaffolds using Povarov reaction.

## 5. ACKNOWLEDGEMENTS

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