# Recent Advances in the Friedländer Reaction

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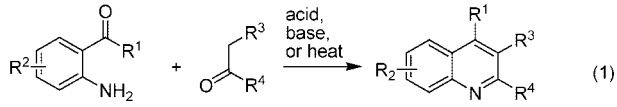
## *Contents*



## *1. Introduction*

The quinoline ring system[1−5] is present in a number of natural[6] and synthetic products often endowed with interesting pharmacological or physical properties.[7,8] Consequently, a number of methods for the synthesis of quinolines have been reported. Among them, the Friedländer reaction is still one of the simplest methods. In its most general and classical form, the Friedländer reaction is the base- or acid-promoted condensation of an aromatic 2-amino-substituted carbonyl compound (aldehyde, ketone, or an equivalent thereof) with an appropriately substituted carbonyl derivative containing a reactive α-methylene group followed by cyclodehydration (eq 1). Friedländer annulations are generally carried out either by refluxing an aqueous or alcoholic solution of the reactants in the presence of a base (eq 2) or acid or by heating a mixture of the reactants at 150−220 °C in the absence of a catalyst.[9]

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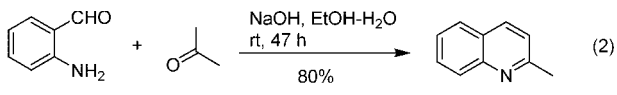


(2)

Since the publication of the chapter dedicated to the Friedländer[10] synthesis of quinolines in volume 28 of *Organic Reactions*,[10b] treatments of this reaction have been included in two books[11,12] and in a series of specialized volumes in the areas of organic chemistry[13] and heterocyclic chemistry.[1,14−20] Some accounts and detailed papers focusing on Friedländer synthetic methodology for the synthesis of organized polyaza cavities have been published by Stille,[16a] Thummel,[17a,b] Jenekhe,[18] and others.[19] The purpose of this review is to

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**Maria do Carmo Carreiras** received her degree in Pharmacy from University of Lisbon in 1977, her Master Sci. in Chemistry from University Nova of Lisbon in 1987, and her Ph.D. in Pharmaceutical Chemistry from University of Lisbon in 1989. In 1985, she was a fellow at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France, working under the direction of Prof. H.-P. Husson. From 1986 to 1988, she was a Ph.D. student at Instituto de Química Orgánica General (IQOG) of Madrid. In 2006, she was appointed Associate Professor at Faculty of Pharmacy, University of Lisbon. Her present research interests include the rational design of dual cholinesterase/monoamine oxidase inhibitors targeted for Alzheimer's disease.

update and review the Friedländer reaction, retrieving the most significant literature from 1981 to 2009, with particular emphasis on the recent developments, new catalysts, and experimental conditions, as well as outlining extensive applications in the synthesis of natural products.

Related quinoline[20] syntheses, such as the Pfitzinger reaction[21] and the Niementowski reaction,[22,23] are extensions of the Friedländer synthesis, differing in the starting materials; they will be discussed in more detail in section 5.

## 2. Mechanism and Regioselectivity

Although the features of the Friedländer reaction are generally well understood, its mechanism has not been

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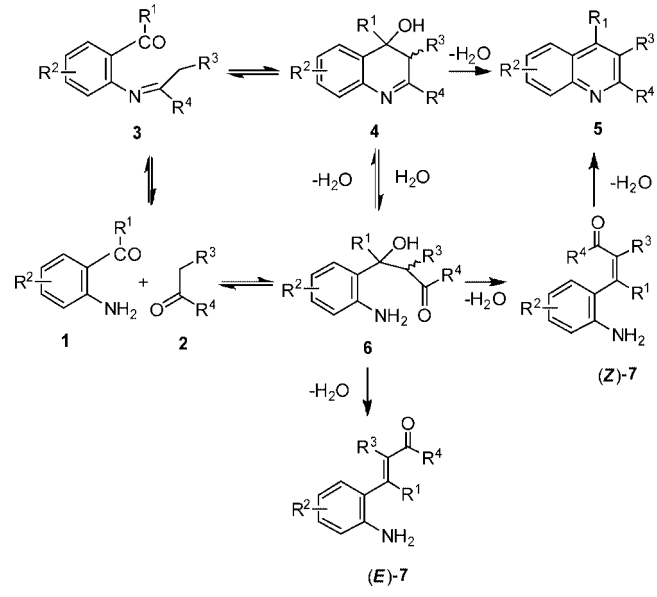
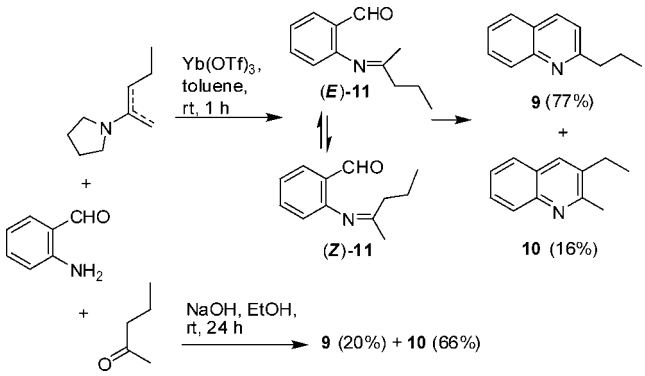
unambiguously established.[24] Experimental reports support two different mechanistic proposals.[10,21] Starting from 2-amino-substituted aromatic carbonyl compound **1** and the carbonyl partner **2**, one pathway involves the initial formation of the Schiff base **3** followed by an intramolecular aldol reaction to give the hydroxy imine **4** followed by loss of water to produce the quinoline **5** (Scheme 1). Alternatively, it has been proposed that the initial rate-limiting step is an intermolecular aldol reaction to afford product **6**, which gives the quinoline via the same intermediate **4** (Scheme 1).

Although mechanistic support for the intermolecular aldol reaction hypothesis exists,[25] most of the evidence favored the first mechanistic pathway, where the Friedländer synthesis involved an intermediate Schiff base.[26−28] However, a recent study[9a] has concluded that under the typically used acidic [$H_2SO_4$, HCl, *p*-TsOH[9d]] or basic (NaOH)[9b,c] conditions, the intermolecular aldol reaction is the first step in the Friedländer reaction of 2-amino benzaldehydes and aldehydes (or between 2-amino aryl ketones and ketones). The aldol

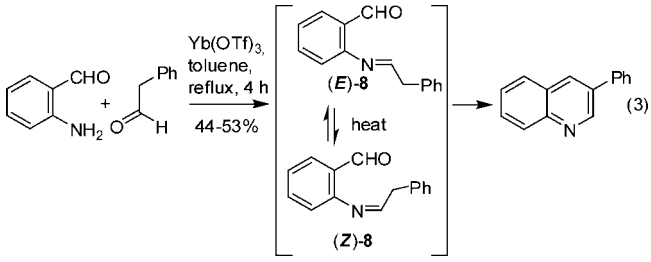
**Scheme 1. Mechanism of the Friedländer Reaction**



**Scheme 2. Friedländer Reaction of 2-Amino Benzaldehyde with 2-Pentanone**



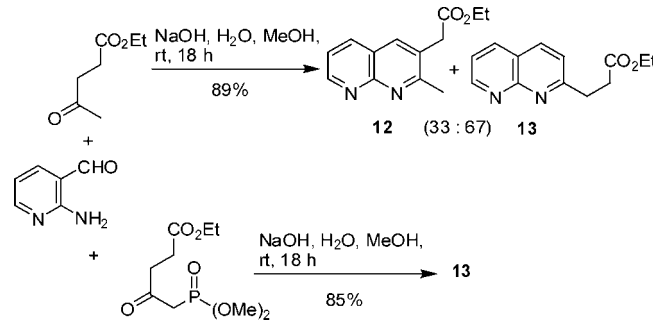

product **6** generated in this manner then undergoes cyclization to render intermediate **4**, which after elimination of water affords quinoline **5** (Scheme 1). To support this hypothesis, enones (*E*)-**7**, the water-elimination products from aldols **6**, have been converted into quinolines **5** under basic or acidic conditions, at high temperature; under these conditions, the favored *E*-Schiff base can isomerize to the *Z*-Schiff base, which is then converted into the quinoline by cyclization (Scheme 1).[9a] When Schiff bases are deliberately prepared from aldehydes, the most stable (*E*)-**8** Schiff base affords non-Friedländer products. For example, $Yb(OTf)_3$-mediated reaction of 2-amino benzaldehyde with phenyl acetaldehyde at room temperature in toluene gives an (*E*)-**8** Schiff base from which tetrahydroisoquinoline derivatives are produced exclusively, but at high temperature, the (*E*)-**8** Schiff base isomerizes to the (*Z*)-**8** isomer from which the 3-phenyl quinoline is formed in good yield (eq 3).



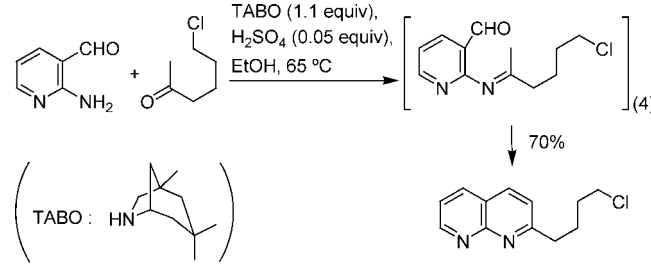

Also, $Yb(OTf)_3$-catalyzed reaction of 2-amino benzaldehyde with the pyrrolidine enamine of 2-pentanone gives a mixture of the 2-*n*-propyl quinoline (**9**) and 3-ethyl-2-methyl quinoline (**10**) in 77% and 16% yields, respectively (Scheme 2).[9a] This result is the opposite of that observed under the usual NaOH-catalyzed Friedländer reaction of 2-amino benzaldehyde with 2-pentanone where the 3-ethyl-2-methyl quinoline (**10**) is the major product (66% yield) (Scheme 2).[9a] The unusual observed regioselectivity in the enamine-promoted Friedländer reaction must be ascribed to the rapid generation of Schiff bases (*Z*)- and (*E*)-**11** in which the (*E*)-**11** isomer is highly predominant (Scheme 2).

As shown, the mechanistic issues, the catalysts, and the experimental conditions are closely associated with the regiochemistry of the Friedländer reaction. With regard to the ketone component, there are a number of examples of symmetrical ketones or ketones with additional activating functional groups alpha to the carbonyl moiety, where no problems or regioselectivity arise. This fact contrasts with the dearth of examples with unsymmetrical ketones such as 2-alkanones; presumably, this is due the lack of regiochemical control in the formation of major 2,3-disubstituted versus 2-monosubstituted products. For example, the standard hydroxide-catalyzed Friedländer reaction of 2-amino nicotinaldehyde provides 2,3-disubstituted and 2-monosubstituted 1,8-naphthyridines in a 2:1 ratio, but a highly regioselective Friedländer reaction results by introduction of a phosphonate group at one of the α-carbons of the ketone (Scheme 3).[29,30]

**Scheme 3. Friedländer Reaction of 2-Amino Nicotinaldehyde with Ethyl 4-Oxo-pentanoate**




In this context, a general and useful solution to the problem of the regioselectivity in the Friedländer reaction has been achieved by using pyrrolidine derivatives as catalysts. High yields and almost exclusive 2-susbtituted products are obtained when the methyl alkyl ketone is added slowly to an ethanolic solution of the 2-amino aryl aldehyde and TABO {1,3,3-trimethyl-6-azabicyclo[3.2.1]octane}, in the presence of catalytic amounts of sulfuric acid (eq 4).[31] This result has been explained by the fast transamination reaction of 2-amino nicotinaldehyde and the intermediate enamine formed between 6-chloro-2-hexanone and TABO, which leads to the rapid formation and cyclization of the corresponding Schiff base (eq 4).[9a]




In summary, the Friedländer reaction is a complex series of events, where competing mechanistic pathways are likely to be occurring depending on both structures of reactants and reaction conditions.[9] Enolates or enol forms of the ketone could be invoked for any reaction employing acids and bases. On the other hand, enamines could be implicated if one proposes that the amino aldehyde forms an enamine with the ketone component, or in reactions in which an external amine is added as a catalyst.

## 3. Scope and Limitations

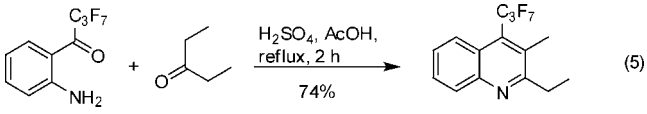
The particular value of the Friedländer reaction is largely due to the broad range of functional group compatibility. Regarding the 2-amino carbonyl component, a wide range of functional groups is tolerated on the aromatic ring system. With respect to the ketone partner, a number of different types have been employed including symmetrical ketones and ketones with additional activating groups alpha to the carbonyl function. However, the Friedländer reaction is not

without its limitations. This is the case with unsymmetrical ketones where the regioselectivity in the formation of 2,3-disubstituted versus 2-monosubstituted products is a major concern. Only $\beta$-ketoesters and 1,3-diketones undergo the Friedländer reaction regioselectively to provide 2,3-disubstituted compounds and their derivatives in excellent yields.[32] In the following subsections we demonstrate in detail particular aspects of the reactivity of both components in the Friedländer synthesis of quinolines, 1,8-naphthyridines,[33−35] and related heterocycles.

## 3.1. The 2-Amino Carbonyl Component

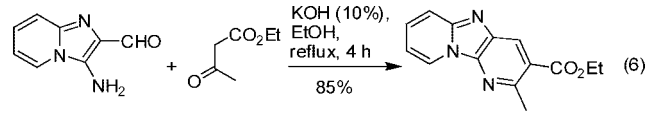
The only limitation with respect to the functional groups attached to the aromatic ring of the 2-amino carbonyl component of the Friedländer reaction is their stability to the basic or acidic conditions used to promote the process. In agreement with this, $R^2$ can be hydrogen, alkyl, aryl, *O*-alkyl, etc. (eq 1). The majority of 2-amino-substituted carbonyl compounds used in the Friedländer reaction are 2-amino benzaldehyde, 2-amino acetophenone, or 2-amino benzophenone, and their derivatives. Both electron-rich[36] and electron-poor[37] 2-amino benzocarbonyl compounds undergo the Friedländer reaction.

2-Substituted and 2,3-disubstituted 4-(perfluoroalkyl)quinolines can be prepared in high yields by Friedländer reaction of 2-(perfluoroacyl)anilines[38] with enolizable ketones or 1,3-diketones using acetic acid in the presence of a catalytic amount of sulfuric acid (eq 5).[39] Analogously, the acid-catalyzed condensation of 2-perfluoroacylaniline acetals with enolizable ketones gives 4-(perfluoroalkyl)quinolines.[40]



(5)

Heterocyclic ring systems containing the 2-amino carboxaldehyde moiety, such as 3-amino-2-formylimidazo[1,2-*a*]pyridine,[41a] are also common partners in the Friedländer reaction (eq 6). Similarly, 2-amino thiophenecarboxaldehyde reacts with 2-amino-1-methyl-imidazolin-4-one (creatinine) using BSA [bis(trimethylsilyl)acetamide] as solvent (eq 7).[42]



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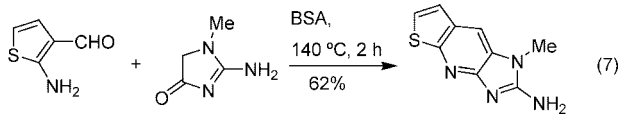
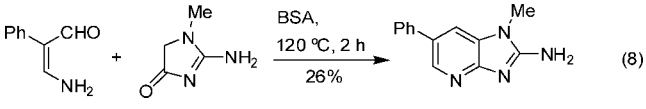


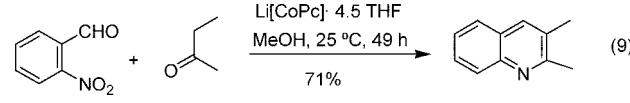
(7)

3-Amino acrolein (3AA) has been used as the 2-amino carbonyl partner in Friedländer-type reactions with some cyclic ketones.[17] 3AA can be obtained by partial hydrogenation of isoxazole, but it is a poor starting material due to its propensity for self-condensation; consequently, condensations with 3AA typically proceed in low yield.[43] In eq 8, we show the preparation of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine from 3-amino-2-phenylpropenal and creatinine.[44]



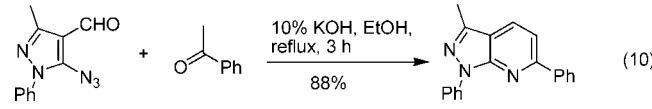
(8)

The classical Friedländer reaction has been extended and applied to 2-nitro-substituted aromatic carbonyl derivatives. This synthesis is usually carried out via a two-step procedure. After the aldol-like condensation with the active methylene component, the reduction of the nitro group to the amine produces in situ the reactive intermediate that cyclizes to give the quinoline, avoiding the usual preparation and isolation of the potentially unstable 2-amino aromatic carbonyl component, which can readily undergo self-condensation reactions.[45−50] This strategy has been used in the synthesis of 2-amino-1-methylimidazo[4,5-*b*]quinoline from 2-nitro benzaldehyde and creatinine, starting with aldol-like reaction under Perkin conditions (AcOH, AcONa, $Ac_2O$), followed by $H_2$−Ni Raney for the reduction step and cyclization.[51] A more expeditious and efficient one-pot analogue of this Friedländer synthesis has been described, in which the intermediate 2-amino benzaldehyde derivative is not isolated, but rather immediately converted in situ to a quinoline.[52−54] The use of Li[$Co^{I}$Pc] [lithium phthalocyaninecobalt(I)], under weakly basic conditions, in protic solvents (alcohols) has been reported for the reduction step, with the Friedländer reaction proceeding cleanly and selectively under conditions compatible with other functional groups such as halogens, double bonds, nitriles, carboxylic acid esters, and amides.[52] The high yields of the products are notable. In the example shown, the regioselectivity was excellent as no 2-ethyl quinoline was detected (eq 9).[52] More recently, the Friedländer reaction using a mixture of $SnCl_2$ and $ZnCl_2$ (1:1) has been reported to provide a large array of quinolines in a two-step reduction−condensation sequence from easily available 2-nitro benzaldehydes.[53] This protocol works under mild reaction conditions and is efficient and high-yielding, but no ratio of isomeric quinolines is provided for the Friedländer condensation with unsymmetrical ketones. Finally, a one-pot procedure for the Friedländer synthesis of quinolines has been implemented using ethyl formate and palladium on carbon in NCW (near-critical water).[54]



(9)

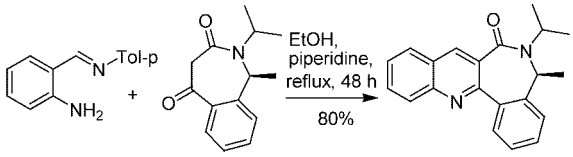
A convenient one-pot route for the preparation of pyrazolo[3,4-*b*]pyridines has been developed by the reaction of 5-azido-1-phenylpyrazole-4-carboxaldehyde with ketones in ethanolic potassium hydroxide at reflux. The formation of pyrazolo[3,4-*b*]pyridine derivatives can be rationalized to proceed via diazo-transfer reaction from 5-azidopyrazole-4-carboxaldehyde to ketones, and subsequent Friedländer reaction of the resulting 5-amino-1-phenylpyrazole-4-carboxaldehyde with ketones (eq 10).[55] Very interestingly, the reaction products obtained in the reaction with acetyl acetone (or benzoyl acetone) are the same as those from reaction with acetone (or acetophenone) (eq 10), which implies that the decomposition of the active methylene component takes place before the Friedländer reaction.[55]



(10)

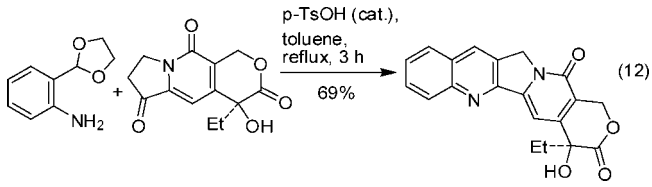
The classical Friedländer reaction conditions make use of a 2-amino benzaldehyde. Problems with self-condensation, which may limit the scope and generality of the reaction,

have found a solution in the Borsche modification,[56,57] which uses the corresponding *N*-(2-aminobenzylidene)-*p*-toluidine as, for instance, in the synthesis of 1*H*-2-isopropyl-1-methyl-2-benzazepino[5,4-*b*]quinolin-3-one (eq 11).[58]



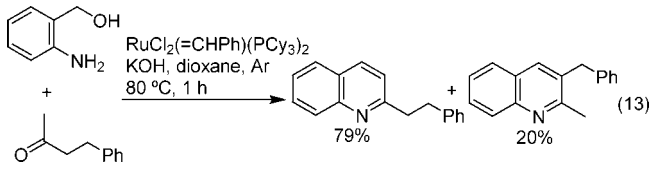
(11)

Condensations of 2-amino benzaldehyde acetal derivatives with different carbonyl compounds have been described.[59,60] Under the experimental conditions (AcOH, or using toluene as solvent, in the presence of p-TsOH), not only does the deprotection of the 2-amino benzaldehyde take place in situ, but the Friedländer reaction is catalyzed in a one-pot reaction (eq 12).[61]



(12)

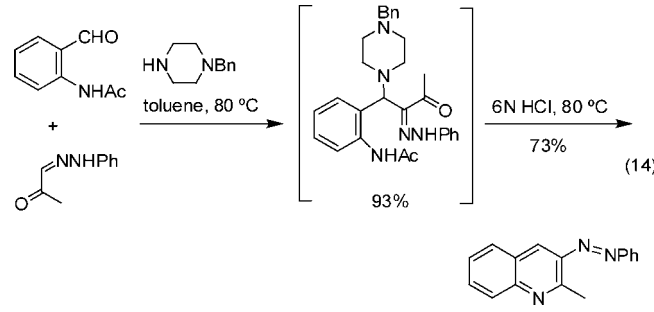
A modified Friedländer quinoline synthesis proceeds in the presence of KOH and iridium(III),[62] ruthenium,[63,64] rhodium,[65] palladium on charcoal,[66] or copper(II)[67] catalyst via consecutive oxidation of 2-amino benzyl alcohol to the corresponding 2-amino benzaldehyde, followed by coupling with the ketones added to the reaction medium or obtained in situ by oxidation of the corresponding alcohol under the same experimental conditions[68,69] and cyclization. Note that two examples of aliphatic ketones are reported to yield the 2-substituted quinolines in excess of the 2,3-disubstituted quinolines (ratios ranged from 70:30 to 80:20) (eq 13).[70]



(13)

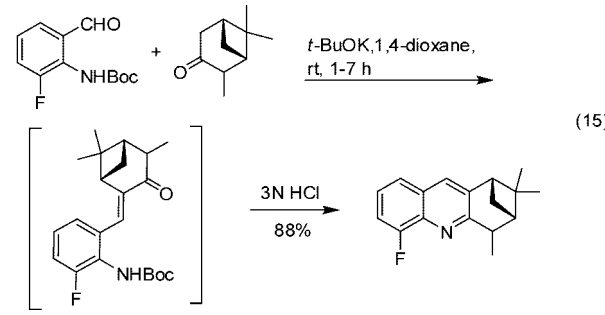
A new azo-Friedländer reaction is based on the reaction of 2-acetamido benzaldehyde with α-ketohydrazones in the presence of *N*-benzyl piperazine. Under these conditions, the expected Mannich adducts are obtained in good to high yields. Deprotection of the *N*-acetyl group was easily carried out in hot aqueous hydrochloric acid solutions. Under these conditions, deprotection, cyclization, and elimination of the *N*-benzyl piperazine took place in a single step giving the 2,3-disubstituted quinoline (eq 14).[71] *N*-Acetylated 2-amino benzaldehydes have been combined with amides to give 2-amino-3-hydroxy quinoline derivatives in moderate yields.[72]

The base-catalyzed intramolecular condensation of 2-acetamido aceto or benzophenones is known as the Camps quinoline synthesis.[73] As one might expect, most of the reported cases of Camps quinoline synthesis involve reactions in which only one of the carbonyl groups is enolizable, affording quinolin-2-ols or quinolin-4-ols, thus eliminating the regioselectivity problem.[74]



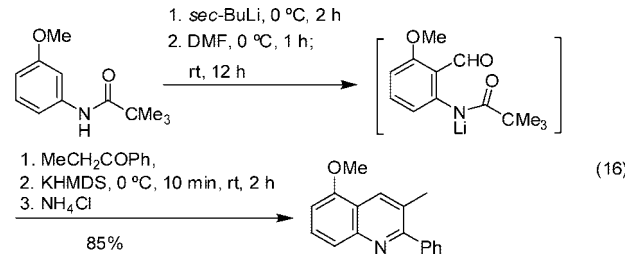
(14)

An alternative method, which also avoids the isolation of the 2-amino benzaldehyde, has been developed based on the direct acid-promoted annulation and aromatization of the intermediate product obtained by condensation of an enolizable carbonyl compound with an *N*-Boc-2-amino benzaldehyde (eq 15).[75,76]



(15)

An attractive new method applied with success to the preparation of naphthyridines[77] and 2,3,5-trisubstituted quinolines involves lithiation of *N*-pivaloylanilines with *s*-BuLi, formylation with DMF, and subsequent condensation with active methylene groups of aldehydes or ketones (eq 16).[78] The formation of the quinoline derivative implies the generation of an aldol product from the lithium amide salt and the α-methylene reactive compound, followed by subsequent cyclization.[79a] Similarly, quinolines substituted on both pyridine and benzo-fused rings have been synthesized by formylation of substituted *N*-Boc anilines followed by direct cyclization and aromatization of the intermediate product obtained by condensation of the formed *N*-Boc 2-amino benzaldehyde with an enolizable carbonyl compound.[80]



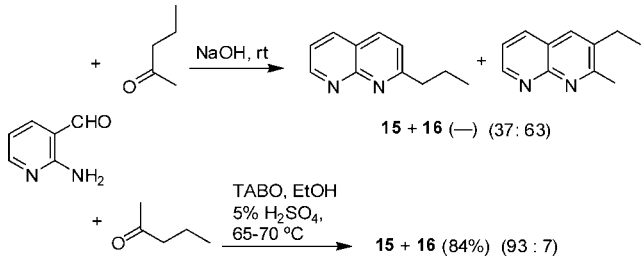
(16)

## 3.2. The Active Methylene Component

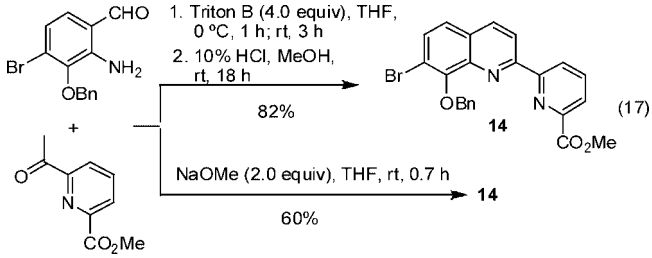
In the carbonyl derivative containing a reactive α-methylene group, $R^3$ (eq 1) may be hydrogen, alkyl, aryl, alkoxy, or amino, and $R^4$ may be hydrogen, alkyl, nitro, acyl, carboxy, carbalkoxy, carboxamide, cyano, hydroxyl, sulfonyl, or related functions.

The Friedländer reaction of 2-amino-3-(benzyloxy)-4-bromo benzaldehyde with methyl 2-acetylpyridine-6-carboxylate provided 8-(benzyloxy)-7-bromo-2-(2′-pyridyl)quin-

**Scheme 4. Friedländer Reaction of 2-Amino Nicotinaldehyde with 2-Pentanone**

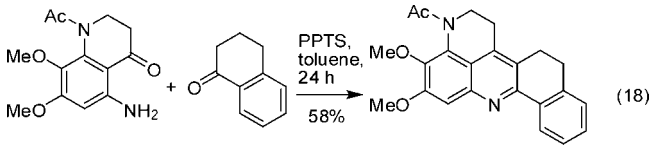



oline-6′-carboxylic acid, which was converted to the corresponding methyl ester **14** by standard manipulation (eq 17).[81] Alternatively, it was found that the sodium methoxide catalyzed reaction gave the same compound **14** in only one step, in moderate yield.[81]




(17)

An efficient synthesis of compounds containing the benzo[*c*]pyrido[2,3,4-*kl*]acridine skeleton has been described using the Friedländer quinoline synthesis between 5-amino-7,8-dimethoxy-2,3-dihydro-1*H*-quinolin-4-one derivatives and α-tetralone as the key step, in the presence of PPTS (pyridinium *p*-toluenesulfonate) (eq 18).[82]



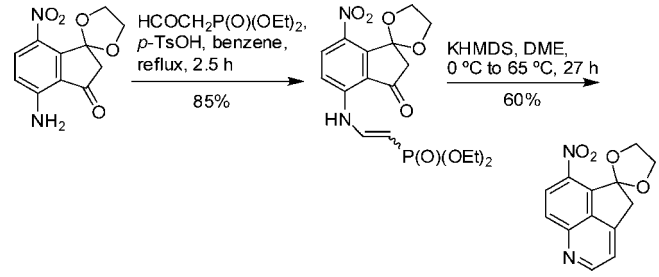

(18)

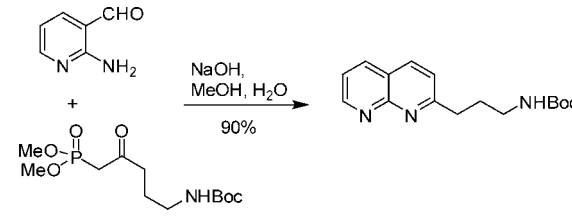
The use of α-ketohydrazones, which are essentially azo-substituted ketones, has been already discussed in the context of an azo-Friedländer reaction based on the reaction with 2-acetamido benzaldehyde derivatives (eq 14).[71]

A major limitation of the Friedländer reaction is the lack of regioselectivity when using unsymmetrical ketones. For example, it has been observed that the usual base-catalyzed Friedländer reaction conditions employing 2-amino nicotinaldehyde and 2-alkanones, such as 2-pentanone, give roughly a 1:2 mixture of 2-monosubstituted 1,8-naphthyridines (**15**) to 2,3-disubstituted ones (**16**) (Scheme 4).[31] A more direct and efficient general solution is based on the application of novel amine catalysts, such as TABO, in the presence of sulfuric acid (0.05 equiv) in ethanol at 65−70 °C, affording 2-substituted products (**15**) with regioselectivities ranging from ≥90:10 for 1,8-naphthyridines (Scheme 4) to ≥84:16 for quinolines with the yields of the isolated single regioisomers being high (65−84%).[31]

One solution to this long-standing problem is the use of methyl ketone surrogates that are activated toward regioselective attack at the terminal position.[29] This is based on increasing the p$K_a$ of the α or α′ protons of the ketone partner by introducing, for example, a phosphonate group at one of the α-positions of the ketone. The use of such a Horner−Emmons type of reagent allows a complete control of the regioselectivity during the Friedländer reaction, as shown in the example (eq 19).[29b] In a similar approach, diethyl formylmethylphosphonate serves as an effective acetaldehyde synthon for the synthesis of a fused tricyclic quinoline (Scheme 5).[83]

**Scheme 5. Diethyl Formylmethylphosphonate As an Effective Acetaldehyde Synthon**

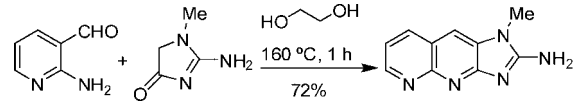



(19)

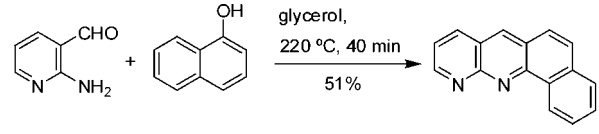
The regiochemistry of the Friedländer reaction depends on the experimental conditions. When $SnCl_2 \cdot 2H_2O$ is used as catalyst for the reaction of standard substrates with unsymmetrical ketones, such as 2-butanone, only the 2,3-dimethylquinoline derivative is isolated.[84] With ionic liquids, such as 1-butylimidazolium tetrafluoroborate {[Hbim][$BF_4$]}, the reaction proves very regioselective with unsymmetrical ketones; accordingly, the reaction of 2-amino acetophenone with ethyl methyl ketone or benzyl acetone gives only the 2,3-dialkyl quinoline in excellent isolated yields.[85] This is in contrast to the mixtures of regioisomers (2,3-dialkyl qinolines vs 2-alkyl quinolines) obtained using basic or acidic conditions.[86,87]

An unusual ketone such as 2-amino-1-methyl-imidazolin-4-one reacts with 2-aminonicotinaldehyde to give 2-amine-1-methylimidazo[4,5-*b*][1,8]naphthyridine in 72% yield (eq 20).[88a]

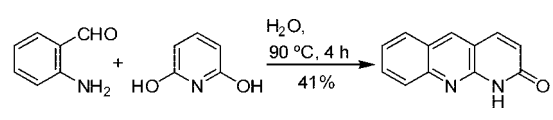



(20)

The phenol moiety in aromatic compounds such as 1-naphthol[89] (eq 21) and 2,6-dihydroxypyridine (eq 22)[90] has been used with success as a carbonyl surrogate in the synthesis of substituted [1,8]naphthyridines in a Friedländer reaction with appropriately functionalized 2-amino benzaldehydes.

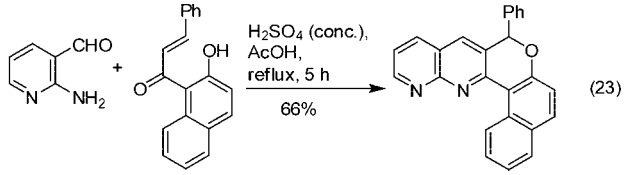



(21)



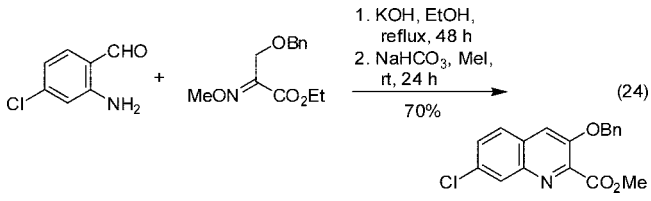

(22)

A related cascade condensation of 2-amino nicotinaldehyde with substituted 2-hydroxy-1-naphthyl styryl ketones, in the presence of acetic acid containing a catalytic amount of concentrated sulfuric acid gives the corresponding 8-aryl-8*H*-naphtho[1′,2′:5,6]pyrano[4,3-*b*][1,8]naphthyridines (eq 23).[91] This reaction may proceed via a typical Friedländer reaction mechanism, where the final intramolecular aldol reaction leading to the resulting product is preceded by an intramolecular Michael addition of the free phenol to the α,β-unsaturated ketone (eq 23).



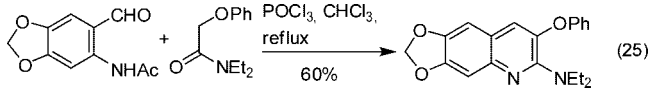
(23)

A modified Friedländer condensation for the synthesis of 3-hydroxyquinoline-2-carboxylates employs the readily accessible *O*-methyloximes, which are sufficiently reactive to condense selectively with 2-amino benzaldehydes, without undergoing self-condensation, on treatment with an ethanolic solution of potassium hydroxide at reflux (eq 24).[92a]



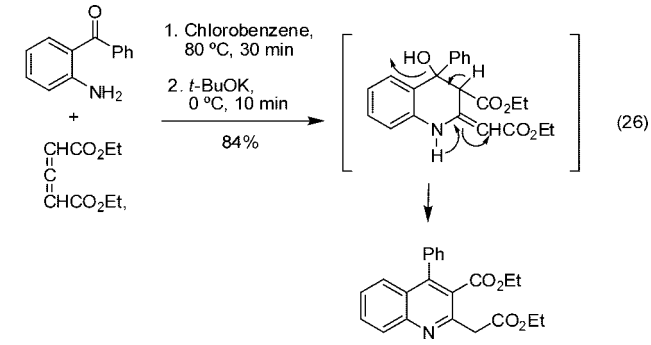
(24)

Esters or lactones[93] and amides[72] are not common carbonyl partners in Friedländer-type condensations. Amides have been combined with *N*-acetylated 2-amino benzaldehydes to give 2,3-disubstituted quinolines (eq 25).[72]



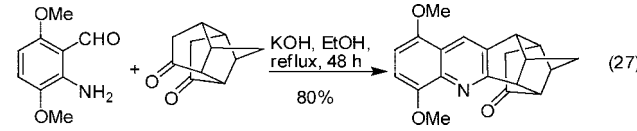
(25)

Diethyl 1,3-allenedicarboxylate has been used as the masked carbonyl partner in an interesting Friedländer-type synthesis of 2,3,4-trisubstituted quinolines (eq 26).[28] Thus, the Michael adducts obtained by addition of the 2-carbonyl-substituted aniline to the allene in chlorobenzene at 80 °C gives the corresponding quinolines in good yields when treated with *t*-BuOK at 0 °C.

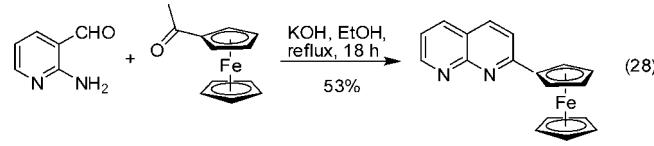


(26)

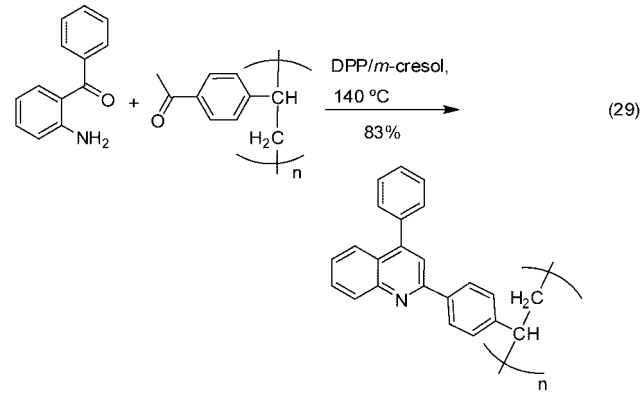
The strained 2,7-dioxotetracyclo[6.3.0.0$^{4,11}$.0$^{5,9}$]undecane[94] and diethyl 3,6-dioxopentacyclo[6.5.0.0$^{4,12}$.0$^{5,10}$.0$^{9,13}$]tridecane-2,7-dicarboxylate[95] have been condensed with 2-amino benzaldehyde,[96] 3-amino-2-naphthalenecarboxaldehyde,[97] 1-amino-2-naphthalenecarboxaldehyde, or 8-amino-7-quinolinecarboxaldehyde[98] and with 2,6-diaminopyridine-3-carboxaldehyde[99] or 3,6-dimethoxy-2-aminobenzaldehyde[100] in research projects directed at the synthesis of host−guest and self-assembling systems (eq 27). Acetyl and propionyl ferrocene react with various aromatic 2-amino aldehydes giving rise to azaaryl-substituted ferrocenes (eq 28).[101] Poly(4-acetylstyrene)[102] and related polymers have been subjected to Friedländer reaction conditions with 2-amino benzophenone (eq 29) to give the corresponding poly(vinyl,diphenylquinoline)s in good yield.



(27)



(28)



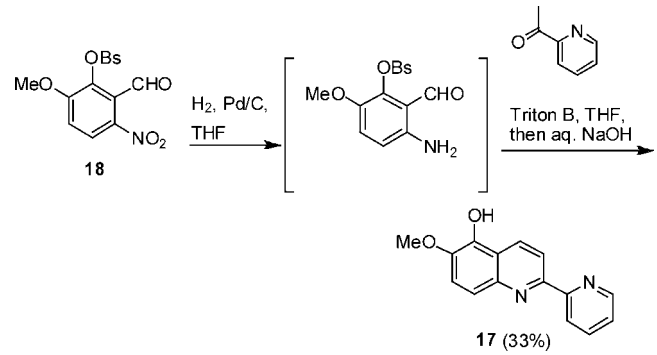
(29)

## 4. Applications to Synthesis

In this section, we highlight applications of the Friedländer reaction for the synthesis of the quinoline moiety embedded in the structures of a number of significant natural or non-natural products with important biological properties.[6]

In a study directed toward the synthesis of novel quinolinequinone antitumor agents related to streptonigrin,[103] the Friedländer reaction has been used to synthesize compound **17** from the 2-nitro benzaldehyde derivative **18**[104] (Scheme 6).

**Scheme 6. Preparation of Quinoline 17, an Intermediate in the Total Synthesis of Streptonigrin, via Friedländer Reaction**



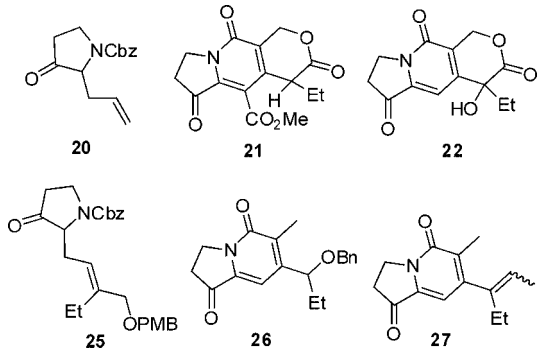
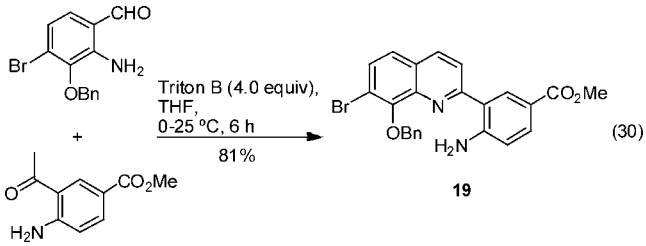


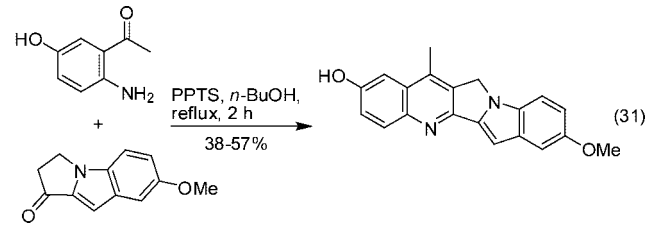

**Figure 1.** Key ketone intermediates in the total synthesis of camptothecin.

Compound **19** (eq 30) has been synthesized to define the role that several functional groups present in streptonigrin and lavendamycin play in the potentiation of the cytotoxic properties of the 7-aminoquinoline-5,8-dione ring system.[81] This compound is prepared by Friedländer reaction of 2-amino-3-(benzyloxy)-4-bromobenzaldehyde with methyl 3-acetyl-4-aminobenzoate.[81]




(30)

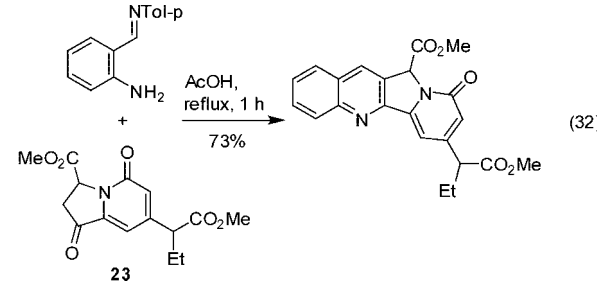
Cytotoxic agents with the benzo(5,6)pyrrolizino[1,2-*b*]quinoline skeleton have been synthesized by a Friedländer reaction between 2-acyl anilines and pyrroloindoles using optimized experimental conditions, namely, PPTS in 1-butanol (eq 31).[105]




(31)

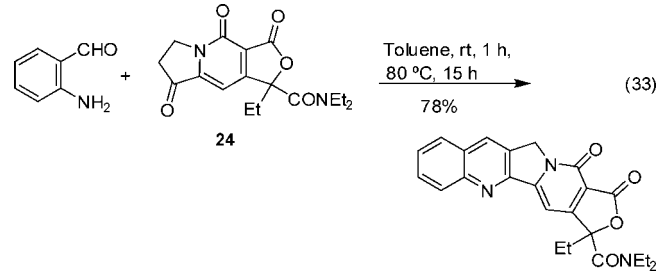
Camptothecin and derivatives, which are powerful antitumor agents,[106] also contain a quinoline ring. Many total syntheses have been published.[107,108] Not unexpectedly, from early efforts, the Friedländer reaction has been routinely used to prepare the quinoline moiety present in camptothecin.[109−114] The Borsche modification[56,57] of the Friedländer methodology, using *N*-(2-aminobenzylidene)-*p*-toluidine instead of the unstable 2-amino benzaldehyde (eq 11), has been used to prepare key intermediates for the synthesis of camptothecin and its analogues. In this strategy, several carbonyl derivatives were selected as appropriate partners for this reaction. Reported examples include (a) ketone **20** (Figure 1) and *p*-TsOH as catalyst in toluene (72%),[115] (b) tricyclic ketone **21** (Figure 1) and *p*-TsOH as catalyst in toluene (75%),[116] (c) pyridone **22** (Figure 1) and *p*-TsOH as catalyst in toluene (75%),[111,117,118a] and (d) ketone **23** (eq 32).[119a]

The Friedländer reaction of ketone **22** (Figure 1) with 2-amino-5-hydroxypropiophenone, followed by standard functionalization of the product, has been exploited in the synthesis of enantiomerically pure irinotecan.[113]




(32)

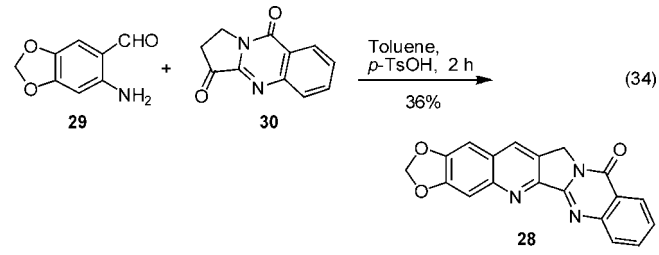
10-Methoxy, 11-hydroxy, 12-aza, benz(*j*), and 18-methoxy analogues of camptothecin[120] and 7-substituted camptothecin analogues[121a] have been synthesized using the Friedländer reaction. A classical Friedländer synthesis, under thermal conditions, with ketone **24** has been used for the synthesis of an advanced intermediate for a total synthesis of camptothecin (eq 33).[122]




(33)

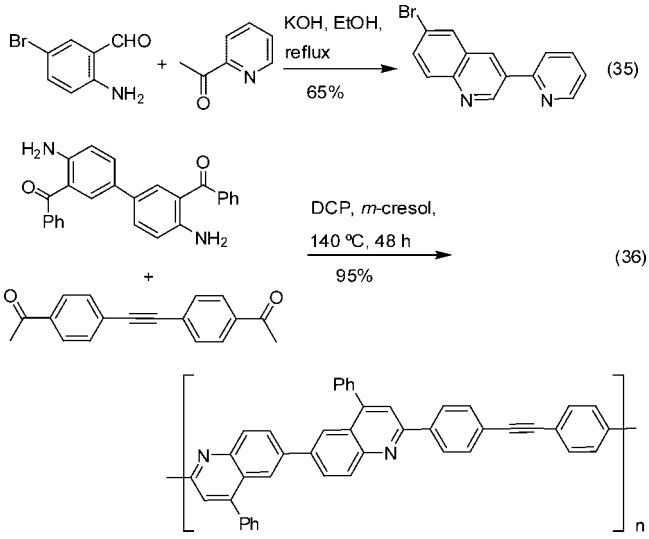
The Borsche modification[56,57] of the Friedländer reaction (eq 11) has been used also for the preparation of an intermediate in the total synthesis of nothapodytine B and mappicine, the carbonyl partner being ketone **25** (Figure 1).[123] The synthesis of mappicine and mappicine ketone (nothapodytine B) has been also achieved using a key precursor prepared by Friedländer reaction of *N*-Boc-2-amino benzaldehyde and 2,3-dihydro-6-methyl-7-[1-(phenylmethoxy)-propyl]-1,5-indolizinedione (**26**) (Figure 1) in 80% acetic acid at reflux.[124] Similarly, 2-amino benzaldehyde has been condensed (*p*-TsOH, toluene, reflux) with ketone **27** (Figure 1) in a synthesis of nothapodytine B.[125]

Substituted luotonin A derivatives like compound **28** have been synthesized in poor yields by the reaction of substituted 2-amino benzaldehyde **29** and ketone **30** (eq 34).[126,127a]

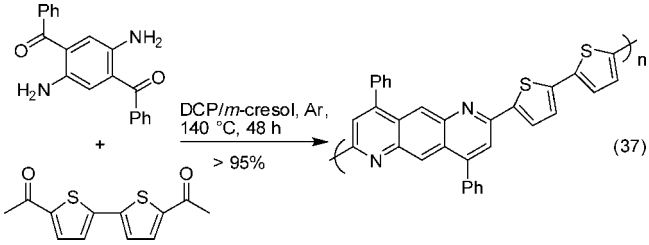



(34)

In the materials chemistry area, the Friedländer reaction has been used for the incorporation of the quinoline motif in a number of compounds of interest as monomers for the synthesis of carbazole−quinoline copolymers with intramolecular charge-transfer properties,[128] for the incorporation of 6-bromoquinolines into new chelating ligands (eq 35),[129] and for the synthesis of functionalized aromatic polyquinolines for electro-optic devices (eq 36).[130−134]



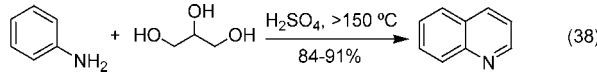

A number of polymers containing conjugated phenylated polyquinolines with interesting electronic and nonlinear optical properties have been synthesized from appropriate monomers using Friedländer reactions for the construction of the quinoline moiety.[135,136] For example, polyanthrazolines have been obtained using a mixture of DCP (di-*m*-cresyl phosphate) or DPP (diphenyl phosphate) and *m*-cresol as the reaction medium (eq 37).[137]



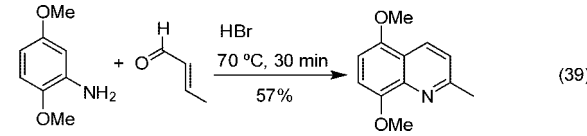

## 5. Comparison to Other Methods

In this section, we illustrate the synthesis of quinolines starting with anilines lacking a 2-C- susbtituent, followed by non-Friedländer quinoline synthesis which uses 2-substituted anilines.

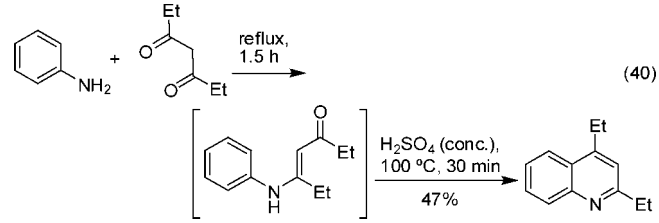
The first group of strategies includes quinoline[20] syntheses such as the Skraup,[138,139] Doebner−Miller reactions,[140] and the Combes method.[141,142] In these protocols, anilines lacking a 2-C-substituent react with substituted three-carbon fragments. For 3- or 3,4-substituted anilines, the problem of regioselectivity arises, an issue where the Friedländer reaction seems superior.

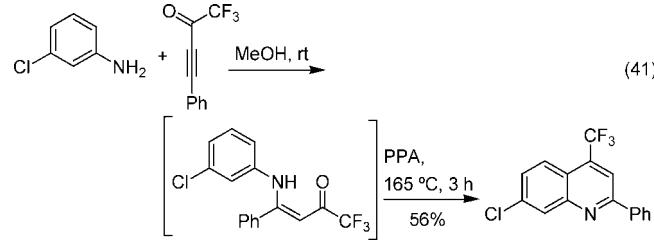



Skraup discovered that heating aniline and glycerol in the presence of sulfuric acid afforded quinoline (eq 38).[138] Doebner and von Miller found that the Skraup's method could be generalized by substituting 1,2-glycols by α,β-unsaturated aldehydes (eq 39).[143] The classical and versatile Skraup synthesis of quinolines[139] suffers from serious limitations that include the harsh experimental conditions (large amounts of sulfuric acid at temperatures above 150 °C make the reaction often violent) and that 3- and 3,4-substituted anilines may give a mixture of regioisomers, which are difficult to separate. A significant improvement in yield is achieved[144,145] by carrying out the Skraup reactions on the surface of silica gel impregnated with indium(III) chloride under microwave irradiation. This modified Skraup reaction is fast, clean, and high yielding but do not take place with acrolein or other α,β-unsaturated aldehydes. The synthesis of 6- and 7-fluorinated quinaldines from the corresponding fluorinated anilines has been described using the traditional Skraup reaction.[146] This method has been applied to poorly nucleophilic trifluoromethyl-substituted anilines; their reactions with *trans*-2-hexen-1-al lead to 2-propyl(trifluoromethyl)quinolines in moderate yields.[147]




The Doebner−Miller reaction (eq 39)[140,141] is a simple and well−established protocol for the synthesis of quinolines, though the yields are not high and the isolation of the reaction products is usually tedious due to extensive acid-catalyzed polymerization of the starting α,β-unsaturated aldehydes. It has been found that running the reaction in a two-phase solvent system decreases this polymerization, improves the yields of the reaction, and simplifies the ease of isolation of the quinolines.[148] In this context, it is interesting to note that a number of quinolines have been synthesized from substituted benzylideneanilines and enolizable ketones in the presence of HCl−DMSO under aerobic conditions.[149a]



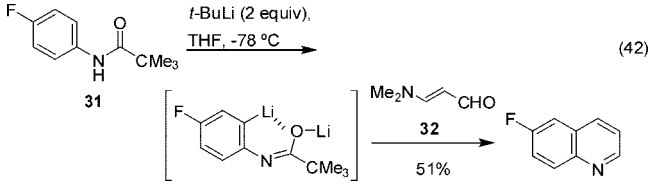




The Combes reaction involves two steps: (a) condensation of an aryl amine with a 1,3-diketone (keto-aldehyde or dialdehyde) to give an intermediate enamine and (b) cyclodehydration to provide a quinoline (eq 40).[141,142] The Combes methodology has been applied to the synthesis of 2- and 4-trifluoromethyl-substituted quinolines using β-enamino ketones obtained by the reaction of anilines with 3-trifluoromethanesulfonyloxy-3-trifluoromethylpropeniminium triflate,[150] by 1,2- or 1,4-addition of anilines to trifluoroacetyl acetylenes,[147,151] or by condensation of aniline with fluorinated ethyl alkynyl-2-carboxylates to give mixtures of the enamino and imino derivatives, which easily cyclize to the corresponding fluorinated quinolines at 170 °C in the presence of PPA (poly(phosphoric acid)).[152] The main advantage of the Friedländer approach is that the $CF_3$ group ultimately is derived from trifluoroacetic acid (eq 41) rather than expensive $CF_3$-substituted aniline (see eq 60 or Scheme

8). Other known approaches, including the Skraup and the Doebner−Miller reactions, also provide a rapid access to fluorinated quinolines, but these methods generally suffer from low regioselectivity if the aniline bears a substituent meta to the ortho positions available for annulation.

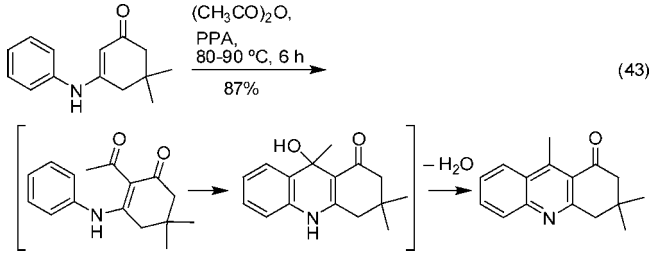
The mechanism of the Skraup−Doebner−von Miller quinoline synthesis has been recently studied by the use of $^{13}C$-labeled ketones in cross-over experiments.[153] On the basis of these experiments a mechanistic pathway for the Skraup reaction is proposed that involves a fragmentation−recombination mechanism. The aniline condenses with the α,β-unsaturated ketone in a Michael-type reaction followed by a fragmentation to the corresponding imine and the ketone itself; then, these fragments recombine to form the quinoline.[153]

A new quinoline synthesis, based on the condensation of *ortho*-lithiated *N*-*t*-Boc anilines or *N*-pivaloylanilines **31** with masked malonodialdehyde derivative **32**, has been reported (eq 42). This modification provides a new and flexible entry to quinolines but is restricted to the synthesis of 6-substituted quinolines.[154]



(42)

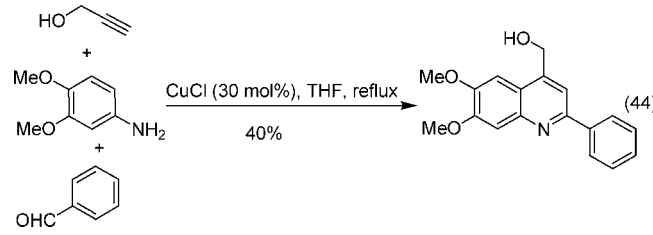
A modified Friedländer reaction starts from cyclic *N*-phenyl enaminones and anhydrides upon treatment with PPA at 60−90 °C for 2−6 h. Under these conditions, the intermediate α-acetylated enaminones undergo a Friedel−Crafts cyclization followed by dehydration affording the quinolines in good yields (eq 43).[155] Similarly, the synthesis of advanced intermediates in the total synthesis of analogues of ascidemin[156] is based on a new methodology[157] where the oxidative amination of a 2-amino acetophenone with quinoline-5,8-dione gives intermediate *N*-phenyl enaminones that smoothly cyclize to the corresponding pyridoacridines upon treatment with a mixture of sulfuric and acetic acids at reflux.



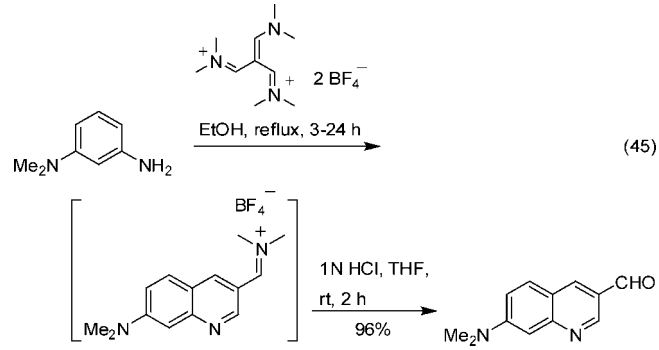
(43)

A novel and efficient approach for the synthesis of 2,4-disubstituted quinolines has been described based on the condensation of aldehydes, amines, and alkynes catalyzed by CuCl (eq 44).[158] This protocol has been improved by using montmorillonite clay impregnated with Cu(I) bromide under solvent free conditions, and microwave irradiation. The reaction is quick (proceeding in minutes), high yielding, and experimentally very simple. A large array of substituted quinolines can be prepared using this procedure.[159]

The synthesis of 3-formylquinolines has not been addressed using the Friedländer reaction. Fortunately, a simple procedure is available based on in the reaction of anilines with 2-dimethylaminomethylene-1,3-bis(dimethylimmonio-)propane bis-tetrafluoroborate (eq 45).[160]

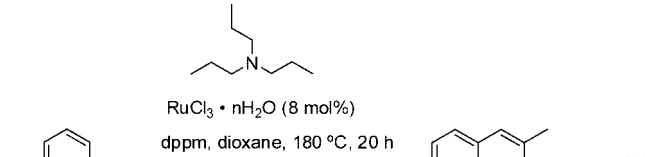


(44)

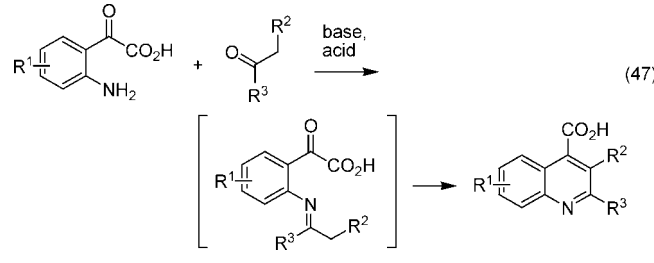


(45)

A regioselective synthesis of trifluoromethyl-substituted quinolines involves the use of Rh(I)-complex catalyzed coupling reaction of *N*-aryl trifluoroacetylimidoyl chlorides with alkynes to give 2-trifluoromethylated quinolines in good yields.[161] Similarly, a very sophisticated method for the synthesis of quinolines relies on the reaction of anilines with trialkylamines in the presence of a catalytic amount of $RuCl_3 \cdot nH_2O$ and dppm [bis(diphenylphosphino)methane] together with $SnCl_2 \cdot 2H_2O$ and 1-hexene as a hydrogen acceptor;[162,163] as shown, in the reaction of aniline with tri-*n*-propylamine, the reaction product 2-ethyl-3-methylquinoline is obtained in 63% isolated chemical yield (eq 46).[164] Although the details of the present reaction are not fully understood, the initial formation of imines by amine exchange reaction between anilines and trialkylamines seems to be the key step, followed by known Schiff-base dimerization and ruthenium-mediated heteroannulation. This protocol has been extended to the ruthenium and tin-catalyzed synthesis of 2,3,4-unsubstituted quinolines from primary aromatic amines and 3-aminopropanol.[165]



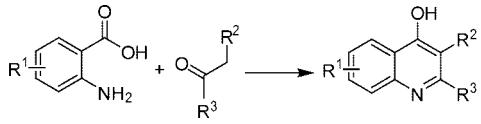
(46)



(47)

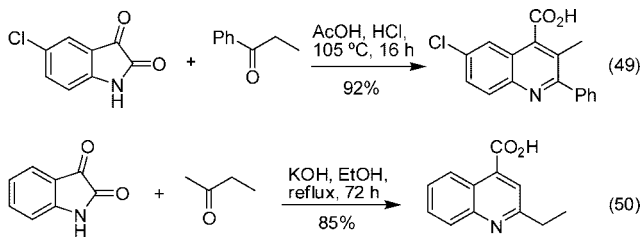
The Pfitzinger reaction (eq 47)[21,166] and the Niementowski reaction,[22,23] (eq 48) are extensions of the Friedländer synthesis, differing in the starting materials.

The Pfitzinger reaction entails the formation of quinoline-4-carboxylic acids from isatic acids and α-methylene car-



(48)

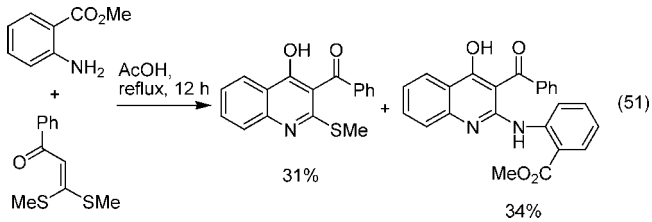
bonyl compounds. Isatic acids are obtained in situ from isatines in basic or acidic conditions (eq 47). Subsequent decarboxylation can afford the corresponding quinolines. For instance, the reaction of 5-chloroisatin and propiophenone in aqueous acid conditions provides a convenient method for the preparation of 3-methyl-2-phenylquinoline-4-carboxylic acids (eq 49).[167] The mechanism of the Pfitzinger reaction involves the initial formation of a Schiff base that evolves to the quinoline after intramolecular aldol reaction between the benzylic carbonyl and the activivated α-methylene of the imine (eq 47).[168] *n*-Alkyl methyl ketones yield primarily 2-monosubstituted cinchoninic acids (eq 50),[169] and aryloxyketones yield the corresponding 3-aryloxy-4-quinoline carboxylic acids.[170] Diversely substituted indanones[171a] and pyruvic acid[172] are also substrates in Pfitzinger protocols to give complex heterocyclic systems. Pfitzinger reaction has also been used for the synthesis of advanced intermediates en route to rigid analogues of camptothecin.[173]



(49)

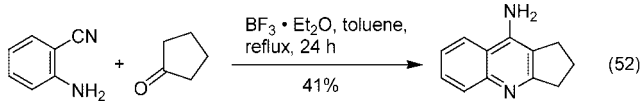
(50)

When $R^1$ (in eq 1) is a hydroxy group, this is the Niementowski reaction (eq 48).[22,23] As an example, the reactions of α-aroylketene dithioacetals with esters of 2-amino benzoic acid give preferentially 2-methylthioquinolones and 2-anilino-3-aroylquinolines through α-aroylketene *N*,*S*-acetal, and α-aroylketene aminal intermediates, respectively (eq 51).[174] A modified Niementowski quinoline synthesis starts from anthranilamides via imine formation and base-mediated intramolecular cyclization.[175]



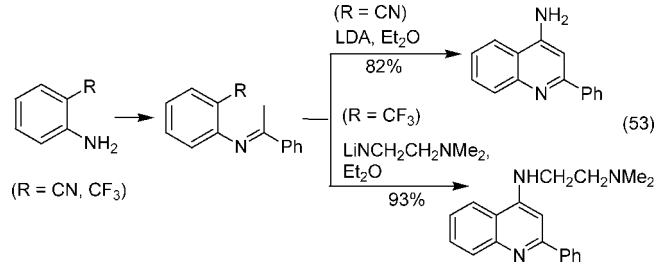
(51)

2-Amino nitriles such as anthranilonitrile (eq 52),[176] 3-amino-4-cyano-1-phenyl pyrazoles,[177] or ethyl esters of 6-amino-4-aryl-5-cyano-4*H*-pyran-3-carboxylic acids[178] give fused 4-aminoquinolines. Typical experimental conditions include mixing the 2-amino nitrile derivative with the selected ketone in zinc chloride in nitrobenzene at 120 °C,[179a,b] aluminum trichloride in 1,2-dichloroethane at reflux,[179b−o] boron trifluoride diethyl etherate in toluene at reflux,[176] or titanium tetrachloride in methylene chloride.[180]



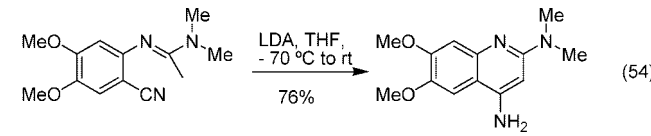
(52)

In an alternative approach, Schiff bases, obtained from 2-amino benzonitrile and aryl or heteroaryl methyl ketones, are deprotonated with LDA (lithium diisopropylamide) at the methyl group giving carbanions that undergo cyclization to give 4-aminoquinoline derivatives (eq 53).[181−183] In the case of 2-(trifluoromethyl)aniline, a different mechanism operates leading to the free 4-amine, the 4-(*N*-alkyl)- or the 4-(*N*,*N*′-dialkyl)-2-aryl-substituted quinolines, depending on the amide lithium salt ($LiNR^2R^3$) employed (eq 53).[183,184]



(53)

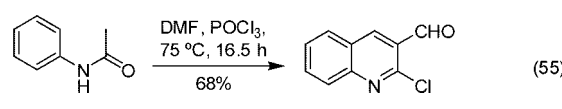
Analogously, 2,4-diaminoquinoline derivatives can be prepared by intramolecular cyclization of 2-amidinobenzonitriles, promoted by LDA/THF at low temperature or by $ZnCl_2$ at reflux (eq 54). The precursors can be synthesized by reaction of anthranilonitriles with triethyl orthoacetate followed by treatment with a secondary amine or, alternatively, by direct reaction of anthranilonitriles with an imidinium chloride, conveniently prepared by brief exposure of an *N*,*N*′-disubstituted acetamide to phosphorus oxychloride.[185]



(54)

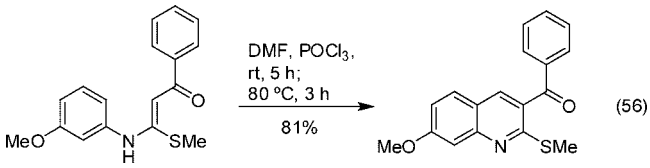
Another current approach for the synthesis of quinolines is based on the reaction of enamines,[186] or imines[187] with Vilsmeier reagents.[188,189]

Similarly, the Meth-Cohn synthesis of quinolines involves the conversion of acetanilides into 2-chloro-3-substituted quinolines[190] by the action of Vilsmeier's reagent in warmed $POCl_3$ as solvent (eq 55).[191] Activated acetanilides reacted faster and in better yields than other strongly deactivated systems; an electron-donating substituent in the meta-position showed notable selectivity affording only 7-substituted quinolines, cyclization occurring para to the substituent; the reaction tolerates also a wide variety of functionality in the acetanilide side chain (alkyl, aryl, pyridyl, and thienyl).[191] Heterocyclic acetanilides such as acetamidothiophenes are substrates for the Meth-Cohn quinoline synthesis.[192] The mechanism of the Meth-Cohn quinoline synthesis involves the initial conversion of the acetanilide into a tautomeric α-iminochloride/α-chloroenamine mixture by the action of $POCl_3$, which is subsequently *C*-formylated by the Vilsmeier reagent derived from $POCl_3$ and DMF, followed by a second formylation, cyclization, and aromatization by loss of dimethylamine to give the final 2-chloro-3-quinoline carboxaldehyde.[191] The reaction can be accelerated in micellar media[193] by ultrasound[194] and microwave irradiation.[195]

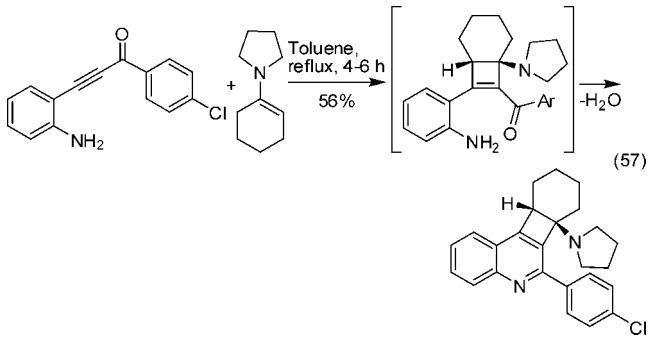


(55)

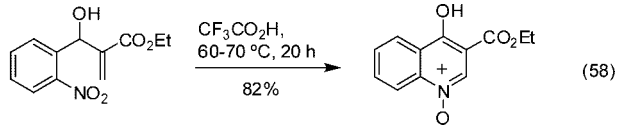
An alternative reverse Vilsmeier strategy is known involving ring closure of the Vilsmeier reagents derived from *N*-aryl-*N*-methylformamides with electron-rich olefins.[196] These methods suffer from some limitations such as requiring a large excess of $POCl_3$ or the nonavailability of highly functionalized imine (or enamine) precursors. To circumvent such problems, the reaction of α-oxo ketene *N*,*S*-acetals with Vilsmeier reagents provides a versatile route to highly functionalized quinolines (eq 56).[197]




Complex fused polycyclic quinolines can be prepared starting from *β*-(2-aminophenyl)-α,*β*-ynones and enamines of cyclic ketones by a domino [2 + 2] cycloaddition/annulation reaction (eq 57).[198a]

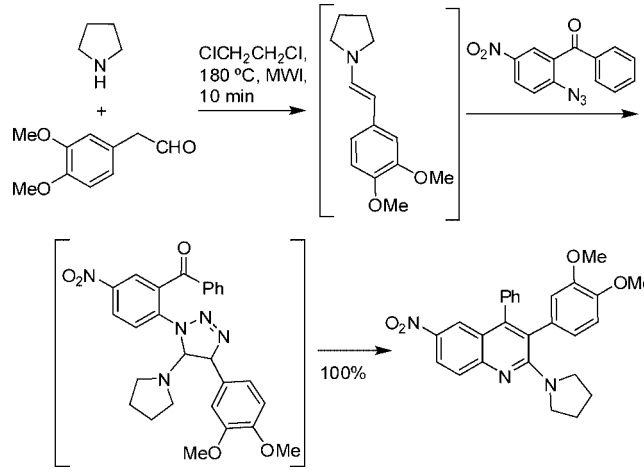



Similarly, polycyclic compounds such as the 7*H*-indeno[2,1-*c*]quinolines, which are difficult to synthesize by Friedländer-type protocols, can be accessed from Morita−Baylis−Hillman adducts after intramolecular Friedel−Crafts reaction followed by dehydration.[199] Morita−Baylis−Hillman acetates give rearranged tosylamide derivatives, which after oxidative cyclization promoted by iodobenzene diacetate afford ethyl quinoline-3-carboxylates in moderate yields via the corresponding *N*-tosylamidyl radical.[200] Similarly, Morita−Baylis−Hillman adducts prepared from 2-halo benzaldehydes and *N*-tosylimines have been used to synthesize quinoline-3-carboxylic acid esters.[201] In this context, one of the most important problems associated with the Friedländer synthesis, the relative instability of substituted 2-amino benzaldehydes, can be solved by using the readily available Morita−Baylis−Hillman adducts obtained from 2-nitro benzaldehyde and α,*β*-unsaturated carbonyl compounds. Although preliminary experiments[202] show that the synthesis of the intermediates using DABCO {1,4-diazabicyclo[2.2.2]octane} as base followed by reduction (10% Pd/C, EtOH) provides the final quinolines in low yields, acid-promoted cyclization to quinoline-*N*-oxides is efficient, as shown in eq (58).[203,204]



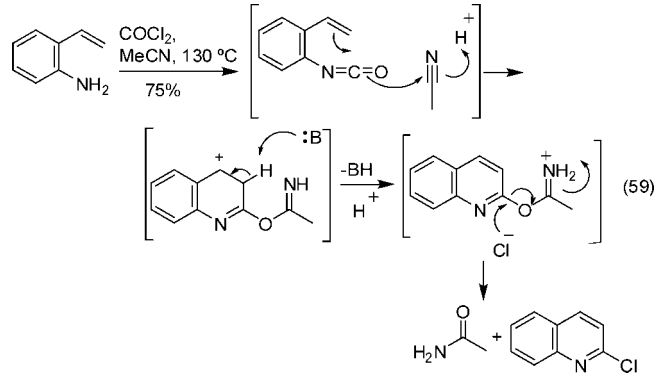

Some heteroatom-substituted quinolines cannot be synthesized by Friedländer reactions, notably, those containing

**Scheme 7. Synthesis of 2-Aminoquinolines by Microwave-Assisted Irradiation of a Mixture of Amines and Aldehydes To Give the Corresponding Enamines, Followed by Reaction with 2-Azido Benzophenones**




halogen or $NH_2$ groups on the newly formed ring. However, 2-aminoquinolines can be easily obtained by microwave-assisted irradiation of a mixture of amines and aldehydes to give the corresponding enamines, followed by reaction with 2-azido benzophenones; in this method, the initially formed triazoline intermediate undergoes a thermal rearrangement and intermolecular base-catalyzed cyclocondensation to produce a quinoline-based pharmacophore combinatorial library (Scheme 7).[205]

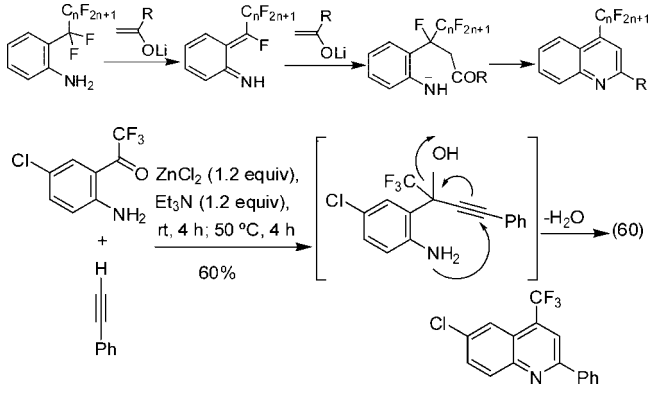
The synthesis of 2-chloroquinolines[206] also cannot be undertaken using Friedländer protocols. However, this type of compound can be directly formed according to the Meth-Cohn methodologies[190] (see above) or from 2-alkenyl-substituted anilines and phosgene by using acetonitrile as solvent. A range of 2-chloro-substituted quinolines have been prepared in this way in good chemical yields, and a possible mechanism has been suggested based on the generation of the aryl isocyanate derivative, quinoline ring formation, and chlorination at C-2 (eq 59).[207]




A new and interesting synthesis of 4-trifluoromethyl-substituted quinolines is based on the tandem reaction of 2-trifluoroacetyl aniline with acetylenes involving a Zn(II)-mediated alkynylation and intramolecular cyclization (eq 60).[208a]

The synthesis of 4-perfluoroalkyl[4-($C_{n-1}F_{2n-1}$)]-substituted quinolines can be achieved by the reaction of 2-($C_nF_{2n+1}$)-substituted anilines with lithium enolates of acetaldehyde,[209] with lithium enolates of methyl ketones (Scheme 8),[209,210] or with lithium reagents derived from phenylacetylene or

**Scheme 8. The Synthesis of 4-Perfluoroalkyl[4-($C_{n-1}F_{2n-1}$)]-Substituted Quinolines by the Reaction of 2-($C_nF_{2n+1}$)-Substituted Anilines with Lithium Enolates of Acetaldehyde**




substituted acetonitriles.[211] However, the classical Friedländer reaction for the preparation of 4-perfluoroalkylquinolines from 2-perfluoroacylanilines with enolizable ketones (eq 5) is more efficient and of broader scope in comparison to the above cited methods.[39] 4-Fluoroquinolines, valuable precursors for the synthesis of amino-substituted quinolines, have been prepared for the first time in a one-pot reaction of *o*-trifluoromethylanilines with methyl ketone lithium enolates in moderate yields (33−40%).[212]

On the other hand, base-mediated cyclization of ketenimines derived from 2-($C_nF_{2n+1}$)-substituted anilines and 1-tetralone[184] or aryl methyl ketones furnishes the corresponding *N*-alkyl- or *N*,*N*-dialkyl-substituted 2-phenylquinolin-4-amines (Scheme 8).[213,214] An analogous, alkoxide base-mediated cyclization is possible; the reaction of (*E*)-*N*-[1-(2-fluorophenyl)ethylidene]-2-(trifluoromethyl)aniline with *t*-BuOK in THF at reflux gave the corresponding fluoro derivative of 2-phenyl-4-ol (Scheme 9).[215]

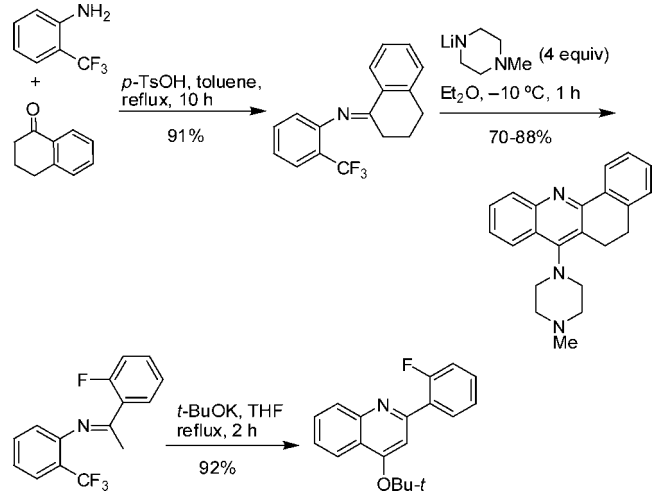
Finally, based on the well-known but low-yielding Friedländer reaction between 2-amino nicotinaldehyde and 2-phenyl acetic acid,[216] an efficient new synthesis of naphthyridines has been disclosed by palladium-catalyzed cross-coupling reaction between enolizable primary and secondary amides and readily available 2-carbonyl-susbtituted aryl halides.[217]

## 6. Experimental Conditions: The Catalysts

The Friedländer annulation can be catalyzed by base or acid or may take place without a catalyst. Standard conditions for the Friedländer synthesis of quinolines include the use of strongly basic potassium hydroxide in ethanol at reflux[10a,b] or pyrrolidine in ethanol containing traces of concentrated sulfuric acid[10c] for compounds containing sensitive functional groups to strongly basic conditions such as the carbamates. The positive influence on yields and in the elimination of byproduct, using argon for purging the solution, is known.[10a] Polar solvents routinely used include acetonitrile, THF, DMF, and DMSO, sometimes leading to tedious workup procedures. The type of solvent used in the Friedländer reaction also produces major changes in the chemical yields. The quinoline synthesis shown in eq 21 gives a 72% yield of compound **28** when ethylene glycol is used[88] but only 30% when the reaction is conducted in acetamide at 160 °C in the absence of base and 12% in DMF.[218]

Under thermal or basic conditions, 2-amino benzophenones fail to react with simple ketones such as cyclohexanone or $\beta$-keto esters.[87] Subsequent studies have demonstrated that

**Scheme 9. Different Base-Mediated Cyclizations of *N*-(Alkylidene)-2-(trifluoromethyl)anilines**




acid catalysts (hydrochloric acid, sulfuric acid, *p*-TsOH,[219] and polyphosphoric acids) are more effective than basic catalysts for this reaction.[39,129] However, many of these classical methods require high temperatures, prolonged reaction times, and drastic reaction conditions, present difficulties in the workup, use stoichiometric or relatively expensive reagents, and give unsatisfactory the yields due to the occurrence of several side reactions. Moreover, the main disadvantage of almost all existing methods is that the catalysts cannot be recovered or reused during the workup. Thus, the development of more efficient, simple, and environmentally benign procedures for the synthesis of quinolines is still needed.

In recent years, the literature on this aspect of the Friedländer synthesis has significantly grown, and modified methods describing the use of new catalysts, such as gold compounds ($AuCl_3$), $ZnCl_2$, or $NiCl_2$[220] have been reported.

The use of sodium fluoride or lithium bromide in a solid state catalyzed Friedländer condensation of 2-amino nicotinaldehyde with different carbonyl compounds furnishes the corresponding 1,8-naphthyridines at room temperature in high yields.[221] A similar excellent result with identical substrates is described using piperidine as catalyst under microwave irradiation.[222]

$Bi(OTf)_3$[223] used in catalytic amounts (5 mol %) in ethanol at room temperature is best among a number of metal triflates examined such as $Cu(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$, and $Ce(OTf)_3$ for the reaction of 2-amino benzophenones with selected ketones, leading to the corresponding quinolines in good yields. It is a very inexpensive reagent, which can be prepared on a multigram scale in the laboratory, and unlike earlier methods, the present protocol does not require high temperatures or harsh conditions. $BiCl_3$ under solvent-free conditions at 60−90 °C gives high yields of poly-substituted quinolines.[224]

Yttrium trifluoromethanesulfonate [$Y(OTf)_3$] is commercially available, significantly less expensive than $Sc(OTf)_3$, and water tolerant.[225] It has been reported as a reusable and efficient catalyst for the condensation of a large array of substituted 2-amino benzo- or acetophenones with cyclic ketones (cyclopentanone or cyclohexanone) or 1,3-dicarbonyl derivatives proceeding in acetonitrile or ethanol at room temperature in short reaction times and in good yields (76−92%).[225]

Silver phosphotungstate ($Ag_3PW_{12}O_{40}$)[226] as a heteropoly acid and heterogeneous catalyst provides an easy isolation of products, as only a simple filtration is needed to separate the reaction product from the catalyst, which can be reused after activation. Furthermore, this method is free from secondary side reactions such as self-condensation of ketones, which is usually observed under basic conditions. Consequently, this method guarantees the synthesis of a wide range of quinolines with different substitution patterns, with high conversions, in short reaction times, and by simple experimental procedures.

$SnCl_2 \cdot 2H_2O$ has been applied to the standard substrates giving the quinolines in excellent yields with short reaction times.[84] The main advantage of this solvent-free, room-temperature protocol is that it is operable on large scale and proceeds even when both of the precursors are solids. In the case of cyclic ketones, where the classical conditions such as heating at 100 °C in HCl or stirring at room temperature usually give unsatisfactory results, the yields with this method are higher than 95%. For unsymmetrical ketones, such as 2-butanone, only the 2,3-dimethylquinoline derivative is isolated.

Proline[227a] and oxalic,[227b] citric,[227c] trifluoroacetic,[227d] and sulfamic acids[227e] have been used as efficient, cost-effective, and recyclable acid catalysts for the Friedländer quinoline synthesis, with a large array of different cyclic or acyclic ketones or $\beta$-keto esters. With sulfamic acid ($NH_2SO_3H$), the best results are obtained with 5% of the catalyst at 70 °C under solvent-free conditions.

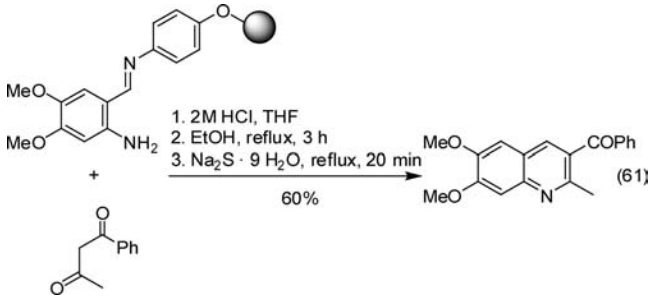
Iodine ($I_2$) is a highly efficient catalyst in the synthesis of quinolines via the Friedländer annulation. The advantages of this method include good substrate generality, use of an inexpensive reagent, and mild experimental conditions.[228]

$Nd(NO_3)_3 \cdot 6H_2O$ has been reported to efficiently catalyze the Friedländer condensation of a series of 2-amino acetophenones and 2-amino benzophenones with a large array of functionalized cyclic or open-chain ketones; the reaction proceeds in ethanol at room temperature, in moderate to excellent yields (62−94%).[229]

$FeCl_3$ and $Mg(ClO_4)_2$ have been also investigated as readily available and efficient catalysts for quinoline synthesis using the Friedländer protocol.[230]

Very recently, $CeCl_3 \cdot 7H_2O$[231] and $KHSO_4$[232] have been added to the long list of easily available, but efficient catalysts to carry out Friedländer syntheses of quinolines.

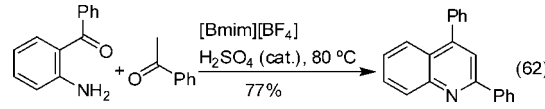
A new traceless solid-phase synthesis of quinolines based on the Friedländer reaction between the resin-bound azomethine and a ketone has been developed (eq 61); the yields are high and the polymer-bound aniline moiety of the azomethine is easily recycled.[233]



(61)

Microwave-assisted synthesis of quinolines[234] catalyzed by montmorillonite KSF clay have been reported.[145,235] The reaction of a series of acetophenones with 2-amino aceto(or benzo)phenones has been examined and optimized with respect to time and temperature effects when DPP is used under microwave irradiation. Under optimal conditions (4 min, 108 °C), the yields of the resulting quinolines are moderate to good.[236] Similarly, poly-substituted quinolines can be efficiently and rapidly prepared under microwave irradiation in solvent-free conditions catalyzed by *p*-TsOH[237a] or HCl.[237b] A series of 4-aryl quinolines have been prepared in excellent yields (70−99%) from 2-amino benzophenones and substituted ketones when mixed in the presence of catalytic amounts of concentrated sulfuric acid under microwave irradiation (70 W).[238] Very interestingly, in the absence of the catalyst, 3-acetyl-4-aryl-2*H*-2-quinolones are obtained in excellent yields (80−91%) when ethyl acetoacetate is used as the carbonyl compound,[238] a result that is in good agreement with the reactivity of 1,3-dicarbonyl derivatives with 2-amino benzophenones in Friedländer reactions, as reported in some seminal communications.[27,86,87]

Ionic liquids at room temperature offer an attractive alternative to conventional organic solvents in that they are nonvolatile, nonflammable and nonexplosive and can be recycled. In addition to these features, ionic liquids can also catalyze organic transformations of commercial importance under ambient conditions without the need for added catalysts or ligands. Consequently, ionic liquids have been used for the synthesis of quinolines in typical Friedländer protocols, in combination with catalytic amounts of sulfuric acid (eq 62)[239,240] or Lewis acids, such as $ZnCl_2$,[241] or in the presence of $FeCl_3 \cdot 6H_2O$ as catalyst.[242] However, the reaction proceeds equally well without any additives under mild reaction conditions, with 1-butylimidazolium tetrafluoroborate {[Hbim][$BF_4$]} as the ionic liquid.[85] Under these conditions, the reaction proved very regioselective with unsymmetrical ketones: the reaction of 2-amino acetophenone with ethyl methyl ketone or benzyl acetone gives only the 2,3-dialkyl quinoline in excellent isolated yields. This is in contrast to the mixtures of regioisomers (2,3-dialkyl quinolines vs 2-alkyl quinolines) obtained using basic or acidic conditions.[86,87]



(62)

In all these cases, the advantages relative to other protocols include environmental friendliness, simple operating processes in both mild and neutral conditions, and the possibility of recovering and reusing the catalyst a number of times.

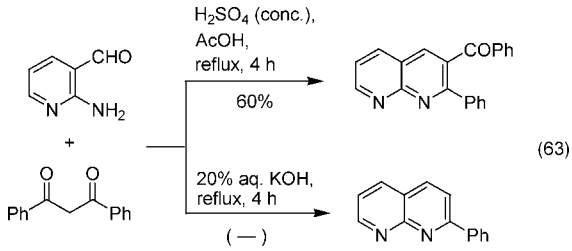
The Friedländer annulation using 2,4,6-trichloro-1,3,5-triazine as catalyst has proven to be simple, efficient, and rapid, providing the desired quinolines in high yields.[243]

Chlorotrimethylsilane has been found to be a convenient promoter and water-acceptor in the Friedländer reaction of a range of 2-amino carbonyl precursors with ketones for the synthesis of quinolines.[244]

$Al_2O_3$[245] or heterogeneous solid acid catalysts for Friedländer annulations[246] have been described, including silica gel supported sulfuric acid,[247a−c] sodium hydrogen sulfate,[247d,e] perchloric acid,[247f] phosphomolybdic acid,[248] $KAl(SO_4)_2 \cdot 12H_2O-SiO_2$,[249] and even sulfonated cellulose.[250]

A catalytic and green procedure for the Friedländer reaction has been reported in aqueous media[251] or using a Lewis acid−surfactant combined catalyst in water.[252]

Finally, we must emphasize that for very sensitive molecules such as 1,3-dicarbonyl derivatives, the type of catalyst used determines the type of the resulting Friedländer product. This can be exemplified in the reaction of 2-amino nicotinaldehyde with $\omega$-benzoyl acetophenones catalyzed by concentrated sulfuric acid or promoted by 20% aqueous potassium hydroxide (eq 63). Under acidic conditions, the 2-aryl-2-phenyl-1,8-naphthyridines are regioselectively obtained without traces of any other possible isomer being formed, whereas under basic conditions the 2-aryl-1,8-naphthyridines are isolated (no yields were reported).[253a] The formation of the latter compounds reflects the fact that $\omega$-benzoyl acetophenones are unstable in the aqueous alkaline conditions, affording aryl methyl ketones, which participate in the Friedländer reaction with 2-amino nicotinaldehyde.




(63)

## 7. Conclusions and Outlook

In the next years, Friedländer-type reactions are going to be still the method of choice for the synthesis of complex new materials bearing the quinoline,[254] naphthyridine,[255−257] phenanthroline,[258] quindoline,[259] or acridone[260] heterocyclic ring systems. Similarly, the synthesis of natural or non-natural products bearing these structural motifs, such as camptothecin,[261] lavendamycins,[262] 22-hydroxyacuminatine analogues,[263a] or rosettacin,[264] will be approached by using Friedländer-type reactions. New strategies or synthetic precursors in order to avoid the use of unstable 2-amino benzaldehydes, will surely be described.[265] The search for new catalytic systems[266] is a particularly active area of research that would provide new, more efficient, and easily available catalysts for the synthesis of quinolines. The modified Friedländer reaction on conveniently functionalized 2-amino benzonitriles, $\beta$-enaminonitriles, or 2-amino-substituted heterocyclic 3-carbonitrile derivatives[267] is expected to grow and expand into new substrates and biologically attractive target molecules such as tacrine analogues with potential pharmaceutical interest targeting neurodegenerative diseases (Parkinson, Alzheimer). Simple base-mediated[268a,b] or transition metal-catalyzed[268c] indirect Friedländer strategies based on the use of different 2-aminobenzylic alcohols and ketones (or alcohols) are very attractive, simple, and environmentally benign methods for the synthesis of polysubstituted quinolines that are expected to grow and develop in the next years. Finally, the problems associated with the type of catalysts and the regioselectivity of the Friedländer reaction when 1,3-dicarbonylic partners are used should find new solutions in order to improve the scope of the reaction.[269] Similarly, very recently the formation of unexpected Friedländer-type products possibly derived from Pinner/Dimroth rearrangements in the presumed intermediates have been reported; the scope, limitations, and potential synthetic applications are still awaiting a detailed investigation.[270]

In summary, despite the long time elapsed since its discovery, the Friedländer reaction continues to be one of the most used and cited name reactions in organic synthesis.

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