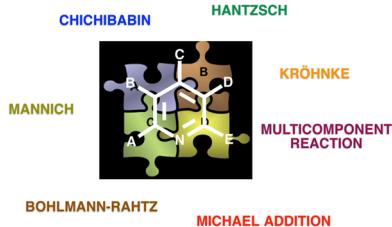


Metal-Free Multicomponent Syntheses of Pyridines

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1. INTRODUCTION

The discovery of the pyridine nucleus (Pyr, meaning fire in Greek, and idine, suffix used for aromatic bases) is linked to a peculiar experiment carried out by Anderson in 1846, who was indeed studying the pyrolysis of bones and was able to isolate picoline as the first known pyridine.¹ Since the proposition of the correct structure by Körner (1869) and Dewar (1871), this ring really became one of the most studied aromatics, and the reasons why the pyridine core is so attractive are numerous. Actually, it has found many applications in diverse chemical domains. In coordination chemistry, monopyridines,² bipyridines,³ or terpyridines^{4,5} can be used to chelate metallic ions as N-donor ligands, affording efficient organometallic catalysts.⁶ Pyridines are also involved in materials and surfaces,⁷ supramolecular structures,⁸ polymers,⁹ and also in organocatalysis, as illustrated by the numerous applications of DMAP and its derivatives.¹⁰ However, especially, pyridines have attracted scientists for their biological interests (Figure 1). They play of course a central role in the biological activity of natural substances including vitamin B₆, nicotine, or oxido-reductive NADP–NADPH coenzymes. Pyridine-containing complex natural products also exist in the sesquiterpene, alkaloid, enediyne, or polypeptide families. Numerous other bioactive elaborated pyridines have been synthesized resulting in different interesting effects like anti-inflammatory¹¹ and antiasthmatic ones,¹² antidepressant,¹³ inhibiting acetylcholinesterase (AChE),¹⁴ treating hypertension¹⁵ or hypotension,¹⁶ inhibiting HIV protease,¹⁷ preventing¹⁸ or inducing apoptosis.¹⁹ Thus, this nucleus constitutes a major scaffold to create antitumor or antiviral drugs. Alternatively, pyridines are also exploited in agrochemistry²⁰ for their herbicide,²¹ insecticide,²² and antifungal²³ properties. As a consequence, chemists have developed a plethora of methods to elaborate this structure, and most of them have been compiled in a series of reviews.²⁴ The present review will constitute a complement to the state of the art by providing a comprehensive compilation of synthetic approaches involving specifically metal-free multicomponent reactions (MCRs).

MCRs²⁵ are very attractive because of their efficiency and simplicity, appealing for pharmaceutical companies interested in rapidly accessing new medicines.²⁶ These sequences imply the use of at least three components present in the reactor since the beginning.

They react according to a succession of mono- or bimolecular processes to form at the end one product that incorporates important portions and functionalities of the starting materials. Each transformation is the consequence of the preceding one. By definition, no other compound (solvent, catalyst, substrate) is added during the reaction, and ideally, the experimental conditions stay unchanged from the beginning until the end.

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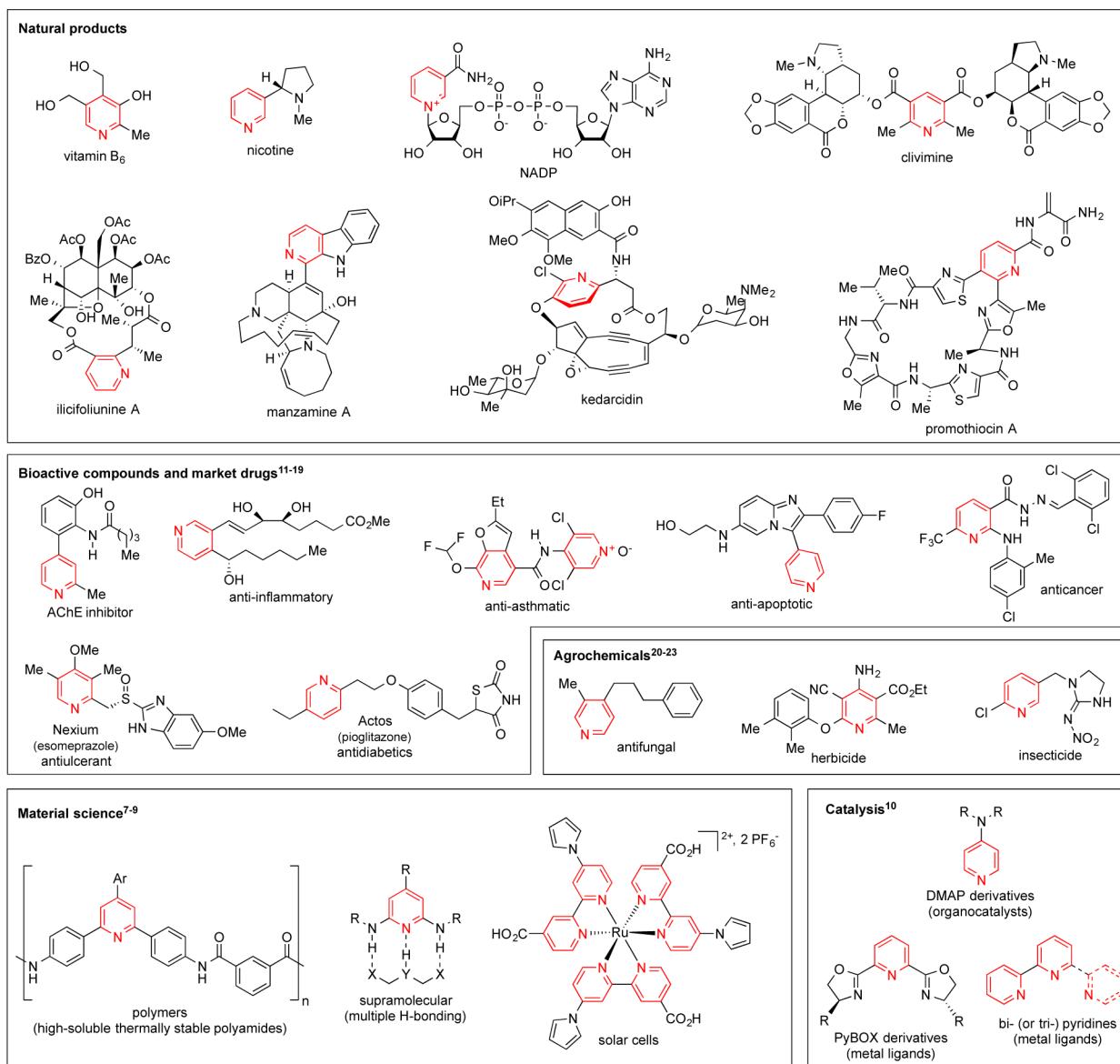


Figure 1. Representative pyridine derivatives and their chemical domains of application.

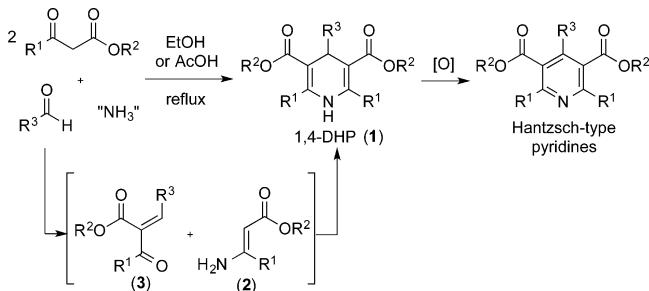
Syntheses of pyridines that do not strictly meet these criteria,²⁷ along with “pseudo” MCRs (*i.e.*, reactions involving 1 equiv of a substrate and at least 2 equiv of a second one),²⁸ have not been included in the present review. Of course, we have to mention here that many authors have used the “multicomponent label” for describing sequential processes involving more than two partners, where some of the reagents or catalysts are added after one or more reactions have taken place. However, all these types of reactions will not be discussed herein. Owing to large spectrum of fascinating applications, the synthesis of pyridine derivatives has long been an area of intense interest, and the development of methodologies for a direct access to highly substituted and specifically functionalized frameworks is a continuing challenge in modern synthetic organic chemistry. In this context, nowadays, the metal-catalyzed [2 + 2 + 2] cycloadditions of alkynes with nitriles largely leads the way in the synthesis of pyridines.²⁹ However, the low availability of some catalysts and substrates along with the lack of regioselectivity in its multicomponent version³⁰ constitute major drawbacks of this approach. Besides [2 + 2 + 2]

cycloadditions, several metal-catalyzed multicomponent processes have been reported to access pyridines with efficiency and creativity. However, the content of this article does not address this area, and interested readers are invited to consult the relevant documentation.³¹ More interesting, MCRs, especially when they are not metal-catalyzed, are “environmentally friendly” processes. They allow direct access to complex structures in one operation, and respect demanding eco-compatibility criteria like step economy and atom economy. Since developing “green chemistry” methodologies has never been such an emergency in our environmental and economical context, we will focus in this article on recent selected advances in the development of metal-free multicomponent strategies toward pyridines. The compilation of the existent literature focuses on the pyridine ring construction and has been organized according to the main reaction involved in each process. It is interesting to note that although they have known significant developments in the past decade, most of them are based on old but well-known reactions.

2. HANTZSCH PYRIDINE SYNTHESIS

One of the most popular methods for the preparation of pyridines is the two-step Hantzsch approach, which involves the oxidation of 1,4-dihydropyridines **1** (DHPs), previously formed through a one-pot pseudo-four-component reaction of 2 equiv of a 1,3-dicarbonyl derivative, an aldehyde, and a source of ammonia (Scheme 1).³² The corresponding symmetrical

Scheme 1. General Hantzsch Pyridine Synthesis



heterocycles are obtained via a cyclodehydration between *in situ* formed enamino ester **2** and alkylidene malonate **3** intermediates. Subsequent oxidation affords the corresponding aromatized products.

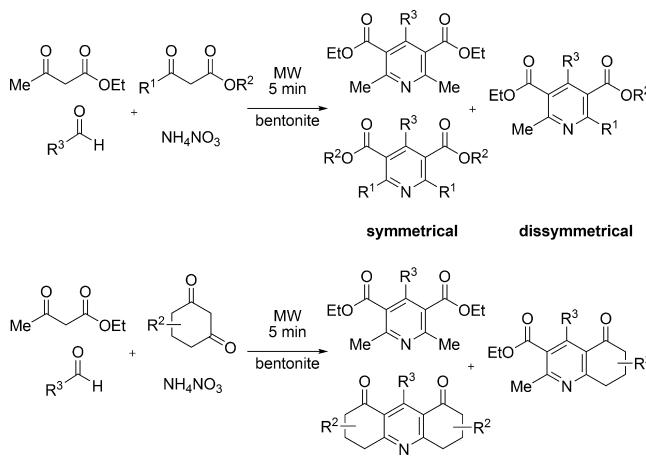
Many conditions have been developed to oxidize the DHPs into pyridines, involving the use of numerous organic or inorganic oxidants. Most of these reagents are derived from transition metals; therefore, the corresponding methodologies will not be discussed herein. Alternatively, for the development of more environmentally friendly conditions, reactions with O₂ as the oxidant have been investigated.³³ Among user-friendly ones, treatment of DHPs with molecular oxygen adsorbed on activated charcoal,³⁴ or simple exposition to air, either in the absence³⁵ or in the presence of palladium on charcoal,³⁶ are also suitable conditions for the oxidation of 1,4-DHPs previously synthesized and isolated. More recently, an enzyme-catalyzed oxidation of DHPs has been explored. Thus, the environmentally benign laccase/O₂ system mildly delivered pyridines with excellent efficiency.³⁷ Although sequential one-pot procedures are known,³⁸ some research groups have alternatively focused their efforts in developing conditions to form and oxidize the DHP in the same pot under multicomponent conditions.

2.1. Classical Four-Component Hantzsch Approach

The classical four-component Hantzsch approach consists of reacting together two 1,3-dicarbonyls, one aldehyde, and 1 equiv of ammonia source. In this context, Cotterill et al. described in 1998 a pyridine synthesis under microwave irradiation (MW), in the presence of bentonite, from a mixture of cyclic or acyclic 1,3-dicarbonyl derivatives, one aldehyde, and ammonium nitrate (Scheme 2).³⁹ Under these conditions, this ammonia source also generated nitric acid, responsible for the DHP oxidation. This work took advantage of the nonselectivity of the reaction to quickly generate a library of symmetrical and unsymmetrical pyridines. Separation conditions were also developed to make this method suitable for combinatorial chemistry.

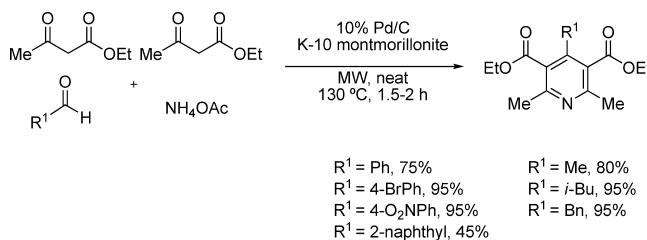
Ten years later, De Paolis et al. described a similar transformation using a combination of K-10 montmorillonite as a catalyst of the Hantzsch reaction and palladium on charcoal as a promoter of the oxidation step.⁴⁰ Starting from ethyl acetoacetate, aliphatic or aromatic aldehydes, and ammonium acetate, this solvent-free microwave-assisted process delivered

Scheme 2. Hantzsch Synthesis Applied to Combinatorial Chemistry



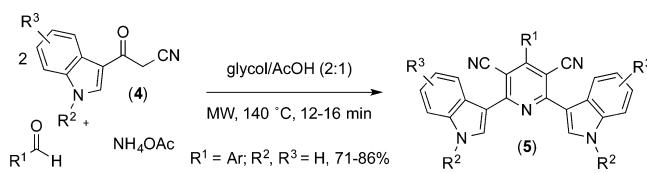
symmetrical pyridines in good yields and short reaction times (Scheme 3).

Scheme 3. MW-Assisted Hantzsch Synthesis of Pyridines



Although β-ketoesters have been identified as partners of choice in the Hantzsch pyridines synthesis, other substrates bearing at least one nitrile functionality have been recently and successfully exploited. Symmetrical bis(3'-indolyl)-dicyanopyridines **5**, for example, have been easily accessed from β-ketonitrile⁴¹ **4** derived from indoles (Scheme 4).⁴²

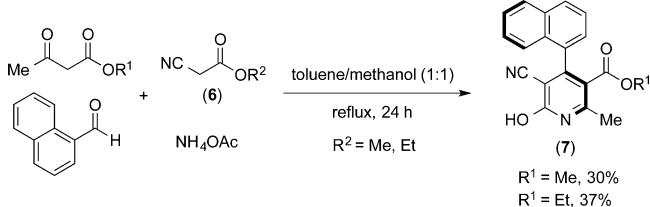
Scheme 4. Synthesis of Bis(3'-indolyl)dicyanopyridine Derivatives



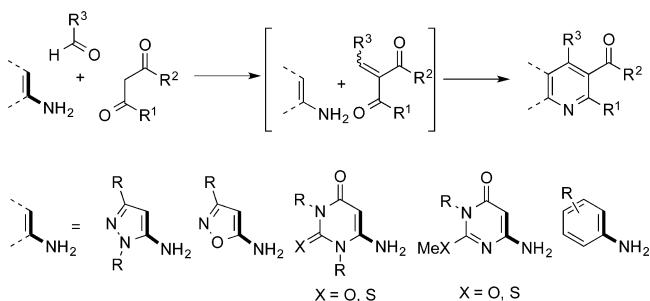
Alternatively, the use of α-cyanoesters **6** allowed Zhou et al. to synthesize 2-hydroxypyridines **7** in a classical four-component process from ammonium acetate, an aromatic aldehyde, and a β-ketoester (Scheme 5).⁴³ The associated yields are relatively low without any specific explanation from the authors. However, the objective was to elaborate atropisomers and to use them as optically active ligands. To this end, sterically demanding naphthaldehyde was principally used, which might explain the low efficiency of the reaction.

2.2. Modified Three-Component Hantzsch Approach

For the Hantzsch synthesis of nonsymmetrically substituted pyridines, the more efficient strategy consists of a reaction involving an aromatic aldehyde, a 1,3-dicarbonyl derivative, and a

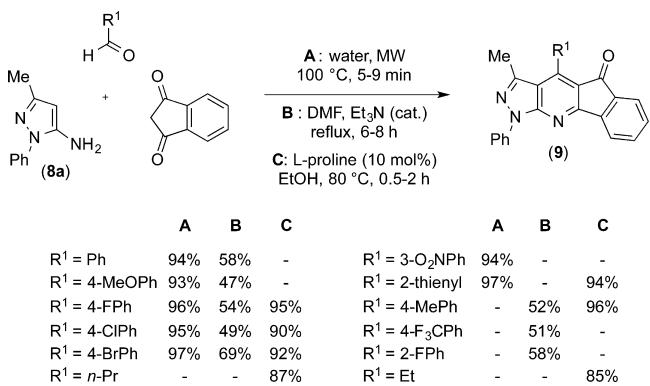
Scheme 5. Synthesis of 2-Hydroxypyridines Atropisomers

preformed enaminoester, usually postulated as an intermediate in the classical Hantzsch version. By the nature of the implied reactants, this approach can be considered as a three-component variation or a development of the Hantzsch pyridine synthesis, that we will name “modified 3-C Hantzsch approach”. This strategy generally involves amino-aromatic or heteroaromatic substrates such as pyrazole, isoxazole, pyrimidine, or aniline, acting as enamine equivalents (Scheme 6).

Scheme 6. Amino-Aromatics as Enamine Partners

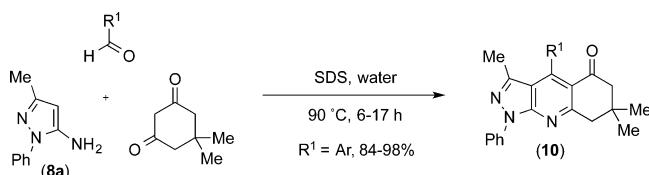
2.2.1. Pyrazole Derivatives. By far, 5-amino-pyrazoles are the most studied heterocyclic amines in this strategy. Although 3-methyl-1-phenyl-1*H*-pyrazol-5-amine was the most intensively studied skeleton, many compounds having various substituents are very well-tolerated substrates in these multicomponent processes. Above all, position 4 must inevitably remain free to allow the final aromatization step.

2.2.1.1. 3-Methyl-1-phenyl-1*H*-pyrazol-5-amine (8a). Using this enamine surrogate **8a** in combination with a large panel of 1,3-dicarbonyl derivatives or equivalents, many operating conditions have been described. First, reactions with 1,3-indandione led to the formation of tetracyclic 4-azafluorenones **9**, either in water under microwave irradiation (Scheme 7, conditions A),⁴⁴ or in refluxing DMF with a catalytic amount of triethylamine (Scheme 7, conditions B).⁴⁵ However, the latter

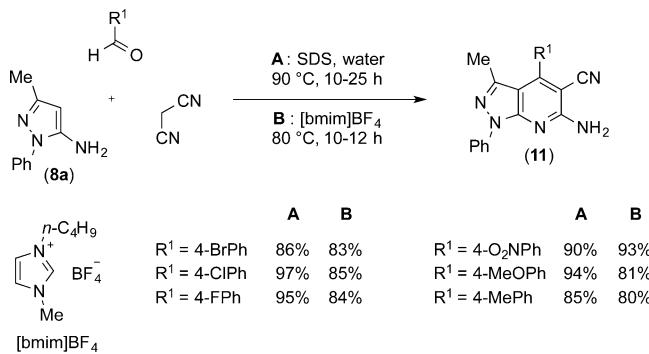
Scheme 7. 4-Azafluorenones from 5-Aminopyrazole 8a

conditions resulted in prolonged reaction times and lower yields. L-Proline-catalyzed reaction in refluxing ethanol also delivered the expected pyridines in excellent yields (Scheme 7, conditions C),⁴⁶ tolerating in this case the use of aliphatic aldehydes, although a slight erosion of the yield was observed.

The outcome of Hantzsch-type reaction with amino-heterocycles is strongly dependent on the 1,3-dicarbonyl derivative involved. It is not unusual to obtain selectively the 1,4-DHP or the pyridine from different 1,3-diketones under the same reaction conditions.⁴⁶ This observation is particularly true for the reaction with dimedone, which tends to furnish 1,4-DHPs instead of pyridines. However, sodium dodecyl sulfate (SDS), an ionic surfactant, was recently reported to induce the reaction between 5-aminopyrazole **8a**, aromatic aldehydes, and dimedone in water.⁴⁷ Heating this mixture at 90 °C provided the tricyclic pyridines **10** in excellent yields (Scheme 8).

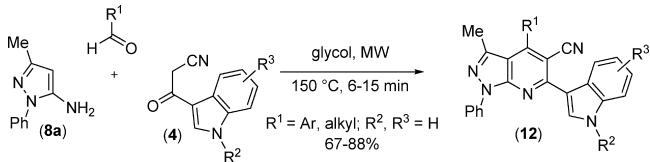
Scheme 8. Tricyclic Pyridine Synthesis from Dimedone

Exactly the same conditions have been previously applied to the synthesis of 2-amino-3-cyanopyridines **11** from malononitrile (Scheme 9, conditions A).⁴⁸ Interestingly enough, the SDS-

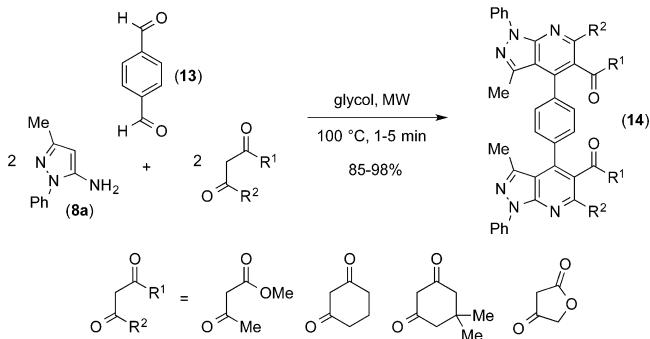
Scheme 9. Synthesis of 2-Amino-3-cyanopyridines

containing reaction mixture can be used up to 5 times without any loss of efficiency. A similar approach from malononitrile was also developed by heating the three partners at 80 °C in [bmim] BF_4^- (Scheme 9, conditions B).⁴⁹ More than a simple solvent, the ionic liquid, according to the authors, would play the role of an activator. Due to the presence of an acidic hydrogen atom between the two nitrogen atoms of the imidazolium nucleus, the ionic liquid may act as an excellent donor of hydrogen bonding, thus activating successively the aldehyde carbonyl during the Knoevenagel condensation, and the nitrogen atom of the nitrile during the cyclization step.

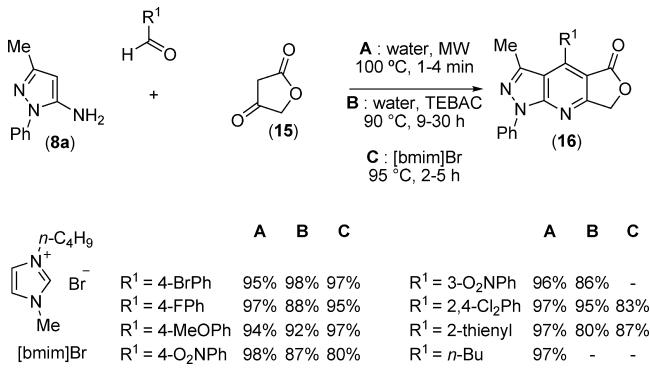
When 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**8a**) was mixed with an aldehyde and a β -ketonitrile **4**, another set of 3-cyanopyridines **12** was synthesized under microwave irradiation in glycol (Scheme 10).⁵⁰ This efficient procedure proved to be suitable with both electron-rich and electron-poor aromatic aldehydes, heteroaromatic aldehydes, and aliphatic ones.

Scheme 10. Use of β -Ketonitrile in Hantzsch-like Reactions

In 2007, Tu et al. employed a series of 1,3-dicarbonyl partners in combination with an aromatic bis-aldehyde **13** and 5-aminopyrazole **8a** in a Hantzsch-type process conducted under microwave irradiation in glycol.⁵¹ This pseudo-five-component reaction resulted in bifunctional products **14** in high yields and short reaction times (Scheme 11).

Scheme 11. Pseudo-Five-Component Synthesis of Symmetrical Bis-pyrazolopyridines

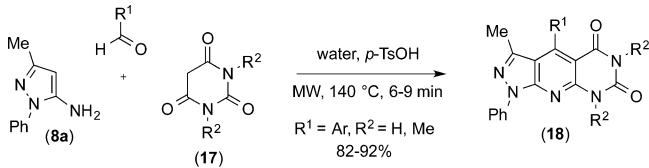
Shortly after, the same authors reported the corresponding three-component reaction starting from tetronic acid (**15**). An aqueous suspension of the three substrates was subjected to microwave irradiation, yielding the tricyclic pyridines **16** with a remarkable efficiency, even from aliphatic aldehydes (Scheme 12),

Scheme 12. Analogues of Podophyllotoxin by Three-Component Reaction

conditions A).⁵² Products thus obtained are *N*-analogues of podophyllotoxin, which influenced the elaboration of many anticancer drugs. Shortly after, the group of Shi reported that triethylbenzylammonium chloride (TEBAC) efficiently catalyzed this three-component reaction in aqueous media (Scheme 12, conditions B).⁵³ A complementary study on these latter conditions suggested that the reaction solution, after simple filtration of the insoluble product, might be reused up to 6 times without any loss of efficiency. However, contrary to what might be thought, water is probably one of the least sustainable

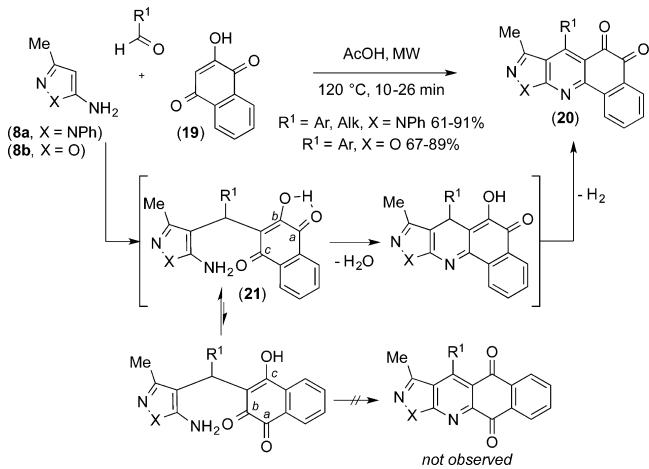
solvents. Although this solvent itself is environmentally benign, cheap, and nontoxic, the associated cost of the purification, decontamination, and recycling process is enormous. For those reasons, the same group also successfully developed the same three-component sequence under classical heating in ionic liquid (Scheme 12, conditions C).⁵⁴

In 2008, Tu and collaborators designed the three-component synthesis of fused pyrazolopyridopyrimidine derivatives **18** by means of the construction of the central pyridine ring.⁵⁵ Barbituric acids **17** were used as the 1,3-dicarbonyl partners in this acid-catalyzed Hantzsch-type reaction performed in water under microwave irradiation. The triheterocyclic products were isolated in high yields after short reaction times (Scheme 13).

Scheme 13. Three-Component Synthesis of Pyrazolopyridopyrimidines

Even though 10 mol % of the acid catalyst was enough to observe the formation of the expected heterocycles with reasonable yields, a stoichiometric amount showed to be optimal. Chebanov's group published in 2009 an extended scope of this reaction as they showed not only that modification of the pyrazole substitution pattern was allowed, but also that 2-thiobarbituric acids were well-tolerated substrates.⁵⁶

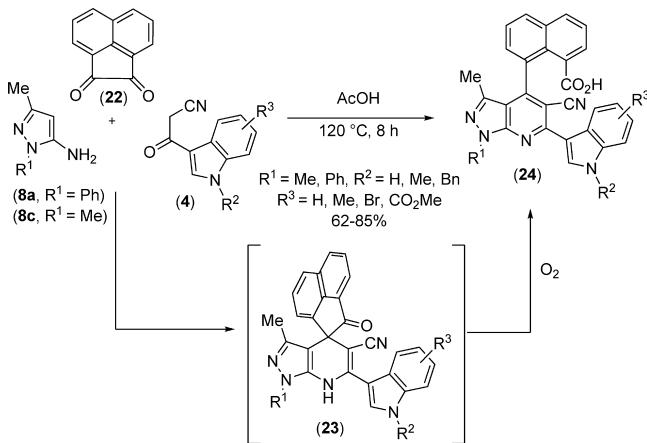
Within their research efforts, the group of Tu reported two years later the introduction of 2-hydroxy-1,4-naphthoquinone **19** as the 1,3-dicarbonyl substrate.⁵⁷ Starting from pyrazole **8a** ($X = \text{NPh}$) as the enamine partner, and aromatic or aliphatic aldehydes, the corresponding tetracyclic pyridines **20** were isolated in good yields and as single regioisomers (Scheme 14). A proposed mechanism suggests that the sequence begins by a Knoevenagel condensation followed by an intermolecular Michael addition affording intermediate **21**. A regioselective cyclodehydration then occurs, with this cyclization being preferentially operated onto carbonyl *c* due to an intramolecular hydrogen-bond between ketone *a* and enol *b*. A final

Scheme 14. Regioselective Synthesis of Pyridines from Naphthoquinones

dehydrogenation leads to the aromatized product. Isoxazole **8b** ($X = O$) may be introduced as well in this sequence with the same efficiency. The use of this substrate as a synthetic equivalent of enamine had already been pioneered by Tu a few years earlier in similar strategies, in combination with aldehydes and 1,3-dicarbonyl derivatives such as tetronic acid, dimedone, or 1,3-indandione.⁵⁸ These three-component sequences, operated in water under microwave irradiation, afforded the corresponding polycyclic pyridines with high yields.

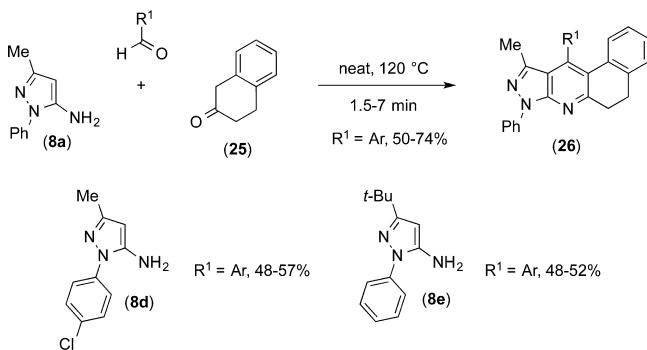
Very recently, an unexpected “aldehyde-free” Hantzsch-type pyridine synthesis has been developed. By mixing pyrazol-5-amine **8a** or **8c**, acenaphthylene-1,2-dione **22**, and β -ketonitrile **4**, Ji and co-workers were expecting to form substituted spirodihydropyridines **23**. Instead, 8-carboxylnaphthyl-pyrazolopyridine derivatives **24** were obtained as major products after heating the three partners in acetic acid (Scheme 15).⁵⁹ The authors postulated that the initially expected spiro-compound might be the precursor of the final product by oxidation under aerobic conditions.

Scheme 15. Unexpected Aldehyde-Free Hantzsch Reaction



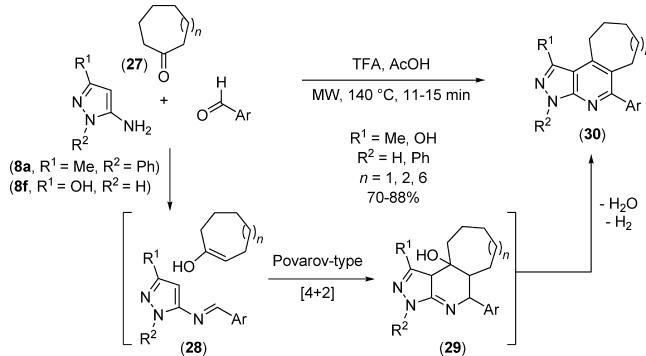
Some groups were interested as well in the use of simple carbonyl derivatives to replace the 1,3-dicarbonyl compounds, giving access to original polycyclic pyridines. For example, Quiroga described the regioselective synthesis of tetracyclic pyridines **26** under solvent-free conditions, at 120 °C from the activated β -tetralone **25** (Scheme 16).⁶⁰ Notably, α -tetralone was not suitable in this multicomponent process. While 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **8a** was mainly used during the study, different substitution on the pyrazole ring (**8d,e**) was well-tolerated.

Scheme 16. Tetracyclic Pyridines from β -Tetralone **25**



In most of the previous examples, the final pyridines usually contain an aryl substituent in position 4, the latter resulting from the use of an aromatic aldehyde. Recently, 2-aryl pyrazolopyridines **30** have been synthesized (Scheme 17) by the three-

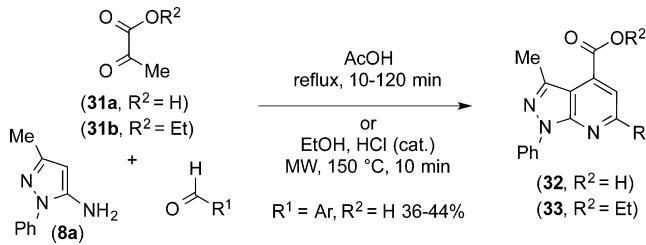
Scheme 17. Pyridines with Reversal of Regioselectivity through Povarov-type [4 + 2] Cycloaddition



component reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**8a**) ($R^1 = Me, R^2 = Ph$), aromatic aldehydes, and cycloalkanones **27**.⁶¹ This unprecedented transformation occurred in acetic acid with an equimolar amount of trifluoroacetic acid (TFA) under microwave irradiation, and a mechanism was postulated in order to rationalize the observed regioselectivity. Thus, instead of the usual Knoevenagel condensation, the first step of the sequence might be the formation of the imine **28**. Then, tricyclic intermediate **29** would result from a Povarov-type [4 + 2] cycloaddition of **28** with the enol form of the cyclic ketone, releasing the pyridine after dehydration and aromatization. A series of macrocyclic ketones successfully reacted, and 3-amino-1*H*-pyrazol-5-ol (**8f**) ($R^1 = OH, R^2 = H$) proved to be an efficient enamine equivalent in this procedure.

Such a rare regioselective outcome had already been observed once during the collaborative works of Chebanov and Kappe.⁶² Indeed, the use of 1,2-dicarbonyl substrates such as pyruvic acid **31a** ($R^2 = H$) and ethyl pyruvate **31b** ($R^2 = Et$) in place of the cycloalkanone derivatives led to the formation of isonicotinic acids **32** and ethyl isonicotinates **33**, respectively (Scheme 18). A

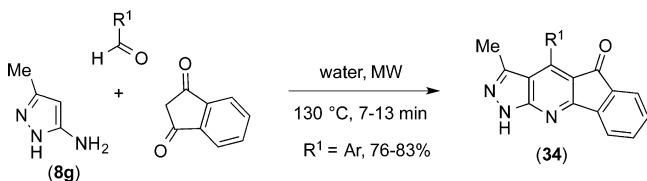
Scheme 18. Pyridines with Reversal of Regioselectivity from Pyruvic Acid Derivatives



Povarov-type cycloaddition might also be invoked to rationalize the regioselective formation of these pyridines. This mechanism is supported by the fact that the bimolecular version, *i.e.*, the condensation between 5-aminopyrazole **8a** and a β,γ -unsaturated α -ketoacid in refluxing acetic acid, led to the commonly observed regiosomer bearing the carboxylic function on position 2 and the aromatic group in position 4. This difference shows once again the benefits from using multicomponent reactions.

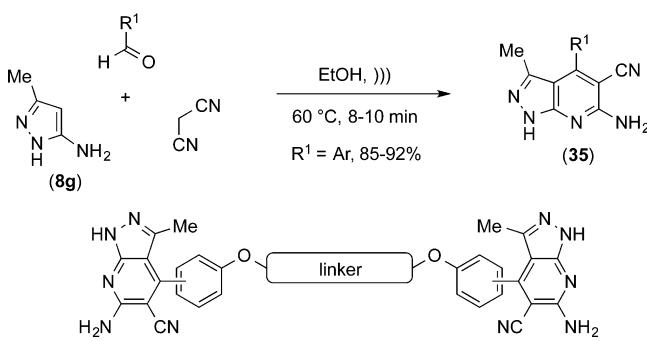
2.2.1.2. 3-Methyl-1*H*-pyrazol-5-amine (8g**).** This enamine surrogate **8g** was described as soon as 2001 by Quiroga in combination with dimedone and paraformaldehyde in refluxing ethanol, affording the corresponding tricyclic pyridine in 87% yield.⁶³ Later, it was successfully involved in the synthesis of tetracyclic pyridines **34**. An aqueous suspension of this pyrazole, 1,3-indanedione, and an aromatic aldehyde was subjected to microwave irradiation, affording expected pyridines in good yields (Scheme 19).⁶⁴

Scheme 19. Pyridines by MCR from NH-Free Pyrazole



A similar transformation was reported in 2011 by Zare et al., in which 1,3-indanedione was replaced by malononitrile.⁶⁵ A series of 2-amino-3-cyanopyridines **35** was elaborated by heating at 60 °C under ultrasound activation an ethanol solution of the three substrates (Scheme 20). The benefits of ultrasound irradiation in

Scheme 20. Synthesis of Pyrazolopyridines from Malononitrile

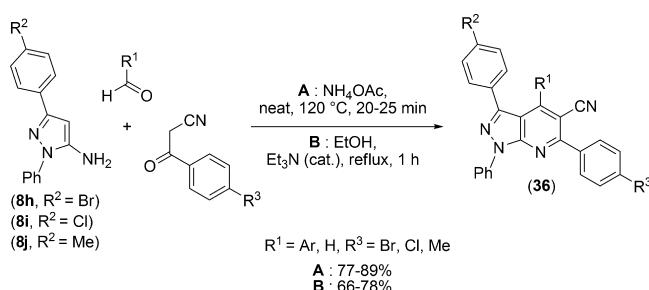


terms of reaction times and efficiency were clearly demonstrated by a comparative study with thermal activation. The scope was extended to bis-aromatic aldehydes with various linkers, willing to display new pharmacological activities of bis-pyrazolopyridines thus obtained.

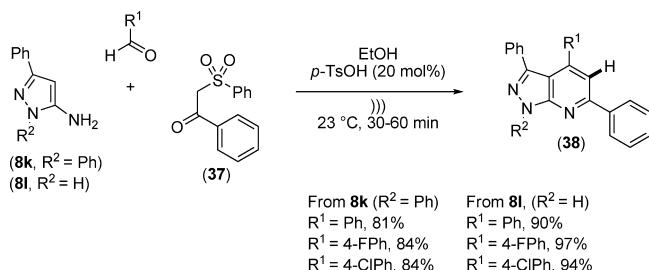
2.2.1.3. 3-Aryl-1*H*-pyrazol-5-amine Derivatives. In 2008, multicomponent synthesis of fully substituted 3-cyanopyridines was achieved through the reaction between 3-aryl-1-phenyl-1*H*-pyrazol-5-amines **8h-j**, an aldehyde, and a β -ketonitrile, leading to the corresponding pyrazolopyridine scaffolds **36** in good yields (Scheme 21).⁶⁶ Two sets of conditions were described: neat with ammonium acetate at 120 °C (conditions A) or in refluxing ethanol with a catalytic amount of triethylamine (conditions B). Environmentally friendly method A proved to be more efficient and cleaner than method B.

Alternatively, new access to pyrazolopyridines from a β -ketosulfone was reported in 2012. An ethanol solution of 1-phenyl-2-(phenylsulfonyl)ethanone (**37**), an aromatic aldehyde, and 1,3-diphenyl-1*H*-pyrazol-5-amine (**8k**) or 3-phenyl-1*H*-pyrazol-5-amine (**8l**) was sonicated at room temperature in the presence of a catalytic amount of *p*-TsOH, affording the 3-unsubstituted pyridines **38** in very good yields (Scheme 22).⁶⁷ Although the scope of the reaction was narrow in this

Scheme 21. Synthesis of Pyrazolopyridines from β -Ketonitriles



Scheme 22. Synthesis of Pyrazolopyridines from β -Ketosulfones

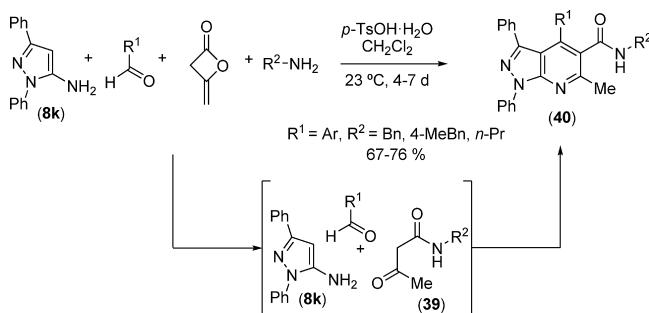


communication, a comparative study shed light on the benefits of ultrasound irradiation in terms of yields and reaction times, as supposed to performing this transformation in refluxing ethanol. Moreover, a mechanism was envisioned to rationalize the mild formation of 3-unsubstituted pyridines by loss of benzenesulfonic acid during the aromatization step.

In 2009, Shaabani's group developed similar reactions using β -ketoamides **39** as the 1,3-dicarbonyl partners.⁶⁸ Note that, unlike its ester analogues, β -ketoamides have been rarely exploited as pronucleophiles in multicomponent processes.⁶⁹ This substrate was formed *in situ* by the reaction between a primary amine and dикетене, and then reacted at room temperature with 1,3-diphenyl-1*H*-pyrazol-5-amine (**8k**) and an aromatic aldehyde in the presence of a catalytic amount of *p*-TsOH (Scheme 23), affording bicyclic derivatives of nicotinamide **40** with good yields. The reaction can last up to 1 week depending on the nature of the substrates.

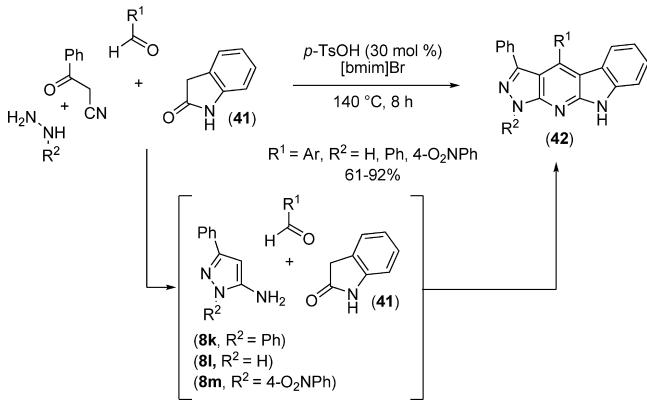
Alternatively, Ghahremanzadeh et al. described a four-component synthesis of tetracyclic pyridines using 2-indolinone **41** as pronucleophile, aromatic aldehydes, and pyrazol-5-amines **8k**, **8l**, or **8m** generated *in situ* by the combination of a hydrazine derivative with 3-oxo-3-phenylpropanenitrile.⁷⁰ As a result, a collection of α -carboline derivatives **42** was elaborated in [bmim]

Scheme 23. Four-Component Synthesis of Pyridines



Br at 140 °C, in the presence of a catalytic amount of *p*-TsOH (Scheme 24). This work represents the first multicomponent synthesis of pyrazolopyridines by *in situ* preparation of the amino-pyrazole enamine surrogate.

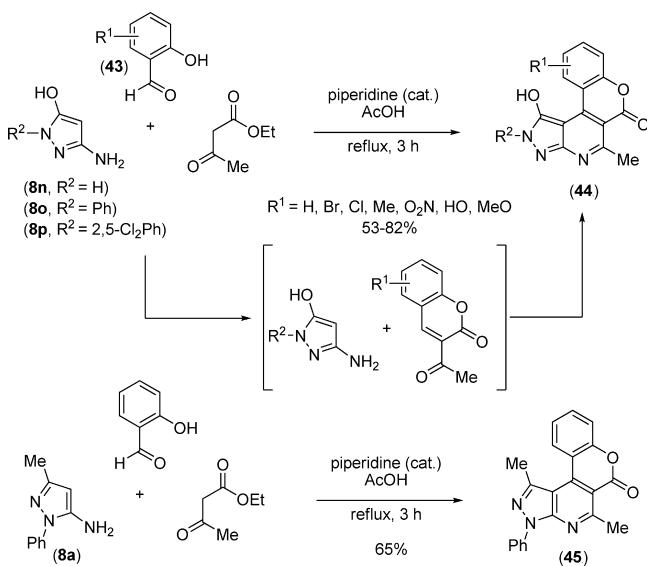
Scheme 24. In Situ Generation of 5-Aminopyrazole 8 Used in the Four-Component Synthesis of Tetracyclic Pyridines



2.2.1.4. 5-Amino-1*H*-pyrazol-3-ol Derivatives. The synthesis of pyrazolopyridines from 5-amino-1*H*-pyrazol-3-ol derivatives **8n–p** has been studied by Frolova et al.⁷¹ To the best of our knowledge, this is the sole synthesis of pyridine by MCR involving this enamine equivalent. Beside this, the originality of the method relies on the use of functionalized salicylaldehydes **43** and ethylacetacetate. The two latter reagents allegedly react together to generate acetyl coumarin intermediates. Then, condensation with the 5-amino-pyrazole and aromatization gave rise to an elaborated library of pyrazolopyridochromene scaffolds **44** in moderate to good yields (Scheme 25). A similar skeleton **45** was obtained when commonly used 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**8a**), salicylaldehyde, and ethylacetacetate were subjected to the reaction conditions, *i.e.*, reflux of acetic acid with a catalytic amount of piperidine.

2.2.2. Pyrimidine Derivatives. Various 6-membered heterocycles have also been used as enamine equivalents in

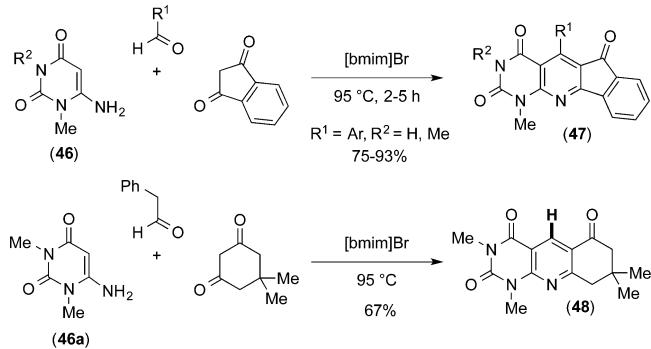
Scheme 25. Synthesis of Pyrazolopyridochromene Derivatives



these Hantzsch-type pyridine syntheses. Among them, amino pyrimidine derivatives have led to a series of interesting synthetic developments that gave access to valuable polycyclic pyridopyrimidines, although similar products may be synthesized from barbituric acids (cf., Scheme 13).

For instance, the reaction between an amino-pyrimidinedione **46**, 1,3-indandione, and an aromatic aldehyde, heated in ionic liquid [bmim]Br, gave rise to a series of tetracyclic pyridopyrimidines **47** in excellent yields (Scheme 26).⁷² Under the same

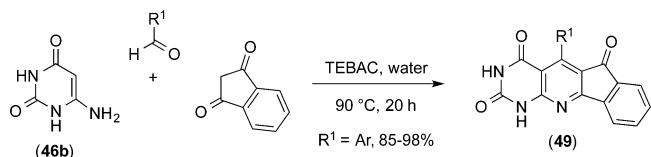
Scheme 26. Synthesis of Tetracyclic Pyridopyrimidines



conditions, the 4-unsubstituted pyridine **48** was isolated in 67% yield when phenylacetaldehyde was treated with amino-pyrimidine **46a** and dimedone. While the authors gave no explanation, the loss of a benzyl substituent during the aromatization step is likely to be a radical process (see section 8.2.2).

The same group recently reported a version of this multicomponent synthesis involving an unsubstituted pyrimidinedione. Thus, the tetracyclic heterocycles **49** were formed by heating a suspension of 6-aminouracil (**46b**), 1,3-indandione, and an aromatic aldehyde in water, in the presence of benzyltriethylammonium chloride (TEBAC) (Scheme 27).⁷³ A

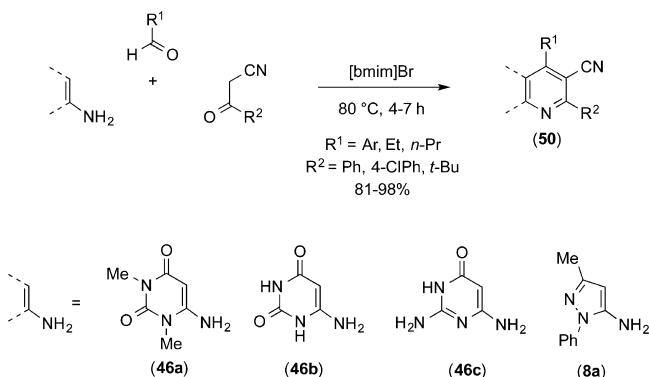
Scheme 27. Pyridopyrimidines from 6-Aminouracil



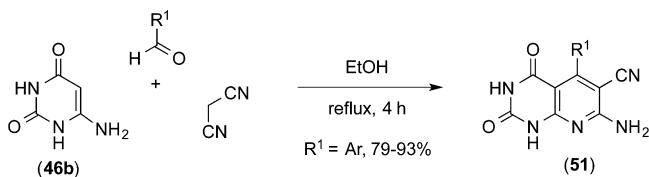
study on the recognition properties of these products as new type of anion receptors was performed. When the same reaction partners were heated at 120 °C in a mixture acetic acid/ethylene glycol (2:1), the corresponding 1,4-DHPs were obtained in moderate to good yields.⁷⁴ An extra oxidation step was required to access the desired pyridines. However, 4-unsubstituted tetracyclic pyridine was obtained directly when formaldehyde was used. Some of these pyridines proved to be promising novel topoisomerase-targeting agents.

This multicomponent strategy was extended to β -ketonitriles by Shi in 2011.⁷⁵ Ionic liquid [bmim]Br was used as solvent for this efficient synthesis of 3-cyanopyridines **50** from either aromatic or aliphatic aldehydes (Scheme 28). It is noteworthy that different amino-pyrimidine derivatives **46a–c** were engaged in this reaction as well as 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**8a**) with the same level of efficiency.

Scheme 28. Synthesis of 3-Cyano-pyridines

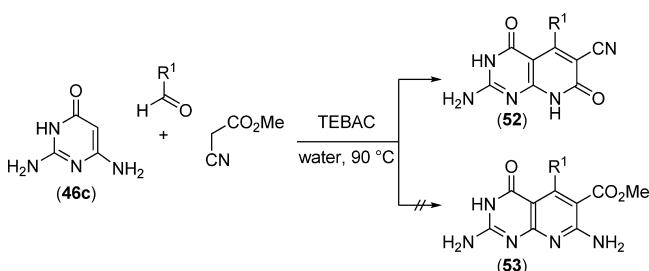


Multicomponent synthesis of pyridopyrimidines from malononitrile has also been detailed as early as 2002.⁷⁶ In fact, a solution of 6-aminouracil (**46b**), malononitrile, and an aromatic aldehyde in ethanol was heated under reflux for 4 h, affording the corresponding 2-amino-3-cyanopyridines **51** in good to excellent yields (Scheme 29). Derivatization of these pyridines led to new products that displayed interesting antiviral and cytotoxic activities.

Scheme 29. Synthesis of 2-Amino-3-cyanopyridines from 6-Aminouracil (**46b**)

The same three-component sequence was developed later in water at 90 °C, in the presence of TEBAC. In these conditions, the scope of the reaction was more substantial than the latter report, especially concerning the enamine substitute.⁷⁷ However, when malononitrile was replaced by methyl cyanoacetate, the corresponding 2-pyridones **52** were obtained (Scheme 30).

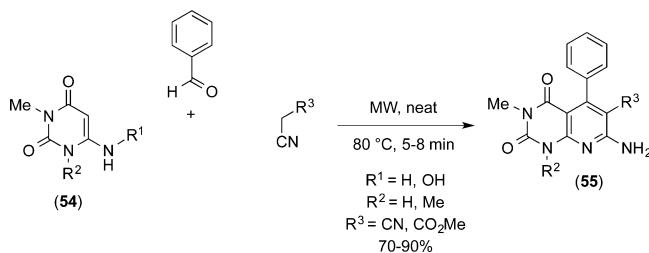
Scheme 30. Attempted Synthesis of 2-Amino-pyridines in Water



instead of the expected 2-amino-nicotinate derivatives **53**, as previously reported by Devi et al. with similar reactions conducted under microwave irradiation.⁷⁸ Indeed, under these conditions, a neat mixture of 6-aminouracil (**46c**) or 6-hydroxylamino-uracil derivatives **54** reacted with benzaldehyde and either malononitrile or methyl cyanoacetate to access pyridopyrimidines **55** in good to excellent yields (Scheme 31).

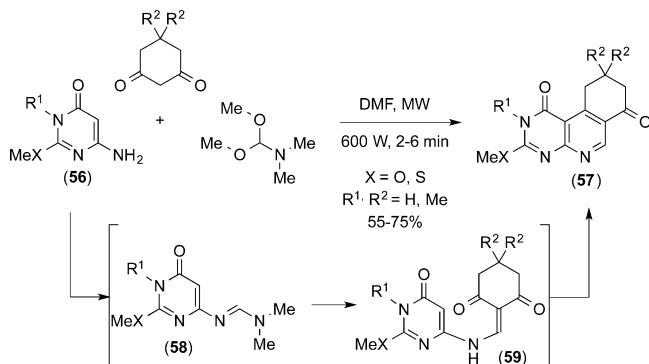
More recently, different 2-amino-pyrimidines, including thiouracils **56** ($X = S$), were used in combination with cyclic

Scheme 31. Pyridopyrimidines from Either Malononitrile or Methyl Cyanoacetate



1,3-diketones and *N,N*-dimethylformamide dimethylacetal (DMF-DMA) in a microwave-assisted process.⁷⁹ Starting from cyclohexanediones, the expected linear tricyclic pyridine has not been observed since Quiroga et al. obtained mainly bent structures **57** (Scheme 32). The authors demonstrated that the

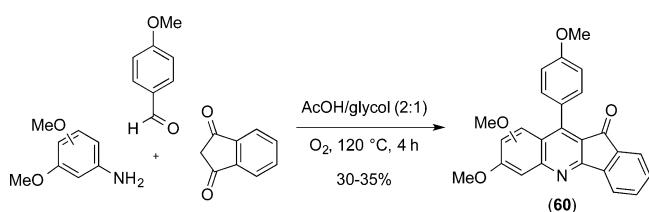
Scheme 32. Original Bent Tricyclic Pyridines from 6-Aminouracil Derivatives



mechanism consists of the preliminary condensation of DMF-DMA with the amino-pyrimidine, affording the formamidine **58**. Then, the addition of dimedone leads to the formation of an enamine intermediate **59** that undergoes a subsequent cyclodehydration. A [4 + 2] cycloaddition between the imine intermediate and the enol form of the 1,3-dicarbonyl derivative has not been considered in this study. From a biological point of view, the resulting bent pyridines **57** showed interesting antifungal properties.

2.2.3. Aniline Derivatives. Finally, electron-rich anilines have been used as enamine equivalents in a straightforward construction of polycyclic scaffolds. Thus, dimethoxyanilines reacted with 1,3-indandione and *p*-methoxybenzaldehyde at 120 °C in a 2:1 acetic acid/glycol mixture under a stream of oxygen, leading to the corresponding azafluorenones **60** (Scheme 33).⁸⁰ The associated yields are modest with these substrates, and the resulting pyridines were inactive against cancer cell lines. Alternatively, the methodology was also

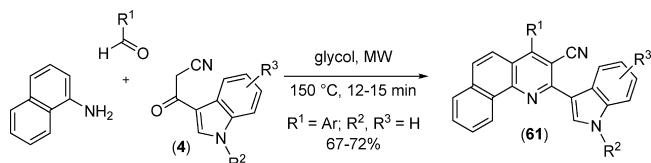
Scheme 33. Electron-Rich Anilines as Enamine Equivalents



extended to several amino-heterocycles resulting in a large library of compounds, among which a pyrimidine-based analogue displayed interesting pro-apoptotic activity.

In 2008, Zhu et al. developed a three-component pyridine synthesis by combining an aromatic aldehyde, β -ketonitrile 4, and α -naphthylamine in glycol under microwave irradiation (Scheme 34).⁵⁰ The corresponding benzoquinoline derivatives 61 were isolated in moderate to good yields, presumably owing to the low reactivity of the naphthylamine as enamine equivalent.

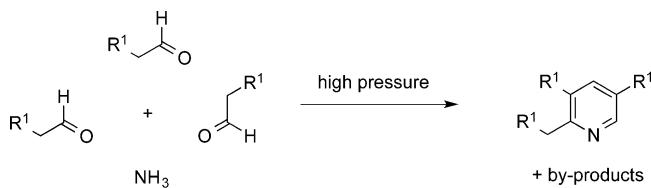
Scheme 34. Naphthylamine as Enamine Equivalent



3. CHICHIBABIN REACTION

In 1906, Chichibabin discovered a pseudo-four-component pyridine synthesis from 3 equiv of an enolizable aldehyde and 1 equiv of ammonia (Scheme 35).⁸¹ The original reaction was carried out under high-pressure conditions, resulting in the formation of numerous byproducts.

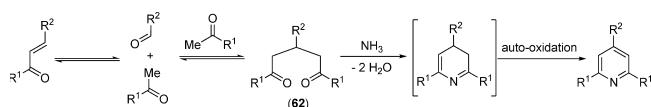
Scheme 35. Chichibabin Pyridine Synthesis



In 1949, Frank and Seven revisited this strategy, trying to understand the mechanism, testing diverse possible intermediates, and they proposed a hypothesis to explain the generation of the numerous byproducts.⁸²

Besides, with an excess of ammonia, the reaction is cleaner and more efficient. But their work showed as well that unexpected 2,4,6-trisubstituted pyridines were obtained from α,β -unsaturated ketones (Scheme 36). This could be explained by the reversibility

Scheme 36. Birth of the Multicomponent Chichibabin Pyridine Synthesis



of the aldol condensation that, by successive equilibria, would result in the formation of a 1,5-dicarbonyl product 62. The latter may undergo a cyclodehydration in the presence of ammonia, with the driving force of the reaction being the aromatization process.

It is on this assumption that many multicomponent synthetic ways have been developed after a while to get 2,4,6-trisubstituted pyridines. These new experimental conditions implied 1 equiv of ammonia, one aldehyde, an enolizable ketone, and either a second equivalent of the same ketone or a 1,3-dicarbonyl

derivative. By the nature of these reactants, this strategy looks like the Hantzsch pyridine synthesis.

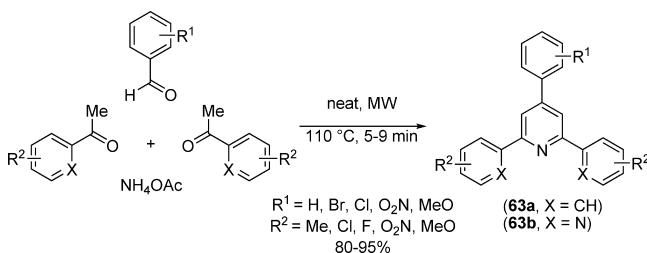
In most of the publications related to this methodology, aromatic aldehydes and acetophenone derivatives are employed, resulting in the formation of 2,4,6-triarylpyridines, known as Kröhnke pyridines. This appellation comes from the Kröhnke pyridine synthesis, which is addressed in section 7, and represents a privileged access to these structures. However, this frequently creates confusions regarding the nature of the employed reaction. As a consequence, it is not unusual to be faced with publications describing a Chichibabin reaction to access triarylated pyridines whereas the authors present their works as a Kröhnke reaction. The aim of this section is also to clarify this tangle with the following examples. Ultimately, it is important to remember that this methodology allows the regioselective formation of polysubstituted pyridines.

3.1. From Acetophenone Derivatives

Ammonium acetate is the ammonia source of choice for this pseudo-four-component reaction. In combination with an aromatic aldehyde and 2 equiv of a substituted acetophenone derivative, this transformation accessed the desired 2,4,6-triarylpyridines. Many successful conditions have been reported since 2005.

For instance, when a neat mixture of the four partners was subjected to microwave irradiation, 2,4,6-triarylpyridines 63a were obtained in excellent yields and short reaction times (Scheme 37).⁸³ This simple catalyst- and solvent-free procedure

Scheme 37. Catalyst- and Solvent-Free Chichibabin Pyridine Synthesis



remains extremely attractive for the sustainability perspective. Moreover, this method proved to be of significant interest for the synthesis of terpyridines 63b. The same group reported similar strategies to access 2,4,6-triarylpyridines using either glycol⁸⁴ or water⁸⁵ as the solvent, while focusing on the straightforward synthesis of terpyridines from acetylpyridine. In both systems, microwave irradiation was used to access the desired products in very good yields (80–96%) compared with classical heating (70–85%) and in shorter reaction times.

Various heterogeneous catalysts have also been encountered in the Chichibabin pyridine synthesis from acetophenone derivatives. In 2007, Heravi found that a Preyssler-type heteropolyacid of general formula $H_{14}[NaP_5W_{30}O_{110}]$ catalyzed efficiently this reaction while being reusable up to 3 times without any loss of activity.⁸⁶ This solvent-free reaction was performed at 120 °C and afforded the expected pyridines in good to excellent yields (Table 1, entry 1). At the same time, Nagaraju reported silica-supported perchloric acid particles as recyclable and efficient heterogeneous catalyst of this reaction.⁸⁷ Similar conditions (neat, 120 °C) were applied to a large panel of aromatic aldehydes and acetophenones (Table 1, entry 2). More recently, closely related conditions were reported with barium chloride

Table 1. Heterogeneous or Homogeneous Catalysts in the Chichibabin Pyridine Synthesis from Acetophenones

entry	conditions	yield	ref
1	120 °C, 3.5–7 h H ₁₄ [NaP ₅ W ₃₀ O ₁₁₀]	50–98%	86
2	120 °C, 4–6 h HClO ₄ /SiO ₂	68–88%	87
3	120 °C, 15–120 min BaCl ₂ /nano-SiO ₂	70–94%	88
4	120 °C, 6 h I ₂ (20 mol %)	48–61%	89
5	120 °C, 1.5–3.5 h [HO ₃ S(CH ₂) ₄ mim]HSO ₄ (20 mol %)	82–93%	90
6	130 °C, 4–7.5 h wet-TCT (5 mol %)	58–86%	91

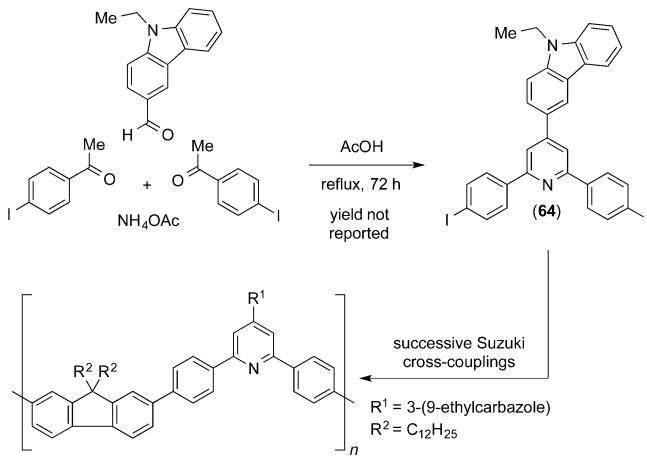
dispersed on silica gel nanoparticles as heterogeneous catalyst (Table 1, entry 3).⁸⁸ Interestingly, the reaction times were considerably shortened with this catalyst while maintaining good to excellent yields.

The Chichibabin-type synthesis of 2,4,6-triarylpyridines has also been carried out with homogeneous catalysts such as, for example, molecular iodine (20 mol %) under solvent-free conditions (Table 1, entry 4).⁸⁹ However, pyridines were usually obtained in moderate yields in comparison with other available conditions. In 2010, a reusable ionic liquid catalyst bearing a Brønsted acid was reported, affording the corresponding pyridines in good yields and reasonable reaction times (Table 1, entry 5).⁹⁰ An optimization revealed that 20 mol % of the ionic liquid was optimal while conducting the reaction without any solvent at 120 °C. Shortly after, homogeneous catalyst 2,4,6-trichloro-1,3,5-triazine (TCT) was also studied.⁹¹ Only 5 mol % of wet TCT was sufficient to reach moderate to good yields of 2,4,6-triarylpyridines at 130 °C under neat conditions (Table 1, entry 6). Best results were achieved with moisturized TCT, which according to the authors might release cyanuric acid along with hydrochloric acid. The latter was supposed to be the effective catalyst of the reaction.

In 2009, Liaw et al. applied this chemistry to the synthesis of a pyridine-containing polymer.⁹² The reaction of *para*-iodoacetophenone, ammonium acetate, and an aromatic aldehyde led to the corresponding triarylpyridine **64**, which was subsequently subjected to successive Suzuki cross-couplings (Scheme 38). The resulting polymer showed good resistance to heat, good solubility in numerous organic solvents compared to all-carbon ones, and above all interesting optical properties.

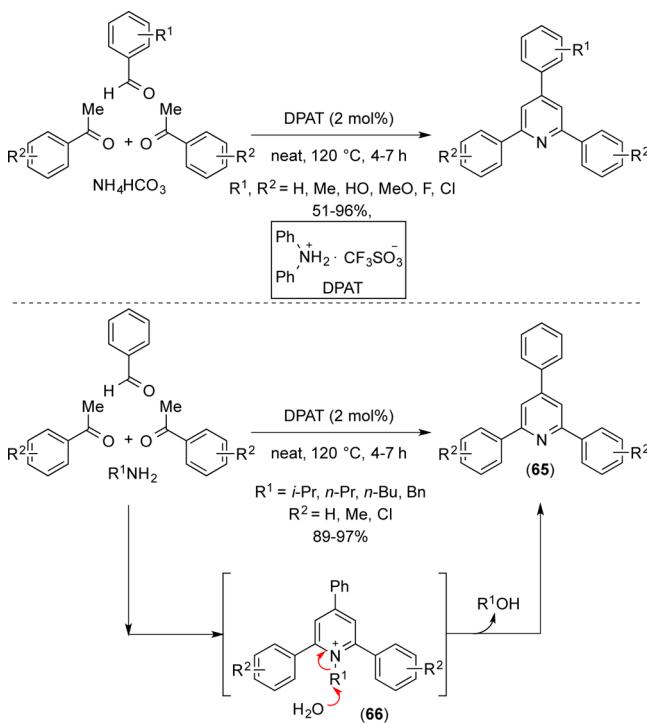
In 2012, diphenylammonium triflate (DPAT) was reported as an efficient catalyst of the modified Chichibabin pyridine synthesis.⁹³ The originality of this work relied on the use of diverse environmentally benign sources of ammonia. First, ammonium bicarbonate proved to be the best nitrogen source, but when the authors turned their attention to the application of

Scheme 38. Polymer Synthesis-Oriented Chichibabin Reaction



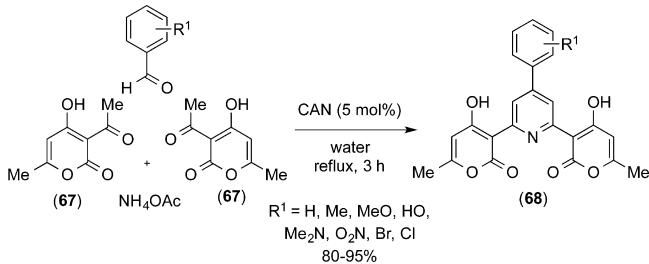
primary alkylamines in this sequence in order to synthesize the corresponding 1,4-DHPs, they surprisingly identified the corresponding pyridines **65** in excellent yield (Scheme 39). By identifying the byproduct as an alcohol, they proposed a mechanism involving reaction of water with a transient pyridinium intermediate **66**.

Scheme 39. DAPT-Catalyzed Chichibabin Reaction

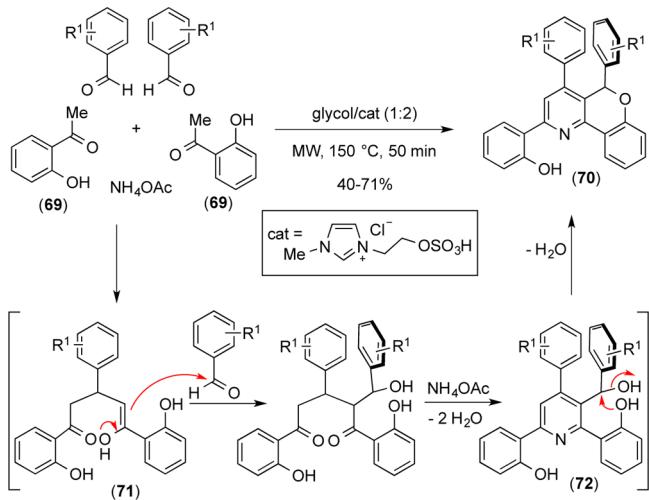


Very recently, Penta and Vedula developed the condensation of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **67** as acetophenone equivalent with aromatic aldehydes and ammonium acetate with 5 mol % of cerium(IV) ammonium nitrate (CAN) in refluxing water (Scheme 40).⁹⁴ A series of 2,4,6-trisubstituted pyridines **68** was formed in good to excellent yields.

An interesting reactivity was described by Wu et al. when 2'-hydroxyacetophenone **69** was used.⁹⁵ In this modified Chichibabin scenario, an extra equivalent of aromatic aldehyde

Scheme 40. Synthesis of 2,6-Bispyranonepyridines

was involved in the reaction (Scheme 41). Diverse 5*H*-chromenopyridines **70** were formed at 150 °C under microwave

Scheme 41. Pseudo-Five-Component Modified Chichibabin Pyridine Synthesis

irradiation in the presence of an imidazolium-type ionic liquid as the catalyst. According to the mechanism proposed by the authors, the first step leads to the expected 1,5-dicarbonyl compound **71**. But rather than a condensation with ammonium acetate, the reaction seemed to evolve first toward an aldolization of this intermediate with a second equivalent of the aromatic aldehyde, followed by the condensation with ammonia and the

aromatization to pyridine **72**. Finally, an intramolecular etherification step occurs between the phenol function and the secondary benzylic alcohol resulting from the aldolization reaction.

3.2. From Cyclic Ketones

Replacing the acetophenone derivatives by cyclic ketones has also been studied in the past decade. Depending on the nature of the ketone, tri- or pentacyclic pyridines are usually obtained by this method.

α -Tetralone and 1-indanone have been widely used in this Chichibabin pyridine synthesis modification. Usually, conditions reported for the synthesis of 2,4,6-triarylpyridines from acetophenone derivatives have been extended to these two substrates with success. Thus, Tu's group reported the synthesis of symmetrical pentacyclic 4-substituted pyridines **73** (*n* = 1) or **74** (*n* = 2) with yields mainly higher than 90%, without any solvent (Table 2, entries 1 and 2),⁸³ in glycol (Table 2, entries 3 and 4)⁸⁴ or water (Table 2, entry 5).⁸⁵ Later, this reaction has been carried out at 70 °C under solvent- and catalyst-free conditions. Heating a mixture of the four partners for only 10 min resulted in excellent yields (90–95%).⁹⁶

Synthesis of pentacyclic pyridines **74** from α -tetralone has also been developed with DPAT as the catalyst of the reaction with ammonium bicarbonate as the ammonia precursor (Table 2, entry 6).⁹³ These conditions were alternatively applied to formaldehyde leading to the 4-unsubstituted pyridine **75** in somehow lower yield (Table 2, entry 7). In 2011, Wu et al. developed an access to these pentacyclic scaffolds under microwave irradiation in acetic acid (Table 2, entry 8).⁹⁷ Moderate yields were obtained for this Chichibabin-like transformation.

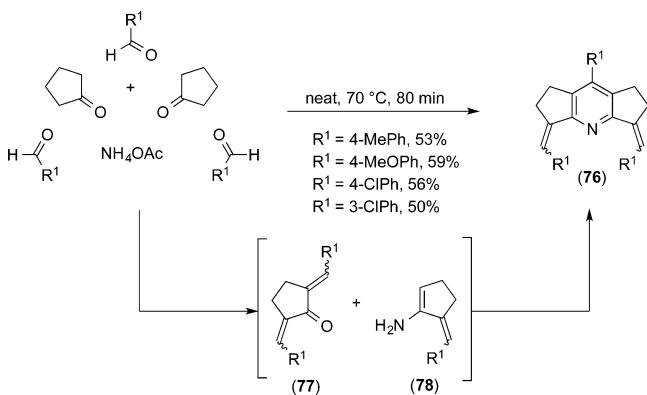
While 1-indanone and α -tetralone have been explored, formation of pyridines from less activated aliphatic cyclic ketones remained a synthetic challenge until 2008. A pseudo-six-component Chichibabin-type reaction was then reported using 2 equiv of cyclopentanone, 3 equiv of an aromatic aldehyde, and ammonium acetate (Scheme 42).⁹⁶ The resulting symmetrical pyridines **76** were obtained under solvent- and catalyst-free conditions at 70 °C. The *E/Z* geometry of trisubstituted alkene intermediates **77** and **78** was not mentioned in the discussion. The associated yields are moderate, and aliphatic aldehydes are not compatible. But this particular reactivity has opened a new

Table 2. Modified Chichibabin Synthesis of Pentacyclic Pyridines from 1-Indanone or α -Tetralone

(73, R¹ = Ar, n = 1)
(74, R¹ = Ar, n = 2)
(75, R¹ = H, n = 2)

entry	ammonia source	R ¹	n	conditions	product	yield	ref
1	NH ₄ OAc	Ar	1	neat, MW, 110 °C, 5–9 min	73	90–96%	83
2	NH ₄ OAc	Ar	2	neat, MW, 110 °C, 5–9 min	74	90–95%	83
3	NH ₄ OAc	Ar	1	glycol, MW, reflux (open flask), 5–9 min	73	90–93%	84
4	NH ₄ OAc	Ar	2	glycol, MW, reflux (open flask), 5–9 min	74	91–93%	84
5	NH ₄ OAc	Ar	1	water, MW, 130 °C, 8–10 min	73	89–97%	85
6	NH ₄ HCO ₃	Ar	2	DPAT (2 mol %), neat, 120 °C, 4.5–8 h	74	75–91%	93
7	NH ₄ HCO ₃	H	2	DPAT (2 mol %), neat, 120 °C, 4.5–8 h	75	43%	93
8	NH ₄ OAc	Ar	2	AcOH, MW (520 W), 2–4 min	74	68–79%	97

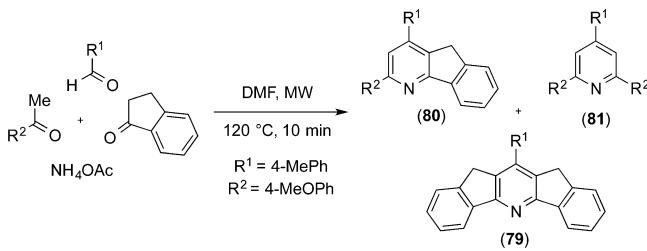
Scheme 42. Pseudo-Six-Component Chichibabin Reaction



window to access original and polysubstituted pyridines in a single operation. Recently, yields have been slightly improved by performing the reaction in acetic acid under microwave irradiation (65–78%). The scope of the reaction has also been extended to cyclohexanone in similar yields (67–75%).⁹⁷

Finally, using 1 equiv of 1-indanone in combination with an acetophenone derivative, an aromatic aldehyde, and ammonium acetate resulted in low selectivities. A mixture of pentacyclic symmetrical and tricyclic or monocyclic pyridines **79**, **80**, or **81**, respectively, is usually observed, but the ratio of the three products was not provided (Scheme 43). To overcome this issue,

Scheme 43. Low Regioselectivity by Combining 1-Indanone and Acetophenone Derivatives

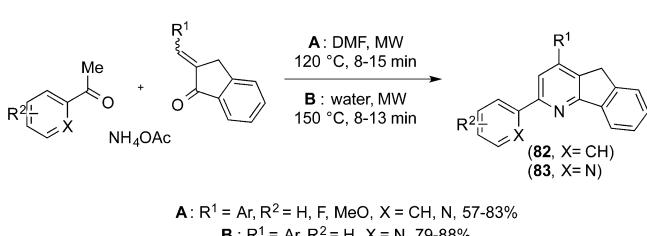


Tu has developed a three-component reaction between an acetophenone derivative, 2-arylidene-1-indanones, and ammonium acetate in either DMF⁹⁸ or water⁹⁹ under microwave irradiation (Scheme 44). This synthesis of pyridines 82 and bipyridines 83 could be ranked as a Michael-addition-based MCR (see section 8).

3.3. From 1,3-Indanedione

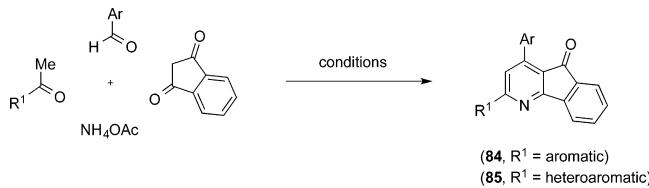
Tu was also interested in the modified Chichibabin procedure when replacing the second equivalent of acetophenone by 1,3-indanedione. The products obtained by this strategy are 4-

Scheme 44. Regioselective Synthesis of Substituted Indenopyridines



azafluorenone derivatives **84** (R^1 = aromatic substituent) or **85** (R^1 = heteroaromatic substituent), and the reaction can be shortened to a few minutes under microwave irradiation (Table 3, entries 1 and 2).⁹⁸ The efficiency of the multicomponent reaction to access complex skeleton is once again remarkable.

Table 3. Chichibabin Synthesis of 4-Azafluorenones



Entry	R ¹	Conditions	Product	Yield	Ref.
1		DMF, MW, 120 °C, 6-15 min	84	65-89%	98
2		DMF, MW, 120 °C, 6-15 min	85	57-89%	98
3		H ₂ O, MW, 150 °C, 6-14 min	85	78-92%	99
4		L-proline (15 mol%) EtOH, 23 °C, 2.5-4 h	85	82-92%	100
5		L-proline (15 mol%) EtOH, 23 °C, 2.5-4 h	84	88-93%	100

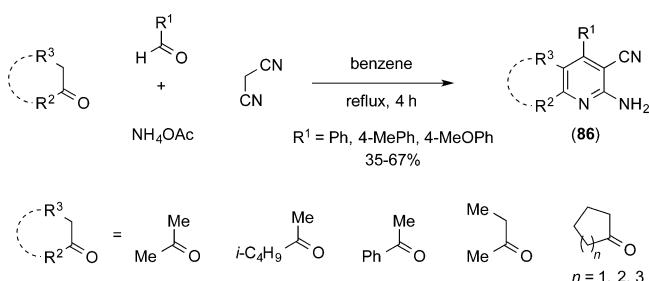
Shortly after, the same group focused on the synthesis of 2,2'-bipyridines **85** using 2-acetylpyridine as a derivative of acetophenone (Table 3, entry 3).⁹⁹ Switching from DMF to water at 150 °C in a sealed tube led to better results and facilitated isolation of the products. Finally, formation of 4-azafluorenones has experienced a dramatic improvement in 2010 with the works of Mukhopadhyay et al.¹⁰⁰ Smoother experimental conditions were developed using L-proline as catalyst at room temperature in ethanol (Table 3, entries 4 and 5). Reaction times remained reasonable, and associated yields were excellent. These mild conditions were also applied to regular Chichibabin pyridine synthesis with 2 equiv of acetophenone derivatives. The corresponding 2,4,6-triarylpyridines were isolated in very good yields (82–93%).

3.4. From Malononitrile

As early as 1980, Kambe and Saito were interested in a synthetic approach to 2-aminopyridines and thought about using malononitrile in the modified Chichibabin synthesis. Thus, they showed that the reaction of malononitrile with aromatic aldehydes, ammonium acetate, and diverse cyclic or acyclic ketones could lead to the desired pyridines in refluxing benzene in only 4 h (Scheme 45).¹⁰¹ The yields were not spectacular, but these pioneering works paved the way for new access to 2-amino-3-cyanopyridines **86**. During the past decade, numerous variations have been reported in order to improve the efficiency of the method. For instance, yields have been increased and reaction times shortened when submitting a mixture of the four partners to microwave irradiation.¹⁰²

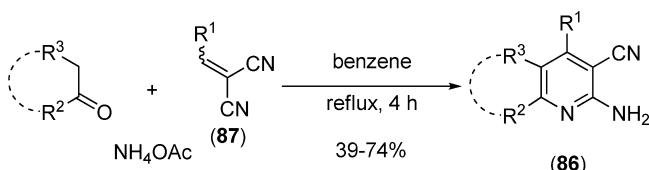
While studying the mechanism,¹⁰¹ arylidene malononitrile **87** resulting from a Knoevenagel condensation was identified as an intermediate. Thus, starting from this intermediate, ammonium

Scheme 45. Kambe and Saito's Pioneering Work on the Modified Chichibabin Synthesis from Malononitrile



acetate, and the same set of either cyclic or acyclic enolizable ketones, identical pyridines were formed in slightly better yields (Scheme 46). This modification of the system might be seen as a

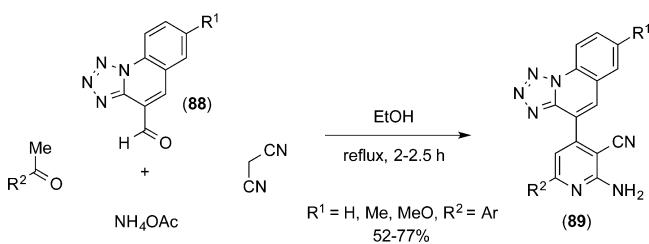
Scheme 46. Michael-Addition-Based Three-Component Modification of the Chichibabin Synthesis



Michael-induced multicomponent synthesis of pyridines. Analogous methods will be discussed in the appropriate section (see section 8).

Combining two potentially bioactive moieties to form new heterocyclic scaffolds is a known process in drug discovery. In 2009, Mungra et al. reported this modified Chichibabin reaction with malononitrile, acetophenone derivatives, ammonium acetate, and tetrazolo[1,5-*a*]quinoline-4-carboxaldehyde (88) in refluxing ethanol (Scheme 47).¹⁰³ Pyridines 89 thus obtained

Scheme 47. Application of the Chichibabin Synthesis to Potential Antibacterial Agents

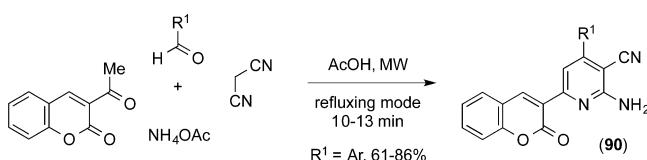


were tested against a panel of bacteria, and their antifungal properties were also studied, resulting in several attractive leads. Among the library of products, a few pyridines exhibited interesting antimicrobial activity against some strains of both Gram negative and Gram positive bacteria.

In order to develop new drugs, the same concept was applied to 3-acetylcoumarine as the enolizable ketone partner under microwave irradiation in acetic acid (Scheme 48).¹⁰⁴ Corresponding 3-(6-pyridyl)coumarins 90 were isolated in moderate to good yields, but no biological activity was established for these products.

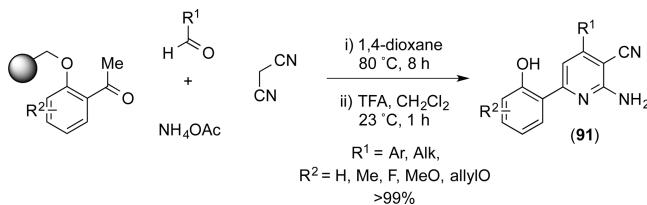
Solid-supported synthesis of 2-amino-3-cyanopyridines through this modified Chichibabin reaction has been studied by Shintani et al.¹⁰⁵ In fact, 2-hydroxyacetophenone derivatives were attached to a Wang resin and reacted with an excess of

Scheme 48. Synthesis of Pyridocoumarin Derivatives



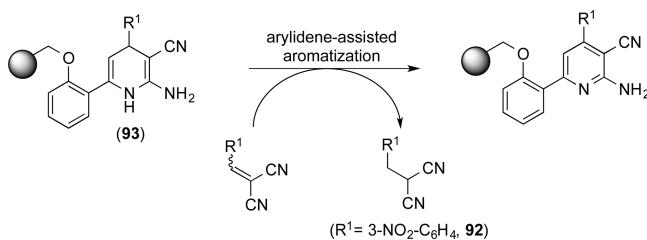
aldehyde (3 equiv), malononitrile (3 equiv), and ammonium acetate (6 equiv) in 1,4-dioxane at 80 °C for 8 h. The polystyrene beads were then cleaved with trifluoroacetic acid (TFA) releasing the expected pyridines 91 in quantitative yields (Scheme 49).

Scheme 49. Solid-Supported Chichibabin Synthesis



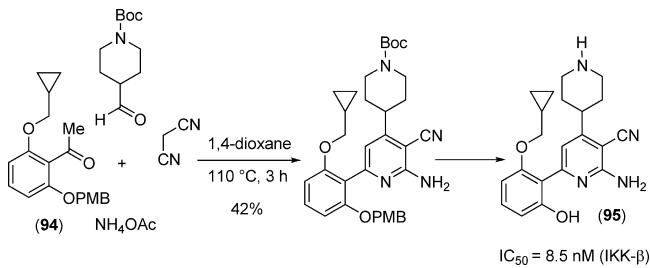
It is noteworthy that these conditions were applied to aliphatic aldehydes, including α -branched ones. α -Branched aldehydes are prone to be cleaved during the final aerobic oxidation step (see discussion in section 8.2.2) and are therefore extremely challenging substrates. To explain this success, another aromatization process must have occurred. It turns out that the authors isolated reduced arylidene malononitriles 92 in the reaction mixture. This product would result from oxidation of the 1,4-DHP intermediate 93 by excess arylidene malononitrile formed during the reaction (Scheme 50).

Scheme 50. Hypothetic Arylidene-Assisted Mechanism of the Aromatization Step

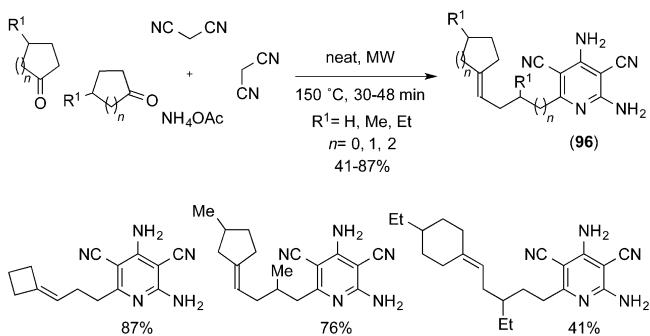


Shortly after, the same group performed an impressive structure–activity relationship study on these pyridines formed by either solid-supported method or homogeneous reactions. Subsequent transformations led to potent inhibitors of IκB kinase (IKK- β) 95, a serine-threonine protein kinase that plays a significant role in the destruction of cells after a cerebral vascular accident.¹⁰⁶ The best inhibitor candidate was synthesized from malononitrile, ammonium acetate, 4-formyl-N-Boc-piperidine, and acetophenone derivative 94 in 1,4-dioxane at 110 °C (Scheme 51). After final deprotections, this inhibitor displayed a significant *in vivo* activity as well as good oral bioavailability in mice and rats.

Finally, an original and efficient synthesis of pentasubstituted pyridines 96 was discovered in 2011. This pseudo-five-component reaction involved 2 equiv of malononitrile with 2 equiv of a cycloalkanone and ammonium acetate under microwave irradiation and solvent-free conditions (Scheme

Scheme 51. Chichibabin-Based Synthesis of IKK- β Inhibitors

52).¹⁰⁷ While yields are moderate to good, this unique transformation featured multiple bonds breaking and forming events in a single, atom-economic operation.

Scheme 52. Modified-Chichibabin Pseudo-Five-Component Reaction

A reasonable mechanism was suggested to rationalize the formation of these pyridines (Scheme 53). Dimerization of the Knoevenagel adduct between cyclic ketone and malononitrile was supposed to lead to the spiro-tricyclic intermediate **97** via a formal [4 + 2] cycloaddition. Then, addition of ammonia onto one of the nitrile functionalities followed by intramolecular aza-Michael addition might form the spiro-tetracyclic intermediate **99** via **98**. Ring-opening and final aromatization of the 1,2-DHP **100** would give the observed pentasubstituted pyridine **96**. To reinforce this hypothesis, spiro intermediate **97** was isolated from the reaction mixture and subjected to ring-opening under the same reaction conditions with ammonium acetate. The corresponding pyridine was then obtained in 83% yield, thus supporting the proposed mechanism.

3.5. From β -Carbonylnitriles

β -Carbonylnitriles are commonly employed in this adaptation of the Chichibabin reaction, and most of it 3-(cyanoacetyl)indoles, easily prepared from Bergmann's method.⁴¹ In combination with 2-acetylpyridine, aromatic aldehydes, and ammonium acetate, these substrates led to the formation of the corresponding 6-(indol-3-yl)-2,2'-bipyridines **101**. For example, Thirumurugan and Perumal developed a catalyst- and solvent-free access to these heterocyclic building blocks (Table 4, entry 1). Reaction times were considerably shortened and yields improved to some extent when the four-component reaction was carried out under microwave irradiation as opposed to conventional heating (Table 4, entry 2).¹⁰⁸ This strategy was also applied to the formation of useful bis(bipyridyl) ligands **102** for the metal catalysis from bisaldehyde **13**. Finally, a small library of 2,2'-bipyridines **104** was also elaborated from bis-Michael acceptors **103**, still with a ligand/metal emphasis. Afterward, in a complete study, the reaction was extended to 2-acetylfuran in place of 2-

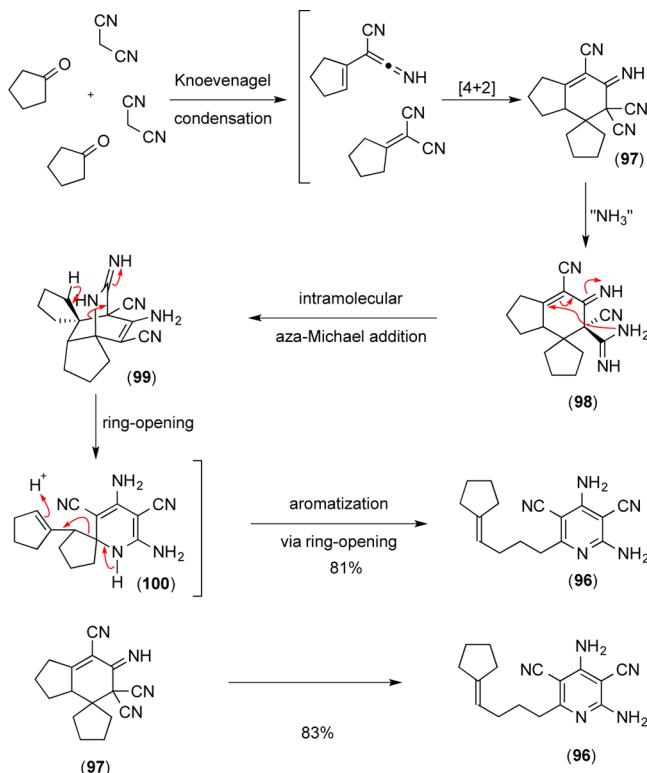
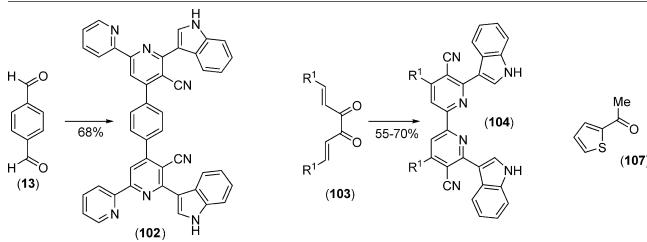
Scheme 53. Proposed Mechanism for the Modified-Chichibabin Pseudo-Five-Component Reaction

Table 4. Synthesis of Indolopyridines from 3-(Cyanoacetyl)indoles

Entry	Ar ¹	R ¹	R ²	Conditions	Product	Yield	Ref.
1	Phenyl	H	H	Neat, 120 °C, 5.5-7.5 h	101	67-89%	108
2	Phenyl	H	H	Neat, MW, 150 °C, 13-18 min	101	72-91%	108
3	Phenyl	H, Me	H, Me, Br	n-BuOH, 100 °C, 6-13 h	101	55-82%	110
4	Phenyl	H	H	AcOH/glycol (1:2), MW, 110-130 °C, 8-12 min	105	72-89%	111
5	Phenyl	H	H	I ₂ (10 mol%), AcOH, reflux, 6-10 h	106	59-77%	112

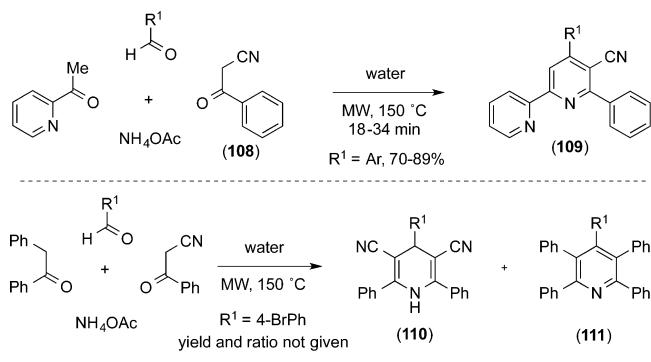


acetylpyridine.¹⁰⁹ Moreover, *ortho*-substituted aromatic aldehydes seemed to hamper the aromatization step since the corresponding 1,4-DHPs were isolated as major products. An extra oxidation step was required to form the desired pyridines.

Contemporaneously, Zhao et al. reported a similar reaction to access indolo-2,2'-bipyridine derivatives from substituted 3-(cyanoacetyl)indoles **4** (Table 4, entry 3).¹¹⁰ The reaction was carried out in *n*-butanol at 100 °C with a large panel of aromatic aldehydes. However, yields remained somewhat moderate (55–82%) owing to the stability of the intermediate 1,4-DHPs. A one-pot, two-step procedure including DDQ-mediated oxidation was alternatively developed to increase the yields (79–95%). On the basis of a similar strategy, substituted acetophenones have also been effectively used for the synthesis of indolopyridines **105** in acetic acid/glycol (1:2) solvent system under microwave irradiation (Table 4, entry 4).¹¹¹ Short reaction times and good yields made these conditions attractive. More recently, Zeng and Cai reported the use of a catalytic amount of molecular iodine in acetic acid or neat to promote this four-component reaction leading to indolopyridines **106**.¹¹² These conditions were not only suitable for 3-acetylpyridine or a variety of substituted acetophenones as substrates, but also allowed extension of the scope to 2-acetylthiophene (**107**) (Table 4, entry 5).

Other types of β -carbonylated nitriles were successful partners in this reaction. The use of 3-oxo-3-phenyl-propanenitrile (**108**) associated with 2-acetylpyridine in water at 150 °C under microwave irradiation resulted in an important chemical library of tetrasubstituted bipyridines **109** (Scheme 54).¹¹³ The reaction

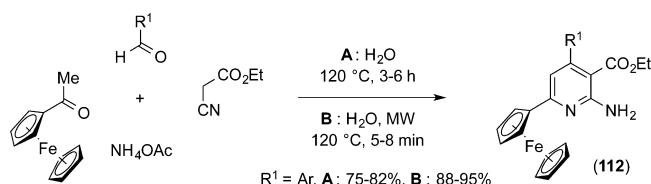
Scheme 54. Chichibabin Reaction with β -Ketonitrile **108**



was also carried out with a series of substituted acetophenones. However, the use of 1,2-diphenylethanone resulted in the formation of symmetrical 1,4-DHP **110** along with pyridine **111**.

Finally, Zhang et al. described the use of ethyl cyanoacetate to synthesize 2-aminopyridines **112** (Scheme 55).¹¹⁴ Under

Scheme 55. Chichibabin Synthesis of Ferrocenyl-2-aminopyridines



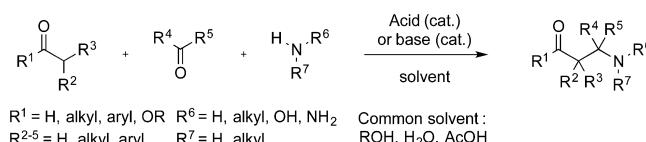
optimized conditions, the cyclization occurred on the nitrile group instead of the ester functionality since no 2-pyridone was observed. These works focused on the use of acetylferrocene, in combination with an aromatic aldehyde and ammonium acetate, reacting together at 120 °C in aqueous medium. A comparative study demonstrated that microwave irradiation was more efficient than conventional heating in oil bath. Besides, these

conditions were also successfully expanded to the synthesis of 2-amino-3-cyanopyridine scaffolds from malononitrile.

4. PYRIDINE SYNTHESIS BASED ON THE MANNICH REACTION

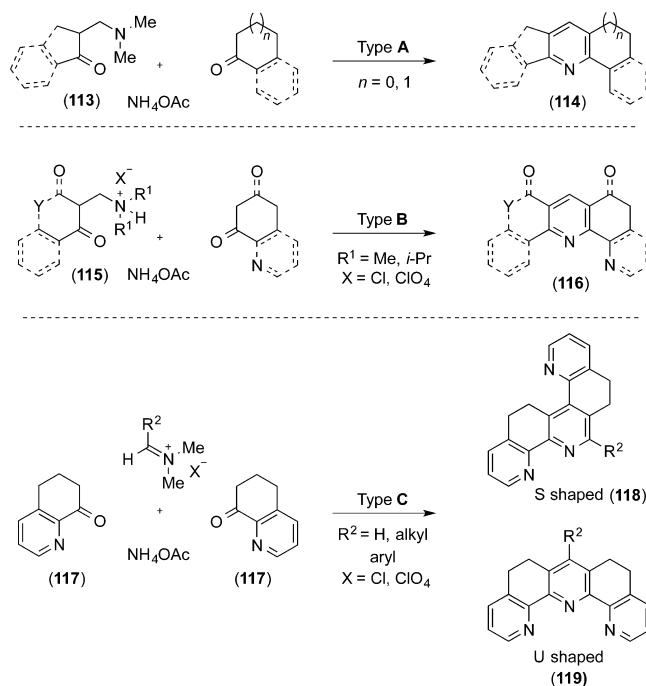
The Mannich reaction discovered in 1912 is typically the condensation of a compound containing an activated C–H bond with a primary or secondary amine, and a nonenolizable aldehyde or ketone to form β -aminocarbonyl derivatives, known as Mannich bases (Scheme 56).¹¹⁵ This sequence is based on the chemistry of iminiums, and is of great interest for building up heterocyclic targets.

Scheme 56. General Mannich Reaction



Risch and co-workers have essentially studied the application of this reaction to the synthesis of pyridines in the 1990s. This methodology was particularly adapted to the synthesis of bi-, ter-, and oligopyridines and, more generally, allowed the access to polycyclic pyridines. The approach developed by this group can be divided in three types of reactions (A–C) depending on the substrates used (Scheme 57). In all cases, ammonium acetate proved to be the ammonia source of choice.

Scheme 57. Mannich-Based Syntheses of Polycyclic Pyridines



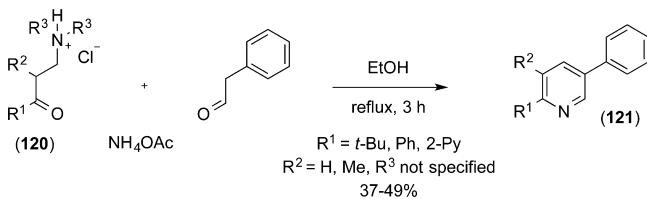
The type A directly implied previously prepared Mannich bases **113** and has been principally used in order to synthesize polycyclic monopyridines **114**. The Mannich base substrate is generally cyclic and was reacted with indanone at 160 °C in DMF¹¹⁶ or with a cyclohexanone derivative in refluxing ethanol.¹¹⁷ Typical yields ranged from 15% to 60%.

The type B employed the protonated forms of Mannich bases **115**. It is, without any doubt, the most exploited version, which principally enlarged the way to polycyclic bipyridines. The protonated Mannich bases have been synthesized from cyclohexanone or cyclopentanone,¹¹⁸ from cyclohexanedione¹¹⁹ or chromanone derivatives, and polycyclic pyridines **116** were usually obtained in moderate yields (30–45%).¹²⁰ This synthetic way is also carried out in refluxing ethanol.

Finally, with type C, two isomers of terpyridines can be reached by using 2 equiv of dihydroquinolinone **117** and an iminium salt. When R² is an alkyl, the S shaped terpyridine **118** is preferentially formed. The presence of an aryl on the iminium salt leads to a mixture of both S and U shaped terpyridines **118** and **119** in a ratio that strongly depends on the electronic and/or steric properties of the substituents in the native iminium compound.¹²¹ The group of Risch proposed two different reaction paths to explain the formation of one or another. The first way would be initiated by a Mannich type reaction leading, after elimination, to an enone undergoing a Michael addition. The resulting 1,5-dicarbonyl compound would then be transformed into U shaped terpyridine by the action of ammonia. A second possibility would be the Knoevenagel type autocondensation between 2 equiv of ketone followed, after ammonia condensation, by an aza-electrocyclization resulting in the S shaped terpyridine.¹²² These works have also shown that the U shaped terpyridine is largely favored when the iminium R² group is a hydrogen atom. Besides, this methodology was applied to the synthesis of hexacyclic ligands by Kelly and co-workers.¹²³

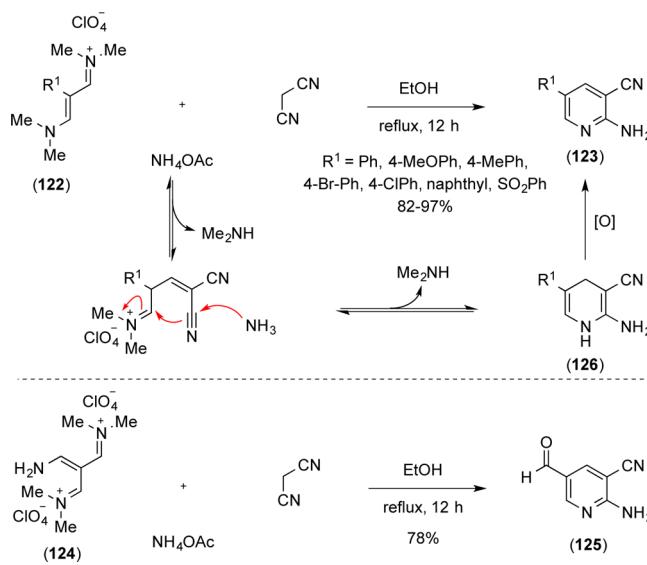
On the other hand, the Mannich type synthesis of non-polycyclic pyridines has been described in 2003.¹²⁴ Risch used protonated Mannich bases **120** combined with ammonium acetate and 2-phenylacetaldehyde in refluxing ethanol to access the corresponding 3-arylated pyridines **121** with yields up to 50% (Scheme 58). This methodology is an extension of type B Mannich-based reactions.

Scheme 58. Mannich-Based Synthesis of 3-Phenylpyridines



In 2013, a unique multicomponent approach from vinamidinium salts was reported on the basis of previously studied sequential synthesis of pyridines.¹²⁵ The nature of these iminium salts makes this transformation closely related to a type C Mannich-based synthesis of pyridines. In fact, a mixture of substituted vinamidinium salt **122**, malononitrile, and ammonium acetate in ethanol was refluxed for 12 h, yielding 2-amino-3-cyanopyridines **123** in excellent yields (Scheme 59).¹²⁶ Interestingly, the reaction tolerated the en amino bis-iminium substrate **124** to generate after hydrolysis the corresponding 5-formylpyridine **125** in good yield. From a mechanistic perspective, the authors suggested a 1,2-addition of malononitrile onto the iminium as first step of the sequence. Elimination of dimethylamine, then addition of ammonia on the nitrile functionality, followed by ring-closure onto the second iminium intermediate and elimination of dimethylamine, would lead to

Scheme 59. Synthesis of 2-Amino-3-cyanopyridines from Vinamidinium Salts



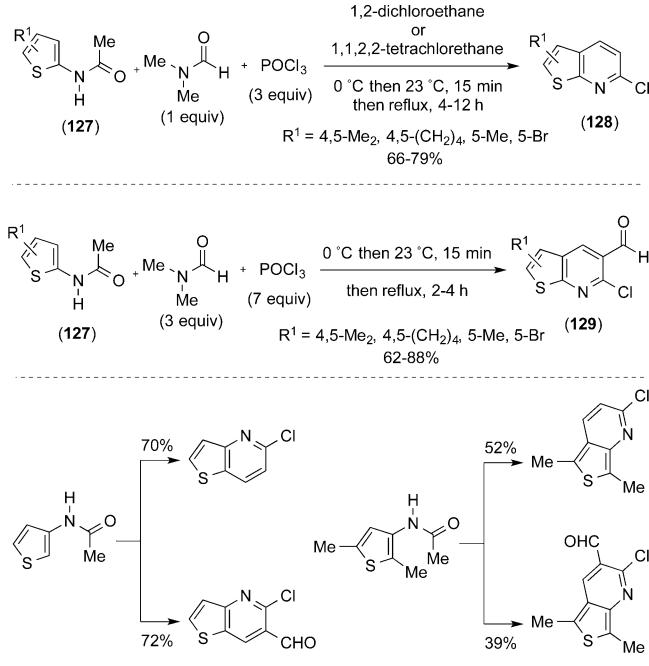
the 1,4-DHP **126**, which then would undergo an oxidation toward the expected pyridine.

The application of the Mannich reaction in multicomponent synthesis of pyridines has been clearly limited. While releasing amine or ammonium salt waste is not fully compatible with the sustainability requirements, these reactions have most likely been set aside because of their low efficiency. However, the last example brilliantly overcame this inefficacy and might open the way to a new set of Mannich-based multicomponent synthesis of pyridines in years to come.

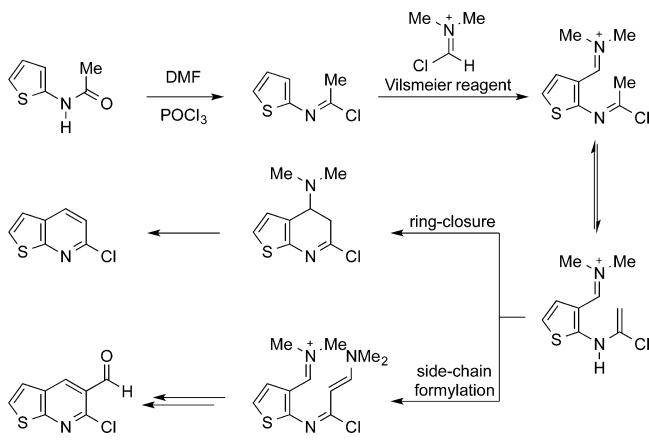
5. PYRIDINE SYNTHESIS BASED ON THE VILSMEIER–HAACK REACTION

The first step of the Vilsmeier–Haack reaction is the formation of a chlorinated iminium, commonly called Vilsmeier reagent (Scheme 61). This intermediate, product of the reaction between DMF and phosphoryl trichloride, has been used in the synthesis of nitrogen-containing heterocycles since the 1980s. The group of Meth-Cohn largely contributed to the development of three-component methodologies for the synthesis of pyridines, especially from acetamidothiophenes, in which a Vilsmeier reagent is *in situ* generated.¹²⁷ A divergent approach to either 2-chloropyridines **128** or 2-chloro-3-formylpyridines **129** from the same substrate **127** was achieved in moderate to good yields (Scheme 60). The proper solvent choice was the key to control the substitution pattern of the products. When a mixture of acetamidothiophene derivative **127**, dimethylformamide (1 equiv), and phosphoryl trichloride (3 equiv) was reacted together in a chlorinated solvent, the 2-chloropyridine **128** was obtained as the major product. On the other hand, the use of phosphoryl trichloride as the solvent (DMF/POCl₃ 3:7 equiv) led to the 2-chloro-3-formylpyridine **129**. Regioisomers of these thienopyridines were also selectively accessed from suitably substituted acetamidothiophenes.

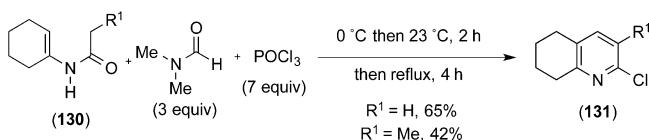
While the exact role of the solvent remained unclear, the DMF/POCl₃ ratio seemed to crucially impact the selectivity of this reaction that relied on the different rates of side-chain formylation versus ring-closure (Scheme 61). Besides, an experiment showed that the 2-chloropyridine was not converted

Scheme 60. Synthesis of 2-Chloro-thienopyridines

into its 2-chloro-3-formylpyridine analogue under the reaction conditions.

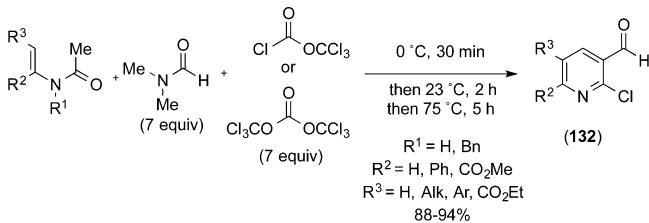
Scheme 61. Proposed Mechanism for the Divergent Synthesis of 2-Chloropyridines

Three years later, the same group adapted this concept to the synthesis of two 2-chloro-tetrahydroquinolines **131** from acetamidocyclohexene **130** (Scheme 62).¹²⁸ Yields were modest, and the scope of the reaction was not further studied. Curiously, in comparison with the results observed with thieno-pyridines, the 3-formylpyridine was not obtained (for R¹ = H) under the reaction conditions (neat, DMF 3 equiv, POCl₃ 7 equiv).

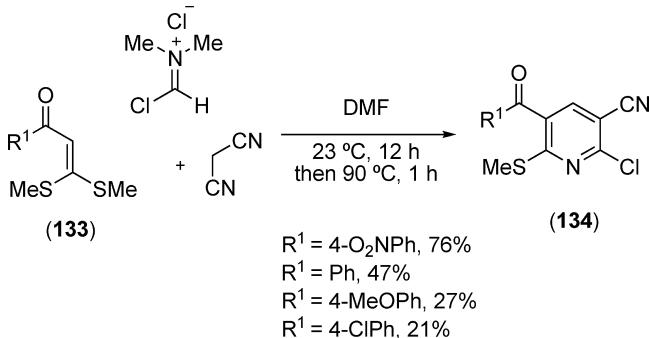
Scheme 62. Synthesis of 2-Chloro-tetrahydroquinolines

seemed than the ring-closure step is faster than the side-chain formylation with substrate **130**.

Relatively dormant for more than 20 years, this Vilsmeier–Haack-based multicomponent synthesis of pyridines was revisited in 2006. A modified procedure was developed in which phosphoryl trichloride was replaced by di- or triphosgene, resulting in excellent yields.¹²⁹ A large panel of N-H and N-benzyl enamides was converted successfully to 2-chloronicotinaldehydes **132**, without any solvent at 75 °C (Scheme 63). During the reaction with N-benzyl acetamides, dealkylation occurred by addition of chlorine anion releasing benzyl chloride before the cyclization step.

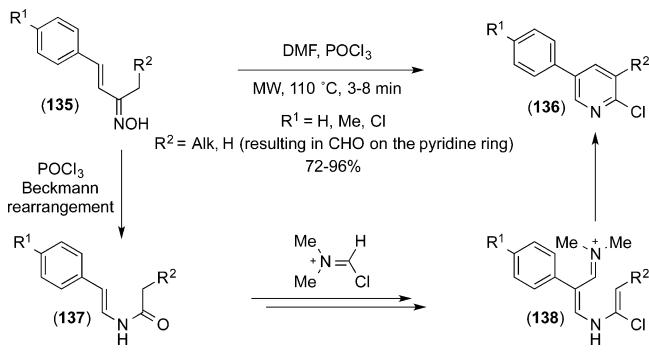
Scheme 63. Improved Synthesis of 2-Chloronicotinaldehyde Derivatives

In 2007, the reaction between the Vilsmeier reagent, malononitrile, and arylketene dithioacetals **133** has been reported for the synthesis of 2-thiopyridines **134** (Scheme 64).¹³⁰ However, the transformation seemed to be highly sensitive to electronic effects. Electron-rich aryl substituents were unsuitable and resulted in low yields.

Scheme 64. Vilsmeier-Based Synthesis of 2-Thiopyridines

Finally, Gogoi et al. adapted this strategy to α,β -unsaturated ketoxime derivatives **135**.¹³¹ Under microwave irradiation, 3,5-disubstituted 2-chloropyridines **136** were formed in good to excellent yields within a few minutes (Scheme 65). The first step of the reaction was supposed to be a POCl₃-promoted Beckmann rearrangement generating the enamide intermediate **137**. Subsequent reactions with Vilsmeier reagent led to iminium **138** that then underwent cyclization and aromatization by loss of a dimethylamine molecule. Importantly, the usually prerequisite *in situ* formation of the Vilsmeier reagent at low temperature was unnecessary under these reaction conditions, which made this transformation significantly attractive.

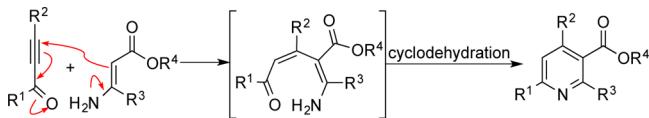
Retrospectively, the Vilsmeier–Haack-based multicomponent synthesis of pyridines, even if efficiently improved recently, respects only partially the criteria of sustainable chemistry, especially in terms of atom economy. Formation of dimethylamine and phosphorus-containing and halogenated side

Scheme 65. MW-Assisted Formation of 2-Chloropyridines

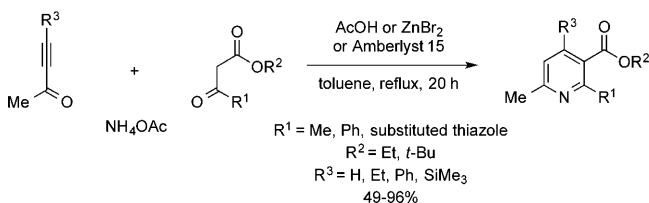
products is a major inconvenience and probably hampered its development. However, the strategy remarkably permits the synthesis of 2-chloropyridines, which most multicomponent processes are not capable of. This challenging substitution pattern is ideal for further transformation of the pyridines thus obtained.

6. BOHLMANN–RAHTZ PYRIDINE SYNTHESIS

The Bohlmann–Rahtz reaction was discovered in 1957 and consists of the conjugate addition of an enaminoester to an alkynone followed by a thermal cyclodehydration leading to the pyridine core (Scheme 66).¹³²

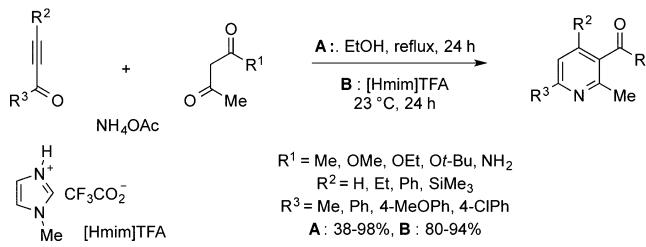
Scheme 66. Original Bohlmann–Rahtz Synthesis of Pyridines

Bagley studied thoroughly this reaction,¹³³ and pioneered in 2002 a multicomponent version forming *in situ* the enaminoester by condensing an ammonia source onto a β -ketoester.¹³⁴ Thus, the reaction sequence involved a β -ketoester, an alkynone, and ammonium acetate in refluxing toluene for 20 h, under acidic catalysis (Scheme 67). Brønsted or Lewis acids, as well as

Scheme 67. First Multicomponent Version of the Bohlmann–Rahtz Reaction

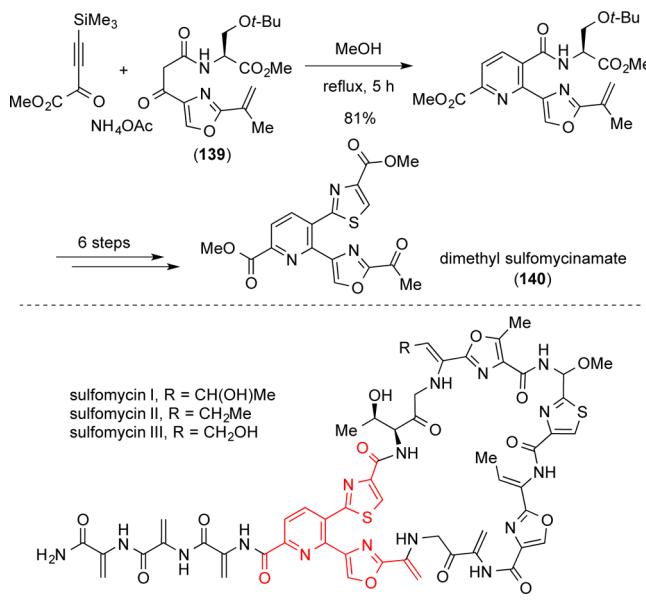
Amberlyst 15, proved to be suitable catalysts for this multicomponent reaction. Since the oxidation state of the substrates is equal to the pyridine one, this methodology proceeded without requiring any oxidation step.

In order to avoid acid catalysis and high temperatures that might impede the use of silicon-substituted alkynones, milder conditions were developed. Thus, an excess of ammonium acetate in refluxing ethanol effectively promoted this transformation from either β -ketoesters or acetoacetamides in moderate to excellent yields (Scheme 68, conditions A).¹³⁵ The reaction can also take place at room temperature with very

Scheme 68. Mild Conditions for the Bohlmann–Rahtz Pyridine Synthesis

good yields in the presence of [Hmim]TFA (Scheme 68, conditions B). According to the authors, this ionic liquid solvent played also the role of Brønsted acid catalyst.¹³⁶ Latter conditions also accommodated acetylacetone as 1,3-dicarbonyl partner.

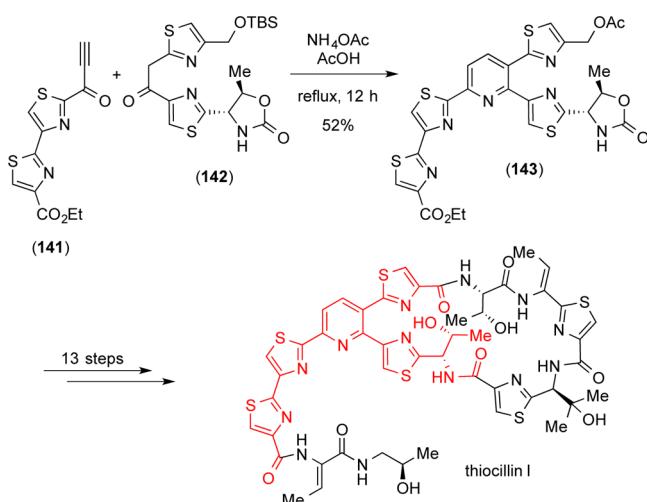
Application of this methodology to the total synthesis of natural products was explored by Bagley. Use of a functionalized β -ketoamide 139 led to dimethyl sulfomycinamate 140, a central oxazole-thiazole-pyridine domain of sulfomycins I–III (Scheme 69).¹³⁷ The multicomponent Bohlmann–Rahtz reaction proceeded in 81% yield, and six steps were necessary to complete the synthesis of dimethyl sulfomycinamate.

Scheme 69. Application of the Bohlmann–Rahtz Reaction to the Synthesis of Dimethyl Sulfomycinamate

Sulfomycins are members of the thiopeptide group of antibiotics. Thiocillin I is another natural product from this family; its total synthesis was completed in 2011 by Aulakh and Ciufolini.¹³⁸ The pyridine-thiazole core was assembled by a three-component reaction involving substituted alkynone 141, 1,2-bisthiazolo-ethynone 142, and ammonium acetate in refluxing acetic acid (Scheme 70). Under these conditions the trisubstituted pyridine 143, in which the TBS protecting group was cleaved and replaced by an acetate group, was obtained in 52% yield. Completion of the synthesis of thiocillin I was achieved in 13 steps.

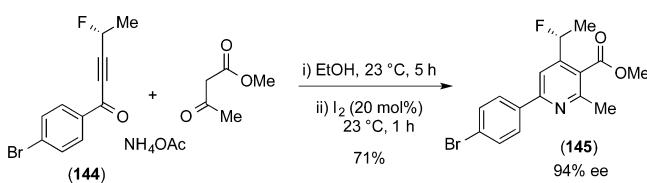
The multicomponent version of the Bohlmann–Rahtz reaction has been recently adapted to the synthesis of an enantiopure monofluorinated pyridine 145, through the reaction of a fluorinated alkynone 144 with methyl acetoacetate and

Scheme 70. Total Synthesis of Thiocillin I via the Multicomponent Bohlmann–Rahtz Reaction



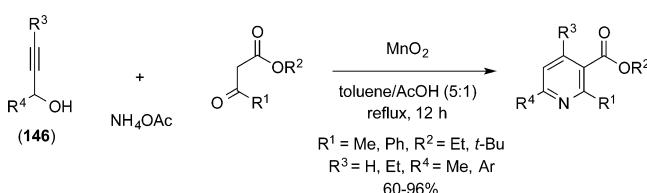
ammonium acetate.¹³⁹ According to conditions previously described by Bagley,¹⁴⁰ the reaction proceeded at room temperature in ethanol, and addition of a catalytic amount of iodine assured full consumption of starting materials (Scheme 71).

Scheme 71. Synthesis of Chiral Fluorinated Pyridine



A limitation of the Bohlmann–Rahtz reaction relies on the fact that only few alkynones are commercially available. Construction of libraries of pyridines implies, therefore, prior synthesis of these substrates, which might hamper the application of this strategy. For this reason, Bagley developed an oxidative multicomponent Bohlmann–Rahtz reaction, in which alkynones were generated *in situ* from the corresponding propargylic alcohols **146**.¹⁴¹ This oxidation/heteroannulation sequence involved a mixture of a propargylic alcohol, a β -ketoester, ammonium acetate, and activated manganese dioxide, heated in refluxing toluene/acetic acid (5:1) system (Scheme 72). Since numerous substituted propargylic alcohols are commercially available and represent a safer, less expensive alternative to alkynones, these conditions paved the way for drug-oriented elaboration of pyridines with improved functional diversity.

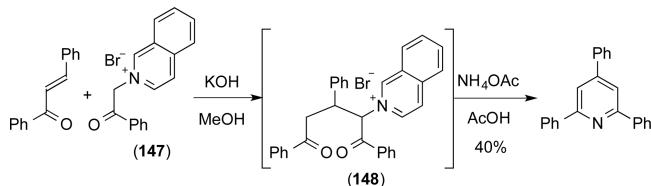
Scheme 72. Oxidative Bohlmann–Rahtz Reaction from Propargylic Alcohols



7. KRÖHNKE PYRIDINE SYNTHESIS

In 1961, Kröhnke and Zecher developed new access to 2,4,6-triarylpyridines through reaction between the *N*-phenacyl isoquinolinium bromide **147** and chalcone in a basic media, followed by an acidic workup in the presence of ammonium acetate (Scheme 73).¹⁴² The initial formation of a 1,5-dicarbonyl

Scheme 73. Kröhnke Synthesis of 2,4,6-Triarylpyridines

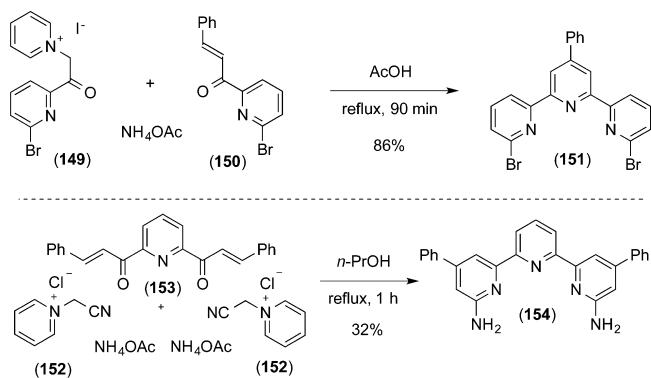


intermediate **148** by Michael addition of the enolate derived from the pyridinium salt of a ketone, onto an α,β -unsaturated carbonyl derivative, was followed by a cyclodehydration in the presence of ammonium acetate releasing 2,4,6-triarylpyridines, known as Kröhnke pyridines.¹⁴³

Owing to this sequential approach, the original Kröhnke pyridine synthesis was not ranked among multicomponent reactions. However, multicomponent versions have been reported since the discovery of the reaction, and diverse applications have emerged in the literature.

As a first illustration of these generalities, the multicomponent Kröhnke reaction has been used to access terpyridines **151** and **154**, by construction of either the central pyridine core or the two side-pyridine rings (Scheme 74).¹⁴⁴ The first strategy consisted

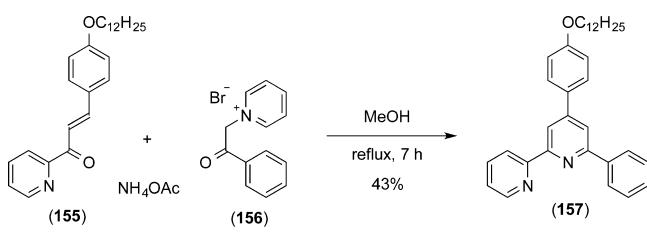
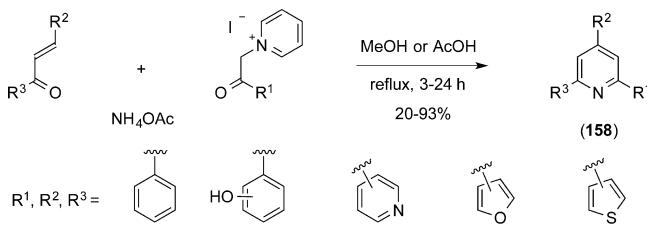
Scheme 74. Kröhnke Synthesis of Terpyridines



of the condensation of a pyridine-containing pyridinium salt **149** onto a pyridine-containing chalcone **150** with ammonium acetate in refluxing acetic acid. The second approach was a pseudo-five-component reaction involving 2 equiv of the cyanomethylpyridinium salt **152**, bis-chalcone **153**, and excess ammonium acetate in refluxing *n*-propanol. The coordination properties of these substituted terpyridines **151** and **154** to various transition metals were also studied.

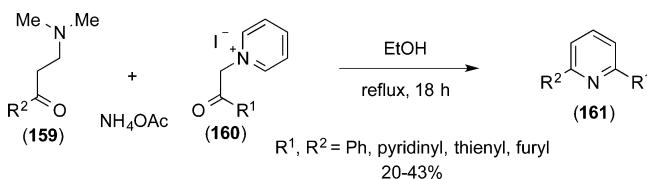
In 1997, the synthesis of bipyridine **157** from functionalized chalcone **155**, pyridinium salt **156**, and ammonium acetate in refluxing methanol was also reported (Scheme 75).¹⁴⁵ Palladium as well as platinum complexes of this ligand exhibited interesting luminescent properties.

Over the past decade, Lee's group thoroughly exploited this methodology to synthesize 2,4,6-trisubstituted pyridines **158** as potential inhibitors of topoisomerases I and II (Scheme 76).¹⁴⁶

Scheme 75. Kröhnke Synthesis of Bipyridine 157**Scheme 76.** SAR-Oriented Kröhnke Synthesis of 2,4,6-Trisubstituted Pyridines

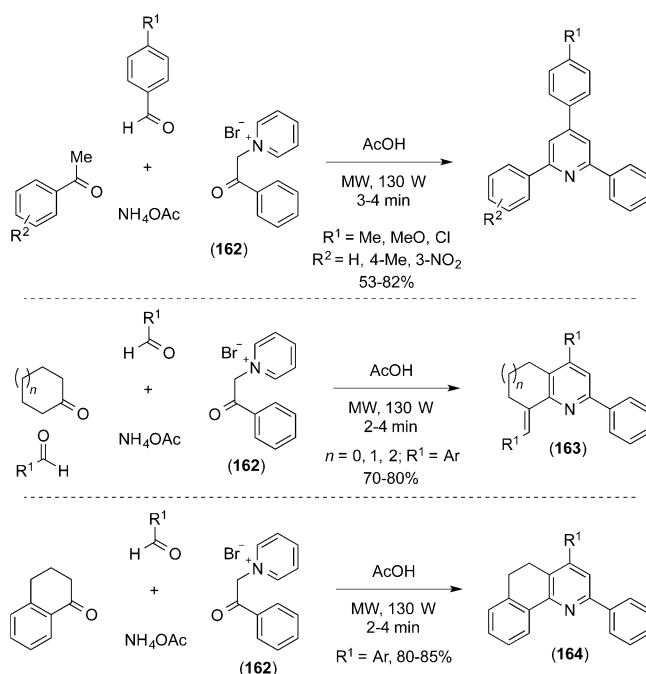
These nuclear enzymes play an important role in DNA metabolism mechanisms and are targets of choice for antibacterial and anticancer drug candidates. The pyridines were formed in low to excellent yields in either refluxing methanol or acetic acid. The substituents of the pyridine core were essentially phenyl, phenol, pyridinyl, furyl, and thienyl groups, and some compounds showed promising inhibition activities.

In 2008, the same group developed a synthetic strategy for 2,6-diaryl-pyridines combining Kröhnke and Mannich approaches. Thus, reaction of a Mannich base **159** with an iodinated pyridinium salt **160**, derived from the corresponding α -iodoketone, and ammonium acetate in refluxing ethanol for 18 h, led to a library of pyridines **161** in moderate yields (Scheme 77).¹⁴⁷ The antitumor activities of these heterocycles and their associated toxicities were studied.

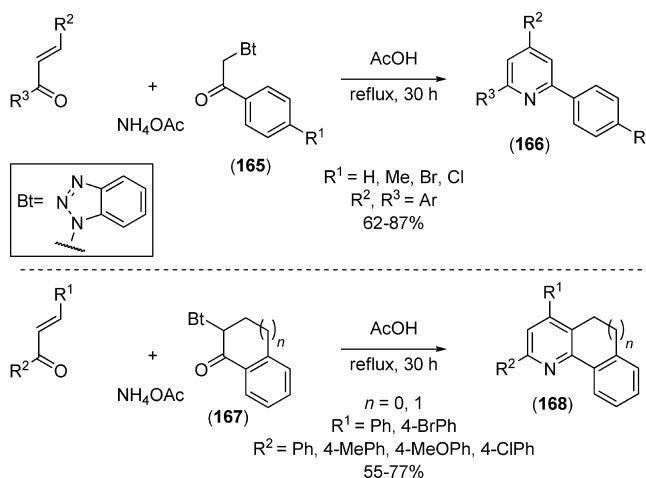
Scheme 77. Synthesis of 2,6-Biaryl-pyridines via an Original Kröhnke/Mannich Approach

Microwave irradiation-assisted Kröhnke synthesis has also been developed, thus shortening reaction times. Yan et al. described a modified four-component procedure from *N*-phenacylpyridinium bromide (**162**), an aromatic aldehyde, an acetophenone derivative, and ammonium acetate in acetic acid (Scheme 78). The method was further extended to bicyclic pyridines **163** through a pseudo-five-component involving a cyclic ketone, and 2 equiv of an aldehyde.¹⁴⁸ Tricyclic structures **164** were also reached when the same pyridinium salt **162** reacted with an aromatic aldehyde, ammonium acetate, and 1-tetralone.

In 1999, Katritzky et al. proposed a different approach that might relate to the Kröhnke reaction, in which the pyridinium salt was replaced by a benzotriazole derivative.¹⁴⁹ Refluxing a solution of this benzotriazole substrate **165** or **167**, a chalcone,

Scheme 78. MW-Assisted Kröhnke Synthesis of Mono-, Bi- and Tricyclic Pyridines

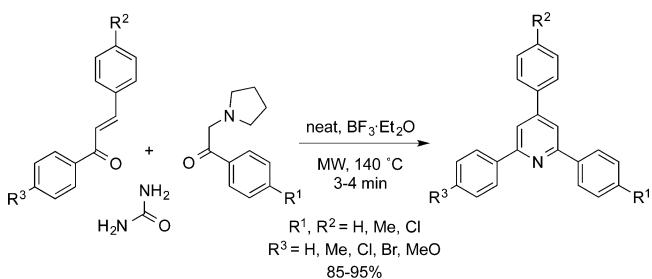
and ammonium acetate in acetic acid led to the corresponding pyridines in moderate to good yields. According to the nature of the benzotriazole, mono- and tricyclic pyridines **166** or **168** were accessed by this method (Scheme 79).

Scheme 79. Modified Kröhnke Reaction from Benzotriazole Derivatives

More recently, a closely related methodology has been developed, in which pyrrolidine served as the heterocyclic leaving group. This new and efficient route toward 2,4,6-triarylpypyridines was performed neat under microwave irradiation in the presence of a catalytic amount of trifluoroborane etherate, and introduced the particularity of using urea rather than ammonium acetate as the ammonia source (Scheme 80).¹⁵⁰ The authors suggested that urea decomposed into ammonia under microwave irradiation.

As the Mannich or Vilsmeier–Haack-based multicomponent syntheses of pyridines, the Kröhnke reaction and related

Scheme 80. Modified Kröhnke Synthesis of 2,4,6-Triarylpypyridines from Pyrrolidine Derivatives



technologies have not encountered popular success although they are totally regioselective. The generation of nitrogen-containing heterocycles (*i.e.*, pyridine, benzotriazole, or pyrrolidine) as side products of this reaction cannot be ignored and certainly limits its applications. This waste production, along with the requirement for synthesis of the starting pyridinium salts, prevent this method from being competitive with fully sustainable approaches, and might explain why organic chemists have shied away from it.

8. PYRIDINE SYNTHESIS BASED ON THE MICHAEL ADDITION

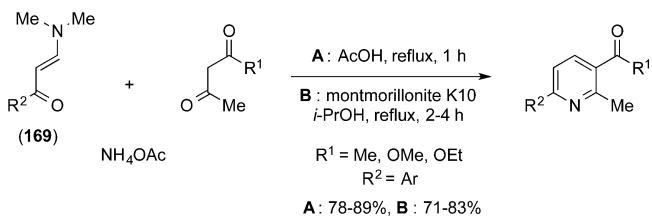
Many multicomponent strategies to access the pyridine ring presented so far in this review exhibited a Michael addition step. The purpose of this section is to combine examples of Michael-addition-initiated strategies for the regioselective synthesis of pyridines.

8.1. From 3-Dimethylamino Michael Acceptors

Numerous Michael-addition-based methods described up to now implied a 1,3-dicarbonyl derivative, an ammonia source, and a Michael acceptor bearing a dimethylamino substituent on position 3. This substituent played the role of a leaving group and facilitated the final aromatization step.

Pioneer works on this strategy were reported in 2002 by Al-Saleh et al. from either acetylacetone or methyl acetoacetate reacting in refluxing acetic acid with ammonium acetate and enaminoketone **169** (Scheme 81, conditions A).¹⁵¹ Three years later, montmorillonite K10 proved to efficiently catalyze this reaction in refluxing 2-propanol (Scheme 81, conditions B).

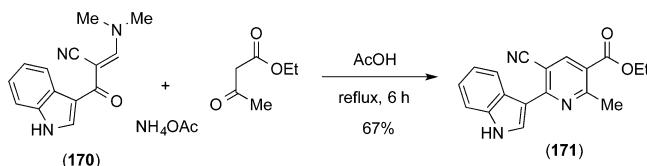
Scheme 81. Initial Studies on the Synthesis of Pyridines from Enaminoketones 169



In 2007, a single example was reported with enamine **170** derived from an indole-containing β -ketonitrile. Reaction of this Michael acceptor with ethyl acetoacetate and ammonium acetate in refluxing acetic acid formed the 3-cyanopyridine **171** in 67% yield (Scheme 82).¹⁵³

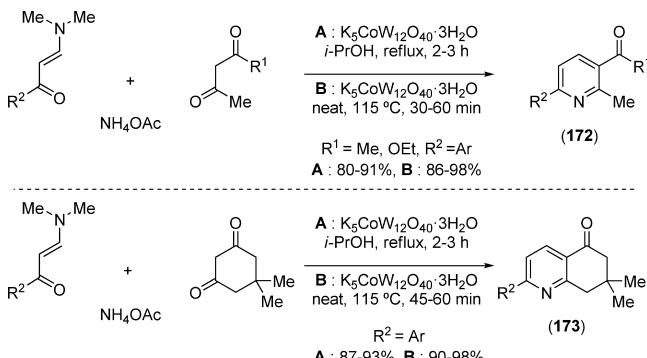
The same year, Kantevari's group became interested in this transformation and developed various conditions enabling access to the desired pyridines. Potassium dodecatungstocobaltate

Scheme 82. Michael-Initiated Synthesis of Indolo-pyridine 171



trihydrate ($K_5CoW_{12}O_{40}\cdot 3H_2O$), a mineral polyoxometalate heterogeneous catalyst, proved to effectively promote this reaction from acetylacetone, ethyl acetoacetate, or dimedone. A comparative study demonstrated that refluxing a mixture of the three partners with the catalyst in 2-propanol provided trisubstituted pyridines **172** or **173** with very good yields (Scheme 83, conditions A),¹⁵⁴ while the efficiency of the reaction

Scheme 83. $K_5CoW_{12}O_{40}\cdot 3H_2O$ -Catalyzed Synthesis of Trisubstituted Pyridines



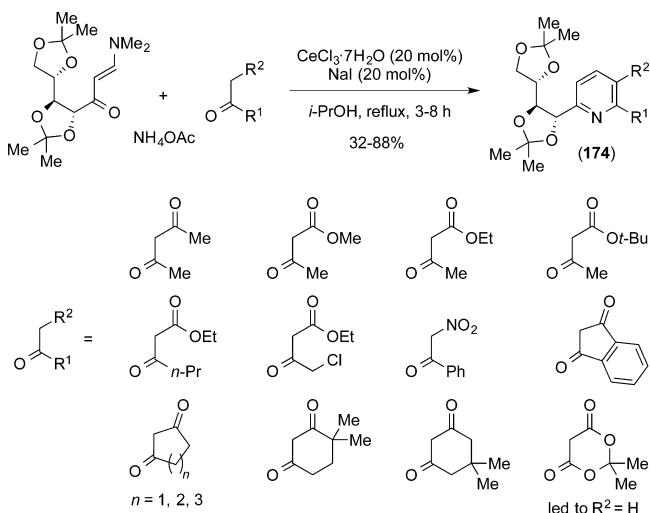
was improved under solvent-free conditions at 115 °C, and the reaction times were shortened (Scheme 83, conditions B).¹⁵⁵ It is noteworthy that the catalyst was reused up to 5 times without any significant erosion of the yields.

More recently, Kantevari's group applied this methodology to a large panel of cyclic or acyclic 1,3-dicarbonyl compounds in the presence of a heptahydrate cerium trichloride/sodium iodide system in refluxing 2-propanol, willing to build a library of acyclo-C-nucleoside analogues **174** (Scheme 84).¹⁵⁶

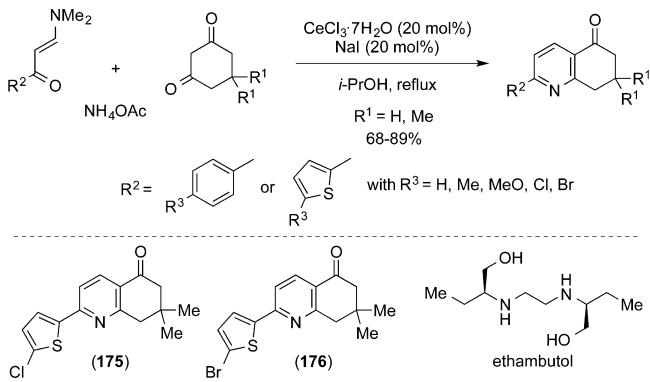
Recently, they studied the scope of enaminoketones in this multicomponent process from ethyl acetoacetate, dimedone, and 4,4-dimethylcyclohexane-1,3-dione.¹⁵⁷ This combinatorial approach was carried under the previously described conditions, *i.e.*, cerium chloride/sodium iodide system in refluxing 2-propanol. The antimycobacterial activity against *M. tuberculosis* H₃₇Rv of the whole library was evaluated, resulting in six promising antitubercular scaffolds. Motivated by these results, Kantevari and co-workers reported new antitubercular agents synthesized through the multicomponent reaction of aryl or thienyl-substituted enaminoketones, cyclohexane-1,3-dione or dimedone, and ammonium acetate (Scheme 85).¹⁵⁸ Among the products obtained, two thienyl-substituted pyridines **175** and **176** displayed a slightly better *in vitro* antimycobacterial activity against *M. tuberculosis* H₃₇Rv than ethambutol, a reference bacteriostatic drug.

In an effort to develop new drug-like polyheterocycles, the same group also applied this strategy to the construction of dihydrobenzofuranyl-substituted pyridines **177**.¹⁵⁹ Under similar reactions conditions and from a panoply of 1,3-dicarbonyl derivatives depicted in Scheme 84, a library of trisubstituted

Scheme 84. Michael-Initiated Synthesis of Acyclo-C-nucleoside Analogues

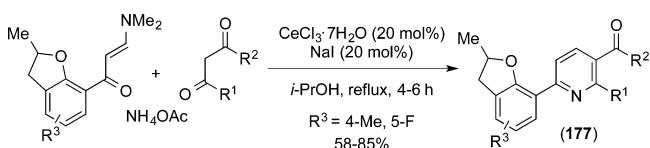


Scheme 85. Synthesis of Antitubercular Pyridines



pyridines was detailed (Scheme 86). These dihydrobenzofuran-tethered pyridines were obtained in moderate to good yields.

Scheme 86. Construction of Dihydrobenzofuranyl-Substituted Pyridines

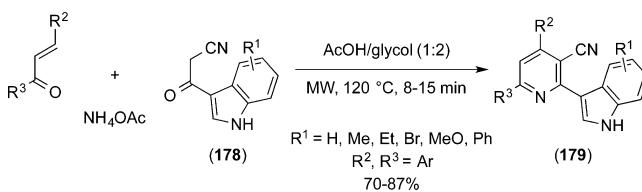


Although the dimethylamino substituent facilitates the final aromatization step, it also constitutes a source of waste for this reaction and prevents any access to 4-substituted pyridines. This represents the major limitation of this regioselective method.

8.2. From Other Michael Acceptors

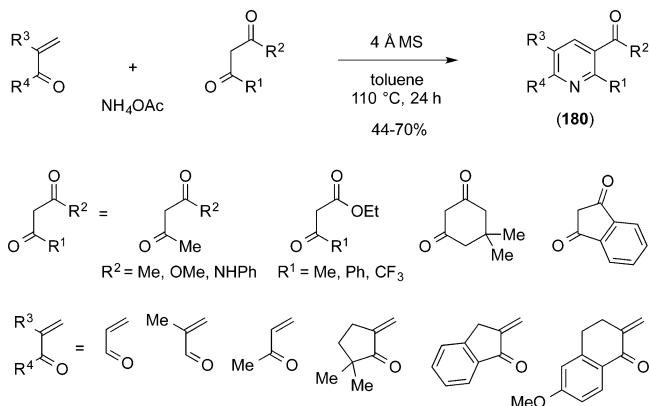
8.2.1. Reactions with β -Ketonitriles. In 2010, Geng et al. reported a Michael-addition-initiated multicomponent route to 3-cyanopyridines from indole-derived β -ketonitriles 178, ammonium acetate, and various chalcones as Michael acceptors (Scheme 87).¹⁶⁰ A mixture of the three partners in acetic acid/glycol (1:2) was subjected to microwave irradiation at 120 °C to provide tetrasubstituted pyridines 179 in good yields and short reaction times.

Scheme 87. Michael-Addition-Initiated Multicomponent Synthesis of 3-Cyanopyridines



8.2.2. Reactions with 1,3-Dicarbonyl Derivatives. Our own group has also developed Michael-addition-initiated MCRs¹⁶¹ for the synthesis of heterocycles of both pharmacological and synthetic interest. In particular, on the basis of pioneering results from Hoelderich group,¹⁶² we reported in 2008 a totally regioselective and metal-free three-component substrate-directed route to polysubstituted pyridines from 1,3-dicarbonyls. Thus, the direct condensation of 1,3-diketones, β -ketoesters, or β -ketoamides with α,β -unsaturated aldehydes or ketones and ammonium acetate, under heterogeneous catalysis by 4 Å molecular sieves (4 Å MS), provided the desired heterocycles 180 after *in situ* oxidation (Scheme 88).¹⁶³ The

Scheme 88. Michael-Initiated Synthesis of Polysubstituted Pyridines from 1,3-Dicarbonyls

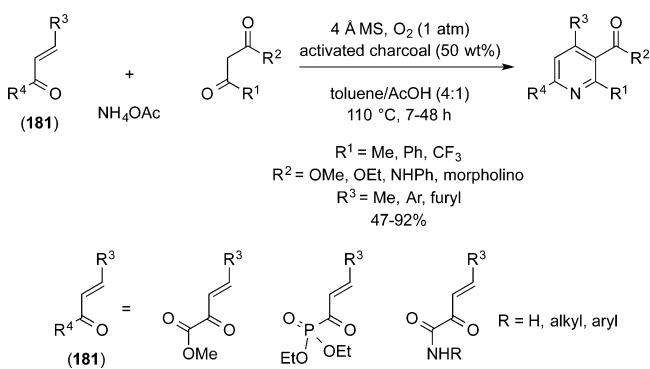


neutral heterogeneous conditions proved to be compatible with sensitive Michael acceptors, resulting in the construction of an important library of mono-, bi-, or tricyclic pyridines.

However, presumably owing to the reversibility of the Michael addition with hindered substrates, this preliminary study was limited to the use of β -unsubstituted aldehydes and ketones, narrowing the functional diversity at the strategic 2-position and preventing any access to 4-substituted pyridines. In order to address the limitations of this first generation synthesis, activated Michael acceptors 181, *i.e.*, β,γ -unsaturated- α -ketocarbonyl derivatives, have successfully been explored. Under optimized dual heterogeneous oxidative conditions, 4-substituted pyridines presenting great functional diversity at the 2-position were obtained in good to excellent yields (Scheme 89).¹⁶⁴ Electron-withdrawing substituent such as ester, amide,¹⁶⁵ and phosphonate effectively enhanced the electrophilicity of the Michael acceptor. Performing the reaction with activated charcoal and acetic acid as cosolvent in the presence of 4 Å MS was crucial to ensure the complete oxidation of the intermediate 1,4-DHP.

Access to biheterocyclic scaffolds is a research area currently under intense investigation, and the commonly developed methods involve (1) cross-coupling reactions, (2) C–H bond

Scheme 89. MCR Synthesis of Functionalized Pyridines from Activated Michael Acceptors



functionalizations, and (3) dehydrogenative cross-coupling transformations. However, these interesting metal-catalyzed strategies are still in the development phase, do not fully satisfy “green chemistry” requirements, and are not totally regioselective yet. Therefore, to tackle this synthetic challenge under metal-free conditions, we extended the Michael-addition-initiated method to the formation of bi- and tri(hetero)-arylpyridines. Thus, in the course of our study on activated Michael acceptors, we also found out that several nitrogen-containing heterocycles (pyridine, imidazole, isoxazoline) were effective toward that end and well-tolerated by the MCR. As a result, several heterocycles were introduced on the central pyridine ring from either the Michael acceptor or the 1,3-dicarbonyl derivative, under oxidative previously reported dual heterogeneous conditions (Figure 2).¹⁶⁶

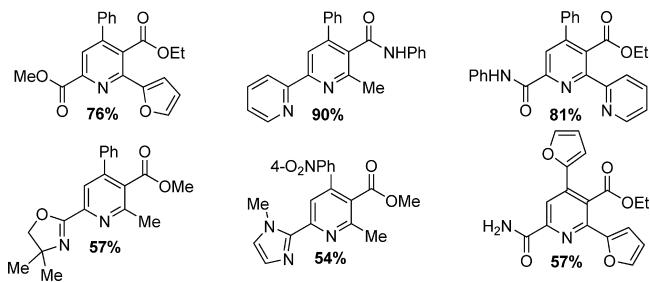
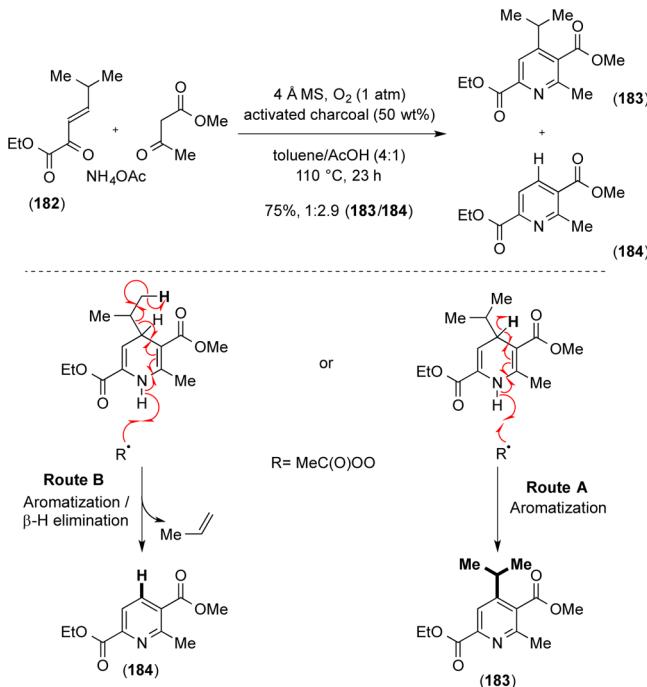


Figure 2. Representative bi- and tri(heteroaryl)pyridines from our metal-free MCR.

A mechanistic study demonstrated that the first step of the sequence was a molecular-sieves-promoted Michael addition between the 1,3-dicarbonyl and the α,β -unsaturated carbonyl compound. The corresponding 1,5-dicarbonyl adduct then underwent a cyclodehydration with ammonium acetate leading to the corresponding dihydropyridine intermediate, which was *in situ* oxidized. Concerning this final oxidation step, we postulated that a radical-based mechanism might be involved and would rationalize the result we observed with activated Michael acceptor **182**. In fact, the expected 4-substituted pyridine **183** was isolated in mixture with its dealkylated analogue **184** (Scheme 90). We believe that a radical-assisted competition between standard oxidation of the 1,4-DHP (Scheme 90, route A) and β -hydride elimination (Scheme 90, route B) would be a reasonable way to explain this observation. While the initiator has not been identified with certainty, experimental facts suggested that a peracetic acid radical (generated by oxidation of acetic acid

Scheme 90. Postulated Radical-Assisted Aromatization

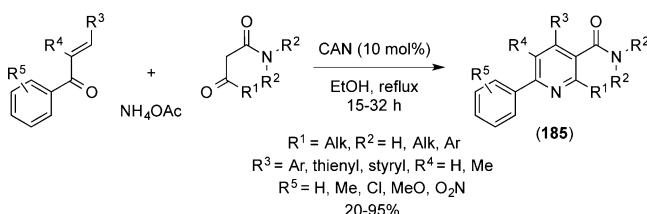


by diradical triplet state of oxygen) could serve as hydrogen abstractor.¹⁶⁷

All these approaches offer an important insight into the development of a new solution for the totally regioselective construction of highly functionalized pyridines of both biological and synthetic interests.

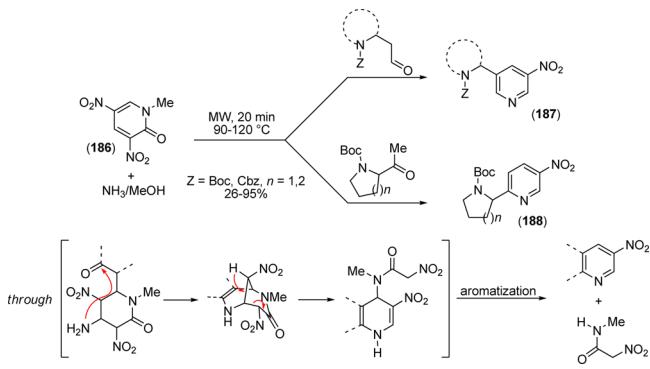
In 2012, Tenti et al. focusing on the regioselective access to functionalized nicotinamide derivatives described a CAN-catalyzed related reaction.¹⁶⁸ Thus, an ethanol solution of a chalcone, a β -ketoamide, and ammonium acetate was heated at reflux with a catalytic amount of CAN, providing nicotinamides **185** in synthetically useful yields and great functional diversity (Scheme 91). Formation of pentasubstituted pyridines with this

Scheme 91. Multicomponent Synthesis of Nicotinamide Derivatives



strategy seemed difficult. Besides, oxidation of the intermediate dihydropyridine was particularly challenging from β -ketolactams.

8.2.3. Reactions with Aldehydes and Ketones. A different approach was imagined to access diverse 3-nitropyridines via a three-component reaction based on a double C/N Michael addition of simple carbonyl derivatives and ammonia, respectively. Indeed, 3,5-dinitro-1-methyl-2-pyridone **186**, ammonia in methanol, and an aldehyde or an enolizable ketone can react together under microwave irradiation to form a library of different 5- or 6-substituted 3-nitropyridines **187** and **188**, respectively, with yields ranging from 26% to 95% (Scheme 92).¹⁶⁹ A 1 equiv portion of α -nitro-*N*-methylacetamide is

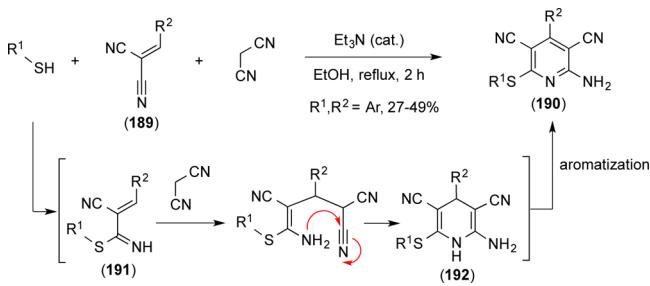
Scheme 92. Multicomponent Synthesis of 3-Nitropyridines

liberated along with the desired pyridine, but although the criterion of atom economy is important in sustainable chemistry, this method described the formation of unique scaffolds, not accessible by any other multicomponent reactions so far.

9. 2-THIO-, 2-AMINO-, AND 2-ALKOXYPYRIDINE SYNTHESIS

9.1. Synthesis of 2-Thiopyridines

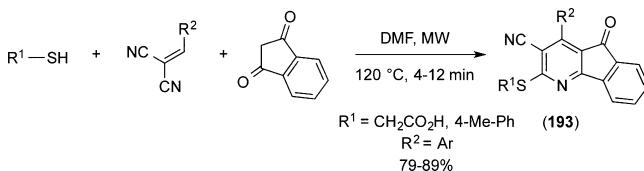
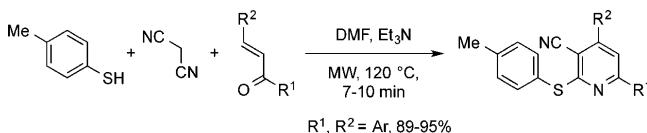
The synthesis of 2-thiopyridines by MCR was described for the first time in 1981 by Kambe and Saito. The reaction of an arylidene malononitrile **189**, a thiol, and malononitrile in refluxing ethanol with a catalytic amount of triethylamine afforded the corresponding 2-thiopyridines **190** in moderate yields (Scheme 93).¹⁷⁰ The nucleophilic addition of the thiol to a

Scheme 93. Pioneering Multicomponent Synthesis of 2-Thiopyridines

nitrile function of the arylidene malononitrile was proposed to initiate the sequence. The resulting intermediate **191** underwent a Michael addition leading to the corresponding 1,4-DHP **192** after cyclization. An air-mediated aromatization step then furnished the observed 2-thiopyridine. A library of pentasubstituted 2-thiopyridines was built with this pioneering regioselective multicomponent reaction.

Quite surprisingly, this reaction has been unexplored for 25 years. Then, in 2007, a related multicomponent synthesis of azafluorenone derivatives was described by replacing malononitrile with 1,3-indandione.¹⁷¹ The three partners were heated at 120 °C in DMF under microwave irradiation leading to the corresponding tricyclic 2-thiopyridines **193** in short reaction times and good yields (Scheme 94).

Use of chalcones instead of alkylidene malononitrile in this three-component access to 2-thiopyridines has been described by Wang et al. in 2009. Triethylamine and DMF was the best system to work with, under microwave irradiation, resulting in high yields within a few minutes (Scheme 95).

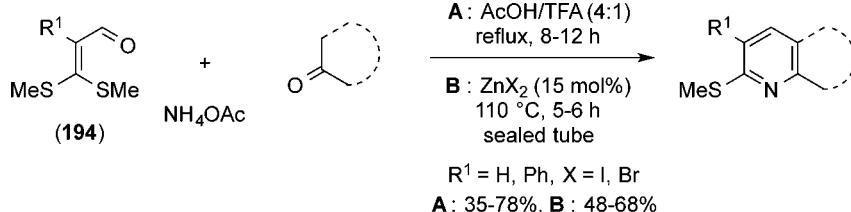
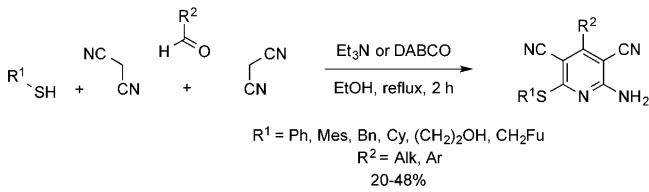
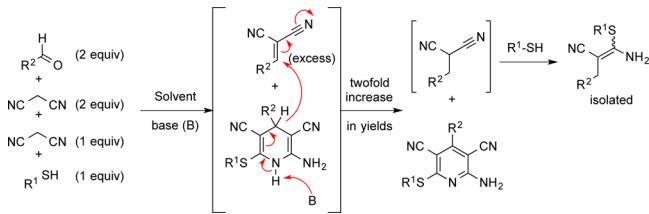
Scheme 94. Multicomponent Synthesis of Thio-4-azafluorenone Derivatives**Scheme 95. Multicomponent Synthesis of 2-Thiopyridines from Chalcone Derivatives**

A Knoevenagel-based¹⁷² method has recently been applied to the three-component synthesis of 2-thiopyridines. This original strategy involved an enolizable carbonyl compound, ammonium acetate, and a ketene α -formyl-dithioacetal **194**.¹⁷³ The reaction can be carried out in a 4:1 acetic acid/trifluoroacetic acid refluxing mixture (Scheme 96, conditions A), or in the presence of zinc dihalide at 110 °C without any solvent (Scheme 96, conditions B). Numerous enolizable ketones or equivalents, including acetophenones, 1,3-indanedi one, acetylferrocene, or even malononitrile, were well-tolerated for this reaction. The yields remained somehow modest, but this unique method resulted in interesting functional diversity on the pyridine ring.

In 2006, Evdokimov et al. revisited the Kambe and Saito's pioneer works and developed a pseudo-four-component variation. In this study, they hypothesized that the arylidene malononitrile could be formed *in situ* by condensation of an aromatic aldehyde onto a second equivalent of malononitrile. A screening of diverse bases resulted in triethylamine and 1,4-diazabicyclo[2.2.2]octane (DABCO) as the best catalysts to form the desired 2-thiopyridines (Scheme 97).¹⁷⁴ Interestingly, 1,4-dihydropyridines were obtained in good yields (>62%, not shown) with *ortho,ortho'*-disubstituted aromatic aldehydes. These divergent results were consistent with an issue during the aromatization step to rationalize the low yields obtained when targeting 2-thiopyridines.

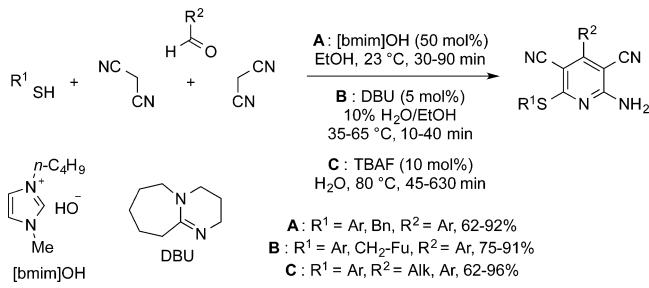
From these results, several groups have concentrated their efforts on this route to 2-thiopyridines, in particular to improve the associated yields, striving to clarify the implied reaction mechanism. In this context, Evdokimov proposed a concerted mechanism,¹⁷⁵ an alternative to the sequential one proposed by Kambe and Saito. Their opinions essentially differ on the final aromatization step. Kambe and Saito's hypothesis implied the role of oxygen, but doubts exist since yields were not that affected by anaerobic conditions. Evdokimov and Chen voiced another hypothesis: the arylidene malononitrile might serve as a hydrogen abstractor, as previously observed by Shintani et al. (Scheme 50). Although its reduced form had not been isolated, the corresponding thiol addition product was isolated from the reaction medium and characterized (Scheme 98).¹⁷⁶ However, these works did not completely eliminate the possibility of an aerobic oxidation, even though the latter seems negligible compared to the arylidene malononitrile-mediated oxidation according to Chen's study.¹⁷⁷

2-Thiopyridines represent a privileged scaffold as potential pharmaceutical cores as shown by Reddy et al.¹⁷⁸ among others.

Scheme 96. Multicomponent Synthesis of 2-Thiopyridines from Ketene α -Formyl-dithioacetal**Scheme 97.** Pseudo-Four-Component Synthesis of 2-Thiopyridines**Scheme 98.** Evidence for the Arylidemalononitrile-Mediated Oxidation of 1,4-DHPs

Therefore, this pseudo-four-component strategy has been thoroughly studied in the past few years, resulting in numerous experimental conditions.

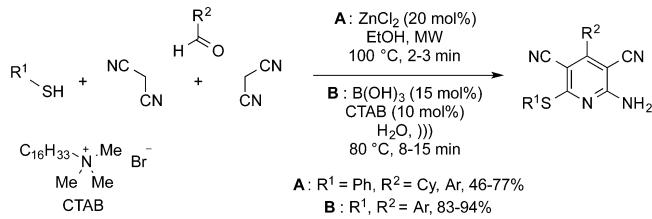
In 2007, Ranu et al. described a basic ionic liquid-catalyzed synthesis of 2-thiopyridines at room temperature. Ethanol was necessary to maintain the reaction in a solution phase. These conditions enabled mild construction of a broad library of pyridines in short reaction times and good to excellent yields (Scheme 99, conditions A).¹⁷⁹ Other homogeneous basic media

Scheme 99. Homogeneous Basic Catalysis for the Pseudo-Four-Component Synthesis of 2-Thiopyridines

have also been reported. For instance, a catalytic amount of 1,8-diazabicycloundec-7-ene (DBU) in wet ethanol at 35–65 °C proved to efficiently induce this pseudo-four-component transformation (Scheme 99, conditions B).¹⁸⁰ In 2001, the use of TBAF in water at 80 °C has been described.¹⁸¹ Interestingly, these conditions accommodated aliphatic aldehydes such as acetaldehyde and propanal in 64% and 62% yield, respectively, albeit requiring longer reaction times. Obtention of 2-thiopyridines from aromatic aldehydes under these conditions

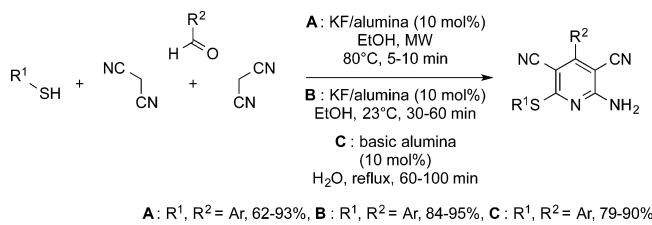
was particularly effective with yields ranging from 87% to 96% in short reaction times (Scheme 99, conditions C).

The reaction also proceeds under homogeneous acidic catalysis. Zinc chloride has successfully been used as Lewis acid to catalyze the formation of these 2-thiopyridines with microwave irradiation (Scheme 100, conditions A).¹⁸² While

Scheme 100. Homogeneous Acidic Catalysis for the Pseudo-Four-Component Synthesis of 2-Thiopyridines

yields were slightly lower than under basic conditions, the authors claimed that neither the intermediate DHP nor reduced arylidemalononitrile were obtained as side products. Therefore, yields did not suffer from incomplete oxidation step. Besides, a plausible Lewis-acid-catalyzed mechanism was proposed. In 2010, a boric-acid-catalyzed formation of 2-thiopyridines was described in aqueous media.¹⁸³ Cetyltrimethylammonium bromide (CTAB) was necessary to carry out the reaction in water, and a collection of 2-thiopyridines was elaborated under ultrasound irradiation in good to excellent yields (Scheme 100, conditions B). These works demonstrated that homogeneous acid catalysis is clearly another option to access these building blocks.

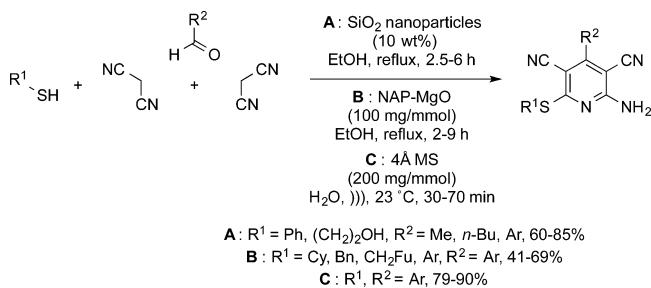
Heterogeneous basic conditions have also been reported to effectively promote this transformation. In this area, two reports emphasized the use of potassium fluoride/alumina as a system of choice. Under microwave irradiation, the reaction of the three partners was catalyzed by 10 mol % of KF/alumina, affording 2-thiopyridines in good to excellent yields (Scheme 101, conditions A).¹⁸⁴ Simultaneously, Das et al. reported that the exact same transformation can be performed at room temperature without erosion of yields in short reaction times (Scheme 101, conditions B).¹⁸⁵ More recently, a commercially available

Scheme 101. Heterogeneous Basic Catalysis for the Pseudo-Four-Component Synthesis of 2-Thiopyridines

basic alumina-catalyzed reaction has been reported.¹⁸⁶ Although the reaction proceeded in high yield at room temperature, refluxing the aqueous suspension of the three substrates and the catalyst enhanced considerably the formation of pyridines (Scheme 101, conditions C). Under the same conditions, both neutral and acidic alumina provided the expected 2-thiopyridines in low yields.

Due to their simplicity of operation and potential for catalyst recycling, other heterogeneous systems have been explored to catalyze this transformation. In 2009, an ethanol solution of the three partners was refluxed in the presence of silica nanoparticles, affording a series of 2-thiopyridines in good yields (Scheme 102,

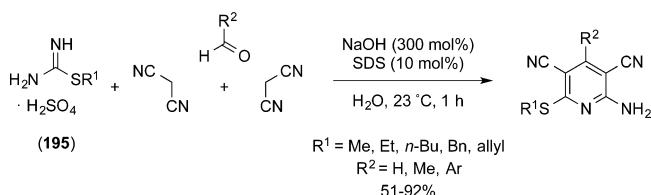
Scheme 102. Heterogeneous Catalysis for the Pseudo-Four-Component Synthesis of 2-Thiopyridines



conditions A).¹⁸⁷ This reusable catalyst accommodated the condensation of both aromatic and aliphatic aldehydes. In 2010, Kantam et al. described the use of nanocrystalline magnesium oxide (NAP-MgO) as heterogeneous catalyst for this reaction, in refluxing ethanol (Scheme 102, conditions B).¹⁸⁸ Moderate yields are probably due to the starting materials ratio since malononitrile and aldehyde were not used in excess as suggested by Evdokimov and Chen.^{185,186} Finally, in 2011, 4 Å molecular sieves (4 Å MS) showed interesting catalytic activity for this transformation in aqueous media.¹⁸⁹ The formation of 2-thiopyridines was efficient under reflux conditions. However, a milder room temperature procedure was enabled by using ultrasound irradiation that increased the rate of the reaction and preserved its efficacy (Scheme 102, conditions C).

Overall, both homogeneous and heterogeneous systems have been studied with success to efficiently promote this pseudo-four-component synthesis of 2-thiopyridines. However, one could criticize the use of generally smelly and toxic thiols, which could hamper further developments and applications of this strategy. An alternative has been recently proposed where the sulfur source is an isothiouronium salt **195** (Scheme 103).¹⁹⁰ This environmentally benign approach was carried out in aqueous medium at room temperature with excess sodium hydroxide and a catalytic amount of sodium dodecyl sulfate (SDS) as a surfactant. While the vast majority of previous methods focused on the insertion of arylthiols, this work

Scheme 103. Alternative Source of Sulfur for the Formation of 2-Thiopyridines

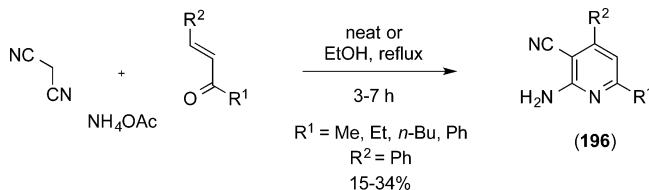


represents a nice complementary way to incorporate a thioalkyl substituent on the 2-position of the pyridine ring. Formaldehyde and acetaldehyde were also well-tolerated by the reaction conditions.

9.2. Synthesis of 2-Aminopyridines

A preliminary study on the synthesis of 2-aminopyridines was performed by Sakurai and Midorikawa several decades ago. As early as 1968, they described a multicomponent access to this scaffold by mixing a ketone, 2 equiv of malononitrile, and ammonium acetate under neat conditions.¹⁹¹ While this strategy is known as the modified Chichibabin synthesis (see section 3.4), they also reported a three-component access to 2-aminopyridines **196** involving an α,β -unsaturated ketone, malononitrile, and ammonium acetate under refluxing ethanol or neat conditions (Scheme 104). The yields were somehow poor due to

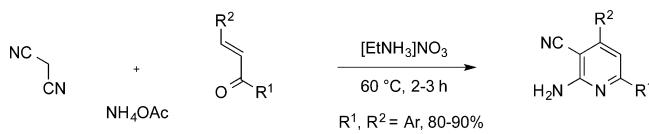
Scheme 104. Pioneer Works on the Three-Component Synthesis of 2-Aminopyridines



the formation of multiple unidentified side products, but this early study opened the window toward a new multicomponent approach to 2-aminopyridines. Eventually, the strategy has been applied to the synthesis of numerous 2-aminopyridines from a variety of chalcones by Manna et al. in the 1990s (Scheme 123).¹⁹² The associated yields were usually low, but the authors focused on some pharmacologic properties of these scaffolds. Thus, presence of an amino substituent on the 2-position of the pyridine ring substantially increased its anti-inflammatory activity, while some compounds also exhibited interesting analgesic properties.

Use of ionic liquid media for this transformation resulted in improved yields within shorter reaction times. Ethylammonium nitrate turned out to be the best ionic liquid to perform this reaction affording the corresponding 2-aminopyridines in high yields (Scheme 105).¹⁹³ This ionic liquid can be reused without significant loss of efficiency in this mild procedure.

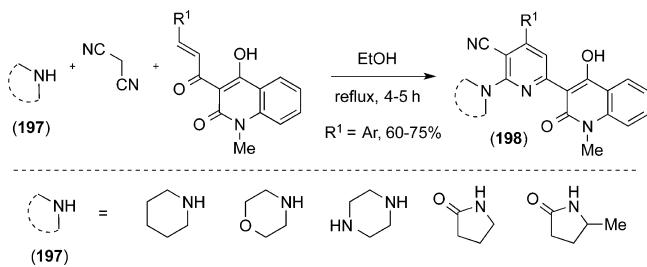
Scheme 105. Multicomponent Synthesis of 2-Aminopyridines in Ionic Liquid



Toche et al. demonstrated that the transformation was flexible enough, under refluxing ethanol conditions, to allow the use of cyclic secondary amine or a pyrrolidone **197** in place of ammonium acetate, thus giving access to diversely substituted 2-aminopyridines **198** in moderate to good yields (Scheme 106).¹⁹⁴ Efficient photophysical properties suggested a promising application of these nicotinonitrile derivatives in optoelectronics.

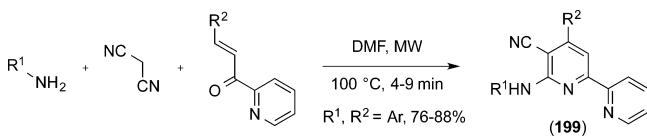
In 2006, Tu et al. extended the method to the microwave-assisted synthesis of 2,2'-bipyridines **199** in DMF, introducing

Scheme 106. Three-Component Synthesis of Potential Organic Light Emitting Diodes



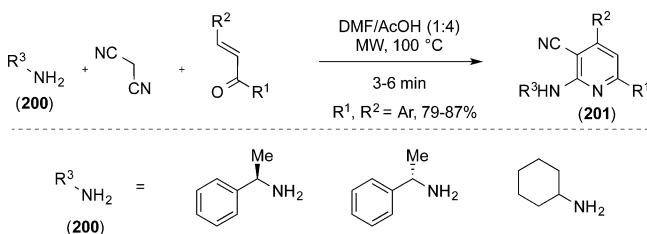
aniline derivatives on the 6-position. High yields were obtained with this reaction that accommodated either electron-withdrawing or electron-donating substituents on both the aniline moiety and the Michael acceptor (Scheme 107).¹⁹⁵

Scheme 107. Three-Component Access to 6-Amino-2,2'-bipyridine Scaffolds



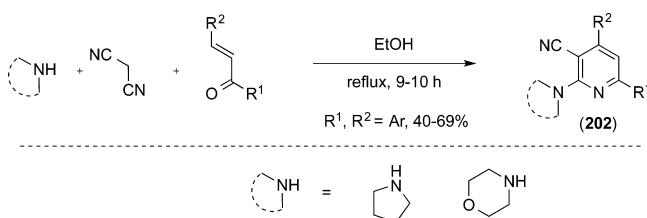
Shortly after, they broadened the scope of this reaction to a variety of chalcones under the same reaction conditions with good yields (76–89%).¹⁹⁶ The crucial role of the solvent in this transformation was also highlighted. Indeed, nonaromatic amine **200** led to the expected 2-aminopyridines **201** using a DMF/acetic acid (1:4) system (Scheme 108).

Scheme 108. Three-Component Formation of 2-Aminopyridines from Primary Aliphatic Amines



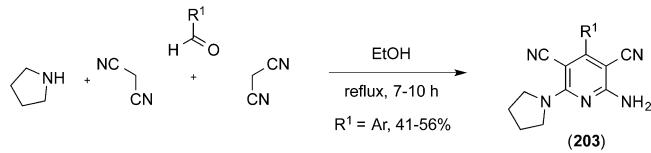
Alternatively, cyclic secondary amines such as pyrrolidine or morpholine, in combination with a chalcone and malononitrile in refluxing ethanol, provided the corresponding 2-aminopyridines **202** in moderate yields (Scheme 109).¹⁹⁷ Interestingly, the authors also reported a pseudo-four-components access to pentasubstituted 2-aminopyridines **203** with 2 equiv of malononitrile and replacement of the chalcone by an aromatic

Scheme 109. Three-Component Formation of 2-Aminopyridines from Secondary Aliphatic Amines



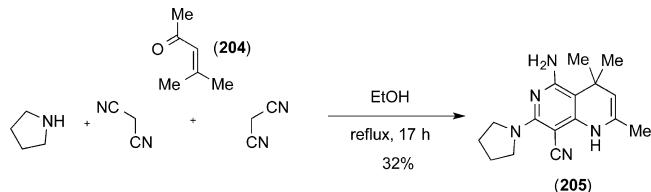
aldehyde (Scheme 110). Finally, the use of a β,β -disubstituted Michael acceptor **204** led to the formation of the original 1,4-

Scheme 110. Pseudo-Four-Component Synthesis of Pentasubstituted 2-Aminopyridines



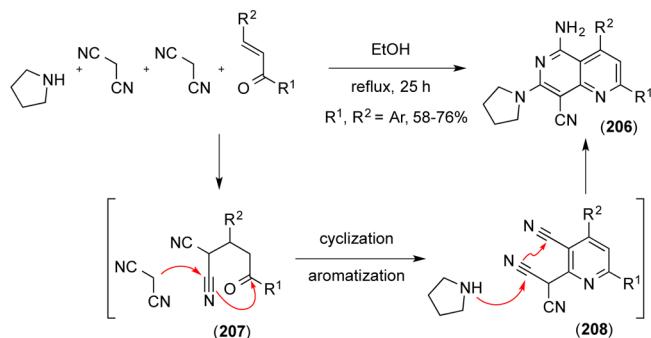
dihydro-1,6-naphthyridine **205** in 32% yield (Scheme 111). Nonlinear optical properties of these compounds were studied resulting in promising sets of data.

Scheme 111. Pseudo-Four-Component Synthesis of 1,4-Dihydro-1,6-naphthyridine **205**



Not surprisingly, 1,6-naphthyridines **206** were obtained from a β -monosubstituted Michael acceptor (Scheme 112). In fact,

Scheme 112. Pseudo-Four-Component Synthesis of Functionalized 1,6-Naphthyridines

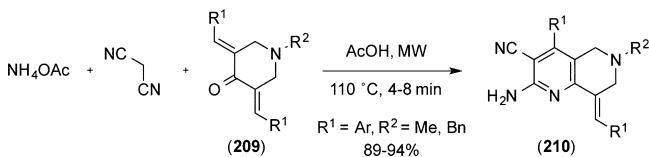


refluxing an ethanol solution of a chalcone, 2 equiv of malononitrile, and pyrrolidine led to this biologically important heterocyclic scaffold in fair to good yields.¹⁹⁸ Rationalization of the reaction outcome was not discussed. However, addition of the second equivalent of malononitrile onto one of the nitrile functionality of the Michael adduct **207** seemed to be faster than addition of pyrrolidine. Once the first cycle was formed affording pyridine intermediate **208**, addition of pyrrolidine induced the second ring-closure, affording highly substituted 1,6-naphthyridines.

In the same series, a library of 2-amino-tetrahydro-1,6-naphthylpyridines **210** has been recently synthesized thanks to a multicomponent reaction between malononitrile, ammonium acetate, and a 3,5-diarylidene-piperidin-4-one **209**. This high-yielding transformation was carried out at 110 °C in acetic acid under microwave irradiation (Scheme 113).¹⁹⁹ These works showed that the choice of solvent was crucial and could greatly

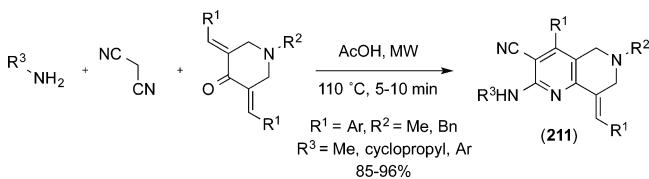
influence the reaction: tetrahydro-1,6-naphthylpyridines were not observed with DMF as solvent.

Scheme 113. Three-Component Synthesis of 2-Amino-tetrahydro-1,6-naphthylpyridines Derivatives



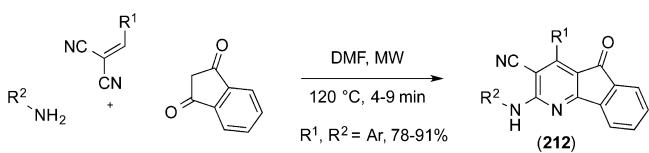
The scope of this reaction has then been enlarged to primary amines with great success.²⁰⁰ A large library of pyridines **211** has been designed from either aliphatic or aromatic amines under the exact same conditions (Scheme 114). Equal efficiency was observed for the formation of these highly functionalized heterocycles.

Scheme 114. 2-Amino-tetrahydro-1,6-naphthylpyridines Derivatives from Primary Amines



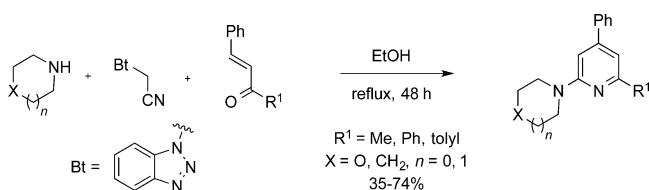
The synthesis of 2-amino-4-azafluorenones **212** can be accomplished from arylidene malononitriles, 1,3-indanodione, and a substituted aniline in DMF in a short reaction time under microwave irradiation (Scheme 115).^{201,179} This approach constitutes an interesting alternative to Hantzsch- and Chichibabin-based methodologies for the synthesis of 2-aminopyridines (sections 2 and 3, respectively).

Scheme 115. Three-Component Synthesis of 4-Azafluorenone Derivatives



Finally, Katritzky's group has proposed another synthetic way to 2-aminopyridines from α,β -unsaturated ketones (Scheme 116). In this strategy, the aza-substituent of the pyridine comes from the nucleophilic attack of an amine to the nitrile functionality of 2-(benzotriazol-1-yl)-acetonitrile.²⁰² The aromatization step is promoted by elimination of benzotriazole. Note that this idea was already exploited in a version of the Kröhnke

Scheme 116. Benzotriazole-Based Multicomponent Synthesis of 2-Aminopyridines

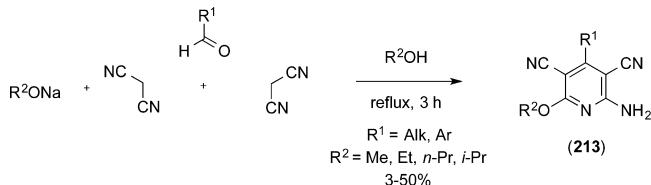


pyridine synthesis (section 7). The reaction occurred in refluxing ethanol with diverse secondary amines, and no competition was observed.

9.3. Synthesis of 2-Alkoxyppyridines

A similar approach to 2-alkoxyppyridines is more challenging since addition of alcohols onto a nitrile functionality requires activated conditions. In this context, alkali media currently lead the way and were reported in the literature as soon as 1970. Alvarez-Insúa et al. described a pseudo-four-component reaction in which an aldehyde, 2 equiv of malononitrile, and a sodium alkoxide were refluxed in the corresponding alcohol as the solvent (Scheme 117).²⁰³ Regioselective access to 2-alkoxyppyridines **213** was

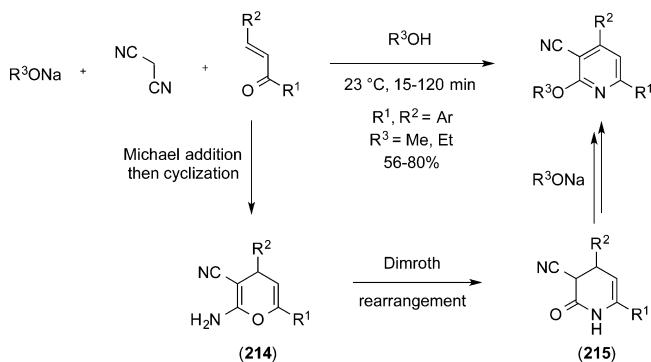
Scheme 117. Pioneering Multicomponent Synthesis of 2-Alkoxyppyridines



achieved in low yields from aliphatic aldehydes (3–32%) and low to moderate yields from aromatic ones (10–50%). The reaction was quite sensitive to steric effects. The authors reported that, in the same series, the yield decreased with secondary alkoxides as supposed to primary alkoxides (*i.e.*, isopropyl vs ethyl). Finally, tertiary alkoxides such as sodium *tert*-butoxide failed to provide the corresponding 2-alkoxyppyridine.

Twenty years later, Al-Arab reported a related three-component reaction involving malononitrile, sodium ethoxide or methoxide, and a chalcone (Scheme 118).²⁰⁴ This mild,

Scheme 118. Three-Component Synthesis of 2-Alkoxyppyridines

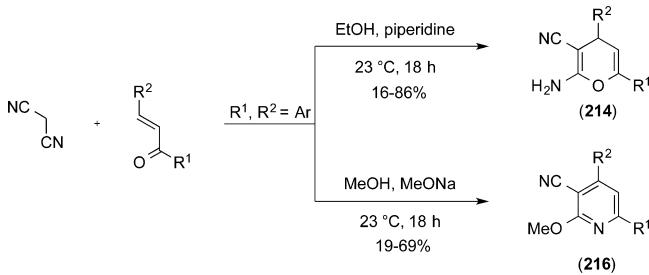


modified procedure positively impacted the overall yields, making this transformation more appealing in its three-component version. Interestingly, Al-Arab was the first to propose an amino pyran intermediate **214** to explain the formation of the alkoxyppyridine. According to him, this pyran could undergo a Dimroth rearrangement leading to the 2-pyridone **215**. Addition of the sodium alkoxide onto the carbonyl moiety followed by dehydration and aromatization would provide the expected pyridine ring.

If the mechanism of this transformation has not been demonstrated with certainty, reaction of malononitrile with chalcones has been a controversial topic. In 1988, Tyndall et al. reported a base-dependent divergent strategy yielding either

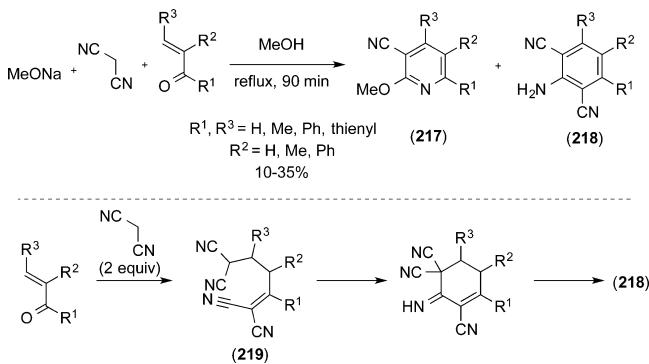
pyrans or pyridines.²⁰⁵ While pyrans were obtained with piperidine in ethanol, use of sodium methoxide in methanol resulted in the three-component formation of 2-methoxypyridines **216** in low to good yields (Scheme 119).

Scheme 119. Divergent Approach to Pyrans and 2-Methoxypyridines



If this method of synthesis of pyridines is reliable, it does not hold true for the synthesis of pyrans, which has been carefully revisited in 1991 by Victory et al.²⁰⁶ This study shed light on these discrepancies and demonstrated that weak bases such as piperidine actually led to a mixture of three compounds. None of these was the pyran reported by Tyndall. However, use of alkoxide did result in the formation of the 2-alkoxypyridine. Shortly after, the same group reported a three-component synthesis of 2-alkoxypyridines **217** from various Michael acceptors.²⁰⁷ The associated low yields were credited to the side-formation of pentasubstituted anilines **218** as mentioned previously (Scheme 120). Over addition of malononitrile onto

Scheme 120. Identification of Aniline Derivatives as Side Products of the Three-Component Reaction

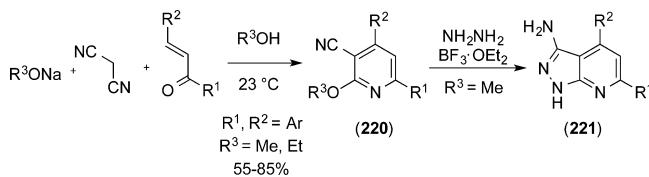


the Michael acceptor afforded the tetracyano intermediate **219**. Cyclization of the latter followed by elimination of hydrogen cyanide and tautomerization explained the formation of the observed anilines.

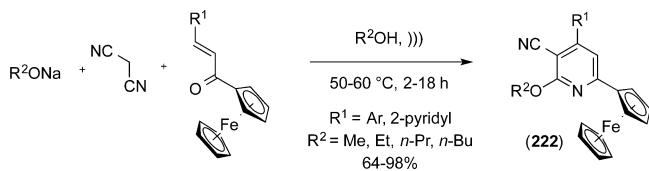
Within the past decade, the three-component synthesis of 2-alkoxypyridines from malononitrile, a Michael acceptor, and sodium alkoxide has been an area of intensive research efforts. For example, in 2004, Goda et al. reported the use of chalcones and sodium ethoxide or sodium methoxide at room temperature (Scheme 121). The 2-alkoxypyridines **220** thus obtained served as intermediates in the synthesis of pyrazolo[3,4-*b*]pyridines **221** that were evaluated as antimicrobial agents.²⁰⁸

In 2006, the scope of this transformation was extended to several ferrocene-containing Michael acceptors. Under ultrasound irradiation, ferrocenyl-substituted 2-alkoxypyridines **222** were obtained in good to excellent yields (Scheme 122).²⁰⁹

Scheme 121. Three-Component Synthesis of 2-Alkoxyppyridines as Pyrazolo[3,4-*b*]pyridines Precursors



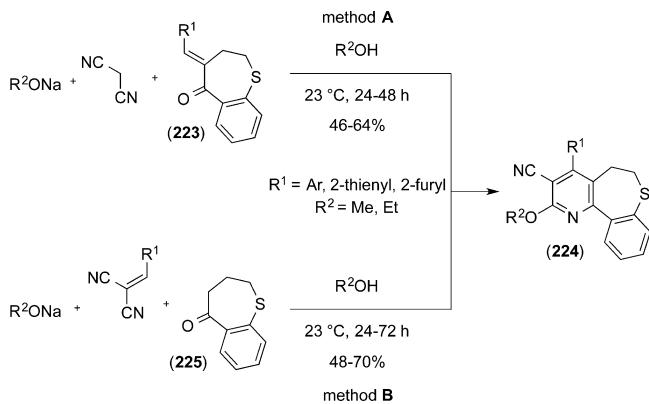
Scheme 122. Three-Component Access to Ferrocenyl-Substituted 2-Alkoxyppyridines



These products might find an interesting application as either metal ligands or drug candidates. It is noteworthy that the mild conditions of this reaction accommodated a variety of sodium alkoxides.

A year later, Girgis et al. adapted the method to the synthesis of benzothiepino[5,4-*b*]pyridine derivatives and studied their anti-inflammatory activity.²¹⁰ Two approaches were developed to regioselectively synthesize this valuable heterocyclic pharmacophore. First the reaction of 4-arylidene-benzothiepinone **223** with malononitrile and sodium alkoxide at room temperature led to the expected 2-alkoxypyridines **224** in moderate yields (Scheme 123, method A). The same scaffold was also accessed

Scheme 123. Multicomponent Approaches to the Benzothiepino[5,4-*b*]pyridine Core

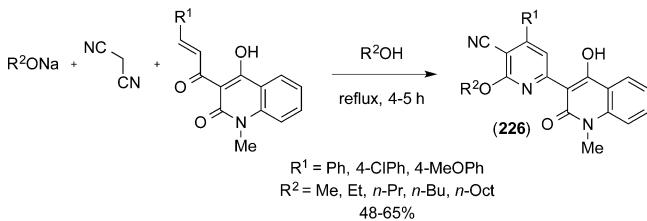


by mixing benzothiepinone **225** with an arylidene malononitrile and sodium alkoxide at room temperature (Scheme 123, method B). Overall, method B seemed slightly more efficient and adapted to this unique multicomponent synthesis of benzothiepino[5,4-*b*]pyridine derivatives.

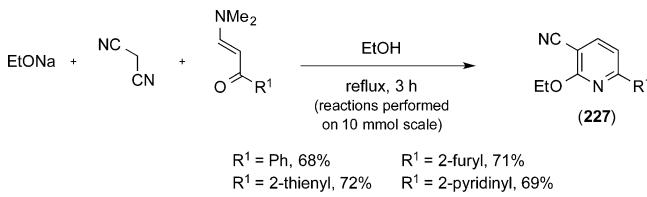
Under refluxing conditions, Toche et al. synthesized a library of 2-alkoxypyridines **226** incorporating various primary alcohols.¹⁹⁴ In fact, the sodium alkoxide species of methanol, ethanol, *n*-propanol, *n*-butanol, and *n*-octanol were successfully incorporated to the pyridine ring in moderate yields (Scheme 124). Optoelectronic properties of these products were studied.

In 1997, enaminoketones have been combined with malononitrile and sodium ethoxide in refluxing ethanol (Scheme 125).²¹¹ This system gave access to 4-unsubstituted 2-

Scheme 124. Multicomponent Synthesis of 2-Alkoxyppyridines as Potential Organic Light Emitting Diodes



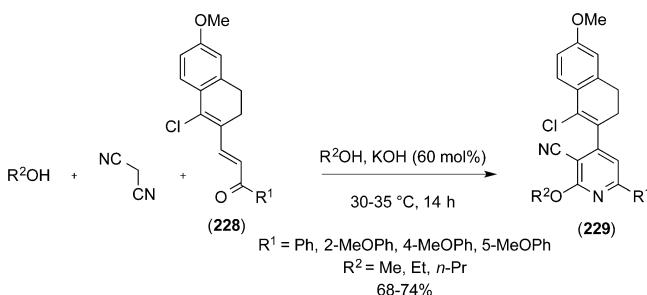
Scheme 125. Three-Component Synthesis of 2-Alkoxyppyridines from Enaminoketones



alkoxyppyridines **227**, by loss of dimethylamine within the aromatization step. This scalable method nicely complements other reports on the multicomponent synthesis of 2-alkoxyppyridines from sodium alkoxides.

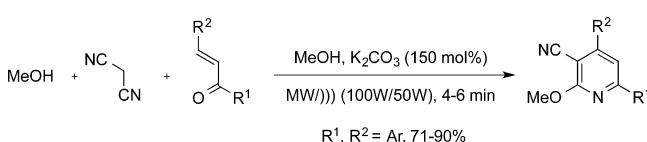
Potassium alkoxides are also suitable partners for this transformation. In 2009, Jachak et al. reported a potassium-hydroxide-catalyzed synthesis of 2-alkoxyppyridines **229** from Michael acceptor **228**, malononitrile, and methanol, ethanol, or *n*-propanol in good yields (Scheme 126).²¹² Photophysical data were collected, and the substitution pattern on aromatic substituent R¹ dramatically influenced the fluorescence properties of these pyridines.

Scheme 126. Three-Component Synthesis of 2-Alkoxyppyridines from Potassium Alkoxides



Recently, a combination microwave/ultrasound irradiation was developed to access 2-alkoxyppyridines using potassium carbonate as the base. Potassium methoxide was generated *in situ* and reacted with malononitrile and a variety of substituted chalcones in good to excellent yields and short reaction times (Scheme 127).²¹³ Better results were obtained with 2 equiv of

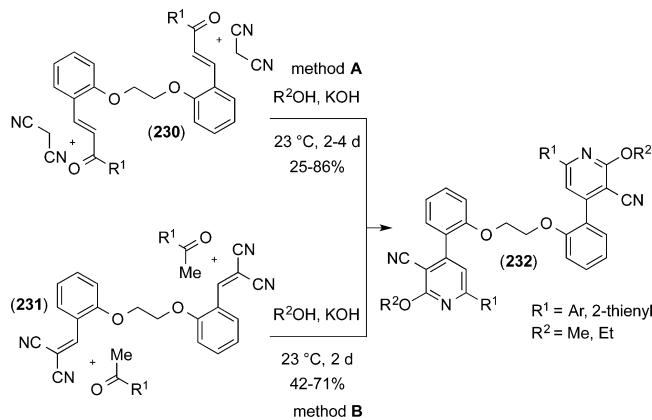
Scheme 127. Microwave/Ultrasound Combination for the Multicomponent Synthesis of 2-Alkoxyppyridines



chalcone: one being substrate of the reaction, and the other one being a hydrogen abstractor that facilitated the aromatization step. This reactivity was discussed in section 9.1 with arylidenemalononitrile according to the works of Evdokimov and Chen.¹⁷⁵⁻¹⁷⁷

In 2010, bis-Michael acceptors have been used as starting materials, resulting in the simultaneous formation of two 2-alkoxyppyridine rings.²¹⁴ The same scaffold was reached by either the reaction of a bis-chalcone **230** with malononitrile and potassium alkoxide (Scheme 128, method A), or by mixing a bis-

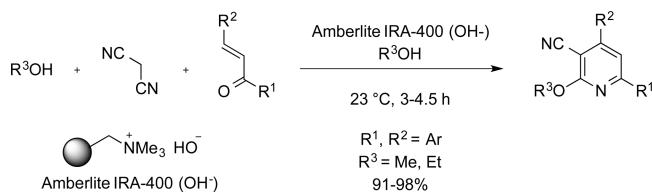
Scheme 128. Double Approach to the Pseudo-Five-Component Synthesis of Bis-2-alkoxyppyridines



arylidinemalononitrile **231** with an acetophenone derivative and potassium alkoxide (Scheme 128, method B). The reaction efficiency was substrate-dependent, and yields ranged from low to high. But the structural complexity and functional diversity associated with this pseudo-five-component reaction remained quite impressive. These bis-pyridine products **232** found their application in the treatment of hypertension. According to this SAR study, best vasodilatation activity was achieved with electron-poor aromatic substituents on the 6-position of the pyridine rings and ethoxy on the 2-position.

In 2013, a mild procedure was described by Bahrami et al. using a polystyrene-supported catalyst with a tetramethylammonium hydroxide functionality [Amberlite IRA-400 (OH^-)].²¹⁵ A series of chalcone derivatives was subjected to this reaction with malononitrile and methanol or ethanol at room temperature (Scheme 129). Remarkable yields of 2-alkoxyppyridines were

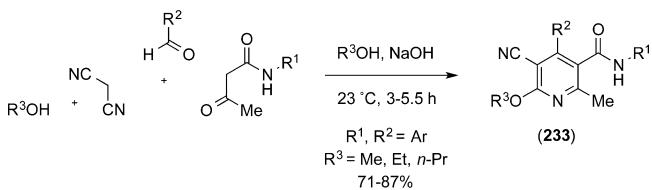
Scheme 129. Mild Three-Component Synthesis of 2-Alkoxyppyridines under Heterogeneous Catalysis



achieved with this system. The main advantage is the ease of manipulation of this recyclable heterogeneous catalyst that avoids harmful, strong homogeneous bases usually required to perform this transformation. However, the scope of the primary alcohol is quite limited, and both *n*-propanol and *n*-butanol failed to undergo this multicomponent reaction.

As originally described by Alvarez-Insúa,²⁰³ pentasubstituted 2-alkoxypyridines are also available by means of a pseudo-four-component reaction. This transformation involves malononitrile, an aldehyde, an activated ketone (usually 1,3-dicarbonyl derivatives), and an alcohol. In this context, an efficient, regioselective construction of nicotinamides **233** was recently proposed (Scheme 130).²¹⁶ The reaction of malononitrile, an

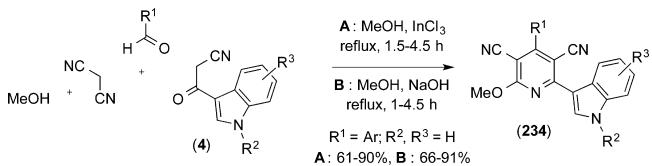
Scheme 130. Pseudo-Four-Component Synthesis of 6-Alkoxynicotinamide Derivatives



aromatic aldehyde, an acyclic β -ketoamide, and a primary alcohol occurred with excess sodium hydroxide at room temperature. It is noteworthy that ethyl acetoacetate was also successfully employed while acetylacetone and 2-propanol failed to provide the corresponding pentasubstituted pyridine.

Interestingly enough, Thirumurugan et al. enlarged the scope of this transformation to the use of β -ketonitriles **4** under Lewis acid activation ($InCl_3$, Scheme 131, conditions A)²¹⁷ or basic

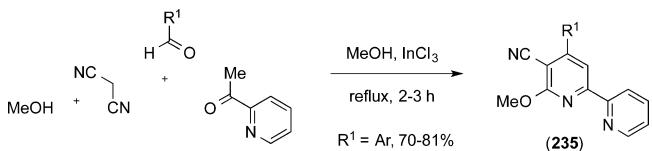
Scheme 131. Lewis Acid- and Base-Catalyzed Synthesis of 2-Alkoxypyridines from a β -Ketonitrile



conditions (NaOH, Scheme 131, conditions B).²¹⁸ In both scenarios, 3-(cyanoacetyl)indole reacted with an aromatic aldehyde, malononitrile, and methanol, providing the pentasubstituted 2-alkoxypyridines **234** in good to excellent yields. These heterocyclic cores displayed promising anti-inflammatory properties.

Indium-catalyzed multicomponent synthesis of 2-alkoxypyridines was further extended to 2-acetylpyridine (Scheme 132)

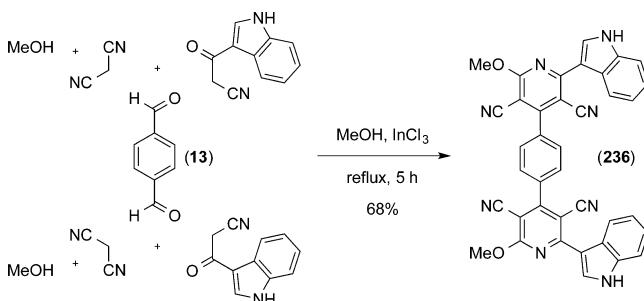
Scheme 132. $InCl_3$ -Catalyzed Multicomponent Synthesis of 6-Alkoxy-2,2'-bipyridines



allowing a direct efficient access to bis-pyridines **235**. On the basis of the same strategy, an impressive pseudo-seven-component reaction from aromatic bis-aldehyde **13** was also performed affording polycyclic bis-pyridines **236** in good yields (Scheme 133).²¹⁷

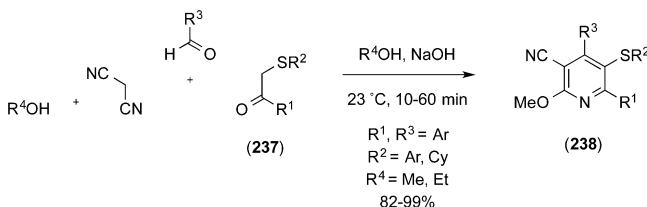
Finally, an original synthesis of 2-alkoxy-5-thiopyridines **238** was reported in 2010 by Manikannan et al.²¹⁹ The use of α -thioketones **237** in combination with malononitrile, an aromatic aldehyde, and methanol or ethanol led to the pyridine ring in

Scheme 133. $InCl_3$ -Catalyzed Pseudo-Seven-Component Synthesis of Bis-pyridines from a Bis-aldehyde



remarkable yields and short reaction times (Scheme 134). The mild basic conditions (room temperature) were applied to the

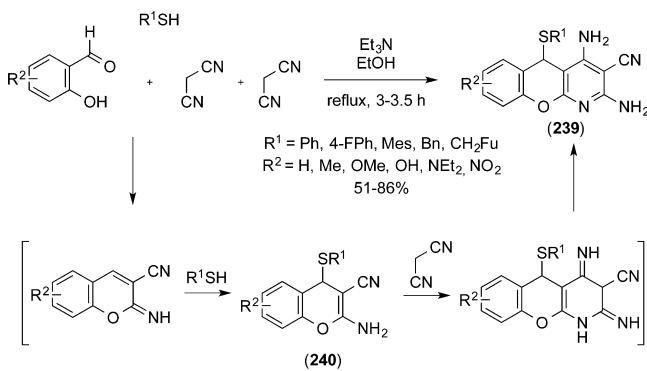
Scheme 134. Multicomponent Synthesis of Pentasubstituted 2-Alkoxy-5-thiopyridines



construction of a large library of pyridines. The latter showed interesting *in vitro* antimycobacterial activity against *M. tuberculosis* H₃₇Rv.

A particular case was discovered by Evdokimov et al. in 2006 while working on the synthesis of 2-thiopyridines. When a thiol and 2 equiv of malononitrile reacted with a salicylaldehyde derivative, chromeno[2,3-*b*]pyridines **239** were obtained instead of 2-thiopyridines (see section 9.1).²²⁰ A small library of these tricyclic 2-alkoxypyridines was elaborated using triethylamine in refluxing ethanol in moderate to good yields (Scheme 135). A

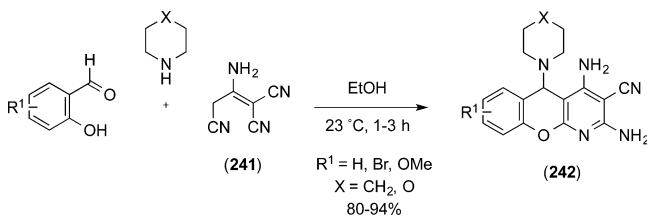
Scheme 135. Pseudo-Four-Component Synthesis of Chromeno[2,3-*b*]pyridines from Salicylaldehydes



mechanism was proposed and empirically determined¹⁷⁵ to rationalize this result, starting from the formation of the arylidene malononitrile. Cyclization of the phenol onto a nitrile functionality followed by thio-Michael addition provided enaminonitrile intermediate **240**. The latter reacted with the second equivalent of malononitrile furnishing after tautomerization the observed benzopyranopyridine scaffold. The expected 2-thiopyridines were not observed in this case.

The same transformation has recently been performed with a catalytic amount of potassium carbonate in refluxing ethanol/water (1:1) system.²²¹ A slight improvement of the yields was observed under these conditions, and the corresponding 5-thio-chromeno[2,3b]pyridine derivatives were formed within a few hours. Alternatively, when the thiol was replaced by a cyclic secondary amine, similar formation of 5-amino-chromeno[2,3b]-pyridines 242 was achieved. Shaabani et al. described a catalyst-free access to this core by means of a three-component reaction (Scheme 136).²²² A mixture of salicylaldehyde derivatives,

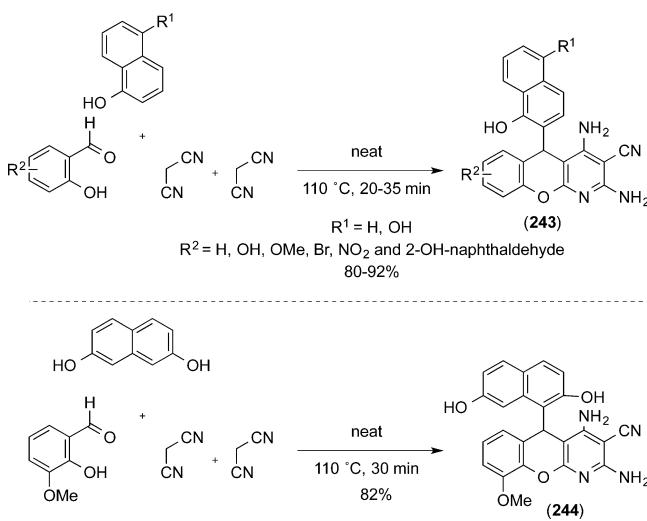
Scheme 136. Three-Component Synthesis of 5-Amino-chromeno[2,3b]pyridine Derivatives



secondary amines, and 2-amino-1,1,3-tricyanopropene (ATCP) 241 was stirred at room temperature in ethanol resulting in good to excellent yields.

Finally, in 2013, 1-naphthols have been successfully used as the nucleophile, leading to the corresponding 5-aryl-chromeno-[2,3b]pyridine scaffolds 243 and 244.²²³ This catalyst- and solvent-free pseudo-four-component transformation afforded the tri- or tetracyclic pyridines in high yields and short reaction times (Scheme 137). During this study, a single example demonstrated that the reaction could be performed with 2-naphthol derivatives as well.

Scheme 137. Pseudo-Four-Component Synthesis of 5-Aryl-chromeno[2,3b]pyridine



As shown in this section, multicomponent syntheses of pyridines from malononitrile have been intensively studied, especially over the past decade. The electrophilicity of the nitrile functionality allowed the incorporation of a variety of nucleophiles on the 2-position of the pyridine: thiol, amines, and alcohols. Concerning the latter, one could emphasize the fact that nucleophilic alcohols have to be the solvent of the reaction, which might limit the method to the use of inexpensive alcohols.

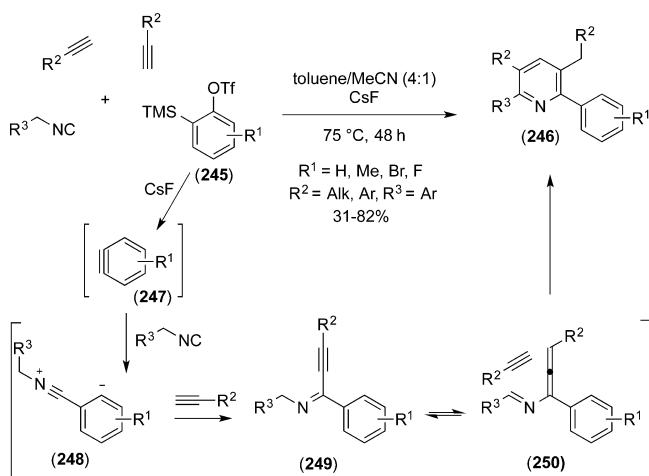
This also means that the field is still open to improvement, aiming to selectively introduce advanced material on the 2-position of the pyridine ring.

10. MISCELLANEOUS

Recently, a few unique multicomponent transformations have been reported to regioselectively access pyridines. These interesting methods demonstrated that creativity and originality can still be achieved in the field, and they will be pointed out in this section.

In 2009, an elegant method was described by Sha et al. to form tetrasubstituted pyridines 246 from an isonitrile, a terminal alkyne, and 2-(trimethylsilyl)-phenyl triflate 245 at 75 °C in a toluene/acetonitrile (4:1) mixture (Scheme 138).²²⁴ The

Scheme 138. Isonitrile-Based Pseudo-Four-Component Synthesis of Tetrasubstituted Pyridines

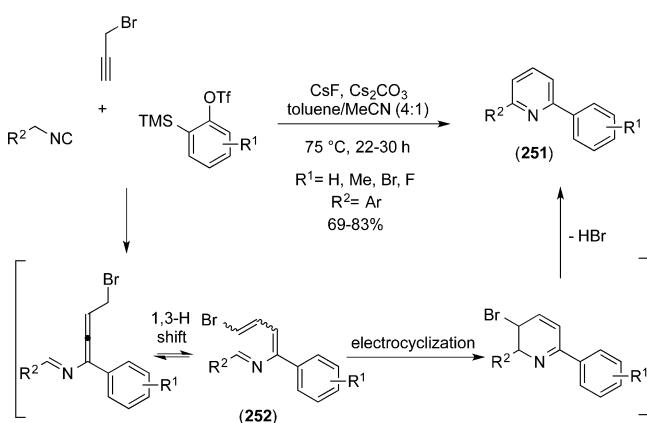


isonitrile added to an aryne intermediate 247, *in situ* generated by the action of cesium fluoride on 2-(trimethylsilyl)-phenyl triflate, inducing the formation of a zwitterionic intermediate 248 that is then trapped by the first equivalent of the terminal alkyne. The resulting propargylic imine 249 then isomerized to an allenyl imine 250, which was the partner of an aza Diels–Alder reaction with a second equivalent of the terminal alkyne. This sequence afforded the corresponding pyridine after migration of the exocyclic double bond. Besides, this study showed that polysubstituted quinolines could be formed using 1 equiv of the alkyne and 2 equiv of the aryne.

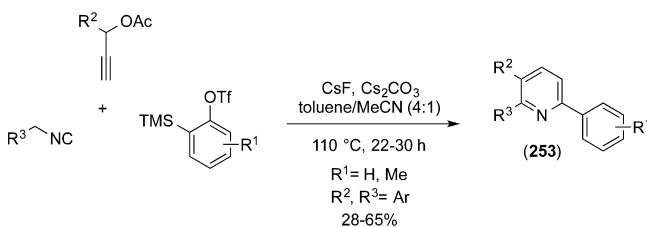
Later, the same authors confirmed their mechanistic hypothesis, by which the pyridine core was assembled through an aryne formation/isonitrile addition/alkyne addition/isomerization/aza-Diels–Alder sequence.²²⁵ More recently, they extended the method to the regioselective synthesis of di- and trisubstituted pyridines 251.²²⁶ To that end, they reasoned that using propargyl bromide as the alkyne partner would result, after 1,3-hydride shift, in an aza-triene intermediate 252, which can undergo an electrocyclization. Elimination of HBr should then afford the expected disubstituted pyridines. Their hypothesis proved correct when using cesium fluoride and cesium carbonate, in a toluene/acetonitrile (4:1) mixture at 75 °C (Scheme 139).

Formation of trisubstituted products from secondary propargyl bromide derivatives was trickier than expected. To tackle this synthetic challenge, the solution lied in the use of propargylic acetates along with higher temperature (Scheme 140). As a

Scheme 139. Isonitrile-Based Multicomponent Access to 2,6-Disubstituted Pyridines



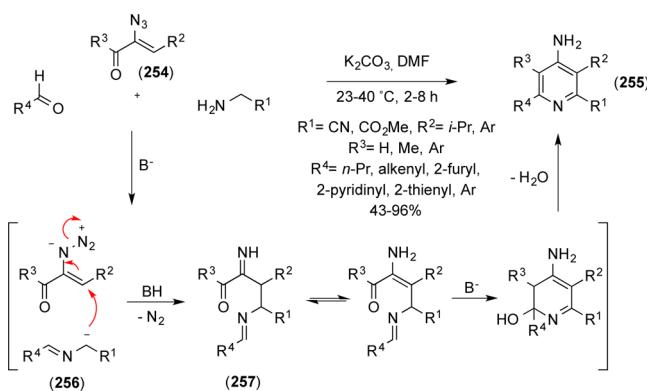
Scheme 140. Isonitrile-Based Multicomponent Synthesis of Trisubstituted Pyridines



result, a series of trisubstituted pyridines **253** was synthesized. However, yields remained low, and only aryl substituents were introduced on the 3-position of the pyridine ring (no reaction with R^2 = alkyl).

In 2012, Shao et al. reported an intriguing three-component synthesis of 4-aminopyridines. Pentasubstituted pyridines **255** were obtained in moderate to good yields by mixing an activated primary amine (*i.e.*, aminoacetonitrile or methyl glycinate), an aldehyde, and an α -azidovinylketone **254** in DMF with potassium carbonate (Scheme 141).²²⁷ Great functional diversity

Scheme 141. Three-Component Synthesis of Pentasubstituted 4-Aminopyridines

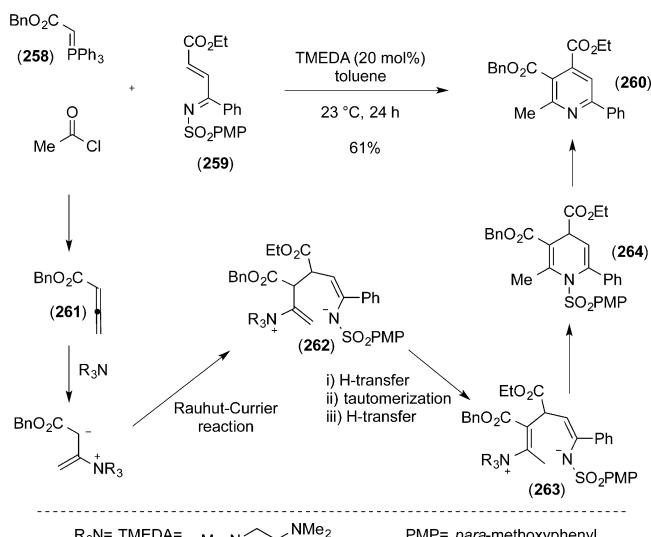


was achieved with this thoughtful strategy that accommodated aromatic, α,β -unsaturated, and aliphatic aldehydes. From a mechanistic standpoint, a sequence initiated by the formation of an imine **256** was proposed. Base-promoted 1,4-addition of this imine onto the α -azidovinylketone followed by extrusion of molecular nitrogen resulted in bis-imine intermediate **257**.

Equilibration toward the enamino-imine followed by base-promoted cyclization and dehydration completed the proposed sequence.

Very recently, an organocatalyzed three-component synthesis of a tetrasubstituted pyridine **260** has been described by Shi and Loh.²²⁸ While they mainly developed a new two-component approach, a single three-component reaction was also reported. This unique and mild access to pyridines involved benzyl 2-(triphenylphosphoranylidene)acetate **258**, acetyl chloride, and *N*-sulfonyl-1-aza-1,3-diene **259** in toluene, at room temperature with an excess of tetramethylethylenediamine (TMEDA). The ylide reacted with acetyl chloride to generate *in situ* benzyl buta-2,3-dienoate **261**. This allene underwent a formal [4 + 2] cycloaddition with the aza-diene leading to the observed pyridine in 61% yield (Scheme 142). However, the role of TMEDA was

Scheme 142. Rauhut–Currier-Based Three-Component Synthesis of a Tetrasubstituted Pyridine



crucial in this transformation, and a Rauhut–Currier-initiated mechanism was proposed. 1,4-Addition of the tertiary amine onto the allene followed by addition of the resulting zwitterionic specie to the aza-diene might lead to the intermediate **262**. From there, a H-transfer/tautomerization/H transfer sequence should furnish the new zwitterionic specie **263**, suitably arranged for cyclization. Intramolecular aza-Michael addition followed by tertiary amine extrusion would give access to the 1,4-dihydropyridine **264** that could suffer a desulfonylation step to complete the cascade.

11. CONCLUSION

This compilation of selected examples of metal-free MCRs applied to the synthesis of pyridines²²⁹ clearly shows that these sequences are generally user-friendly and eco-compatible methodologies of high synthetic interest. With pyridine and its derivatives having great relevance in many areas of chemistry, further developments in this field will probably involve the application of MCR-based approaches to target-oriented and regioselective synthesis of these heterocycles. Over the past 100 years, the organic chemist toolbox has been filled with many improvements of well-known reactions to access the pyridine ring with usually high regioselectivity. There is no such thing as the best multicomponent synthesis of pyridines, and as highlighted in this review, it is a matter of substitution pattern

when it comes to choose a method. The very last section of this article also demonstrated that the field is still widely open to creativity and thoughtful new strategies to efficiently build new pyridine scaffolds. For example, to date, there is no highly efficient and environmentally friendly multicomponent access to halogenated pyridines (see section 5). This could be the next area of innovation since such heterocyclic building blocks would be highly valuable as intermediates in drug discovery. In summary, multicomponent strategies toward pyridines encompass the vast majority of “green chemistry” criteria and represent a solid, efficient, experimentally simple, and somehow elegant alternative to other methods.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies



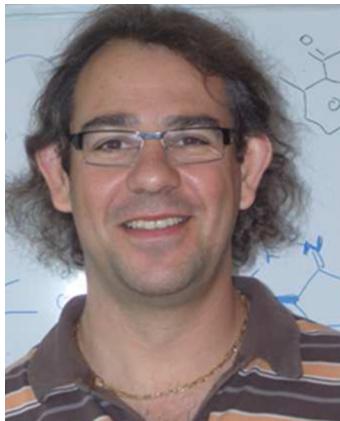
Christophe Allais was born in Cavaillon, France, in 1984. After studying chemistry at Aix-Marseille Université (France), he completed his Ph.D. under the supervision of Prof. T. Constantieux and Prof. J. Rodriguez in 2010. His work focused on the development of new, convergent, and selective approaches to various heterocycles, including multicomponent synthesis of highly functionalized pyridines. He then moved in early 2011 to The Scripps Research Institute as a postdoctoral research associate under the supervision of Prof. W. R. Roush. There he developed highly stereoselective boron-mediated methodologies in acyclic systems and studied their applications to the total synthesis of polyketides and alkaloids natural products. Since 2014, he has been a Senior Scientist at Pfizer in Groton, CT.



Jean-Marie Grassot was born in Valence, France, in 1980. After studying chemistry at l'Ecole Supérieure de Chimie Physique Electronique de Lyon, in 2004 he got his Master's degree in the laboratory of Professor Marco A. Ciufolini. He completed his Ph.D. under the supervision of Professor Jieping Zhu in December 2007 at the University of Paris-Sud XI. Then, he went to Edmonton, Canada, where he spent 18 months as a postdoctoral fellow in the laboratory of Professor Dennis Hall. In 2009, he joined the group of Professor Thierry Constantieux and Professor Jean Rodriguez at the University Paul Cézanne in Marseille to find new methodologies to access N-heterocycles. He moved then to the team of Dr. Jean-Luc Parrain, and worked on a medicinal chemistry project financed by Valorpac. After a period as medicinal chemist at Galapagos in Romainville, he is currently Head of project at AtlanChim Pharma in Saint-Herblain.



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