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The Xanthate Route to Pyridines[†]

Samir Z. Zard*

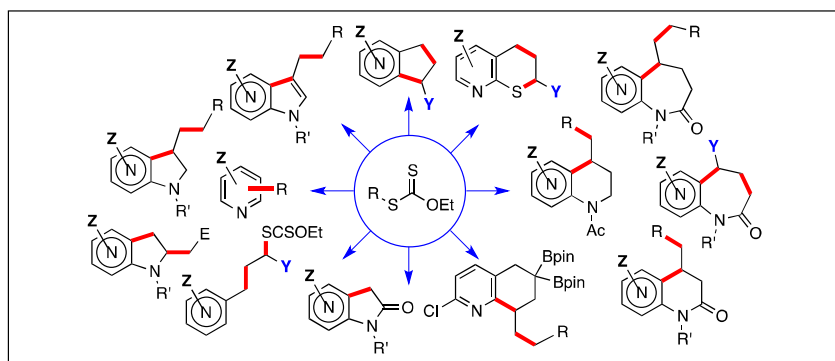
Laboratoire de Synthèse Organique associé au C. N. R. S., UMR 7652, Ecole Polytechnique,
91128 Palaiseau, France.

Fax: +33 169335972; Tel: +33 169335971

E-mail: samir.zard@polytechnique.edu

[†] This paper is dedicated to Professor Stephen G. Davies.

Graphical abstract



Abstract: Convergent routes to a variety of pyridines involving radical additions of xanthates are described. Emphasis is placed on reactions leading to tetrahydropyridines, which can be oxidized to pyridines, and to the formation of 1,5-diketones or 1,5-ketoaldehydes or their synthetic equivalents, which can then be condensed with ammonium acetate/–acetic acid under air in a variation of the classical synthesis of pyridines. The construction of pyridines fused to five-, six-, and seven-membered rings by intramolecular radical additions to the pyridine nucleus is also presented in detail. These include azaoxindoles, azaindoles, azaindanes, tetrahydronaphthyridines, and tetrahydropyridoazepines. Finally, the modification of pyridines by direct radical addition is discussed.

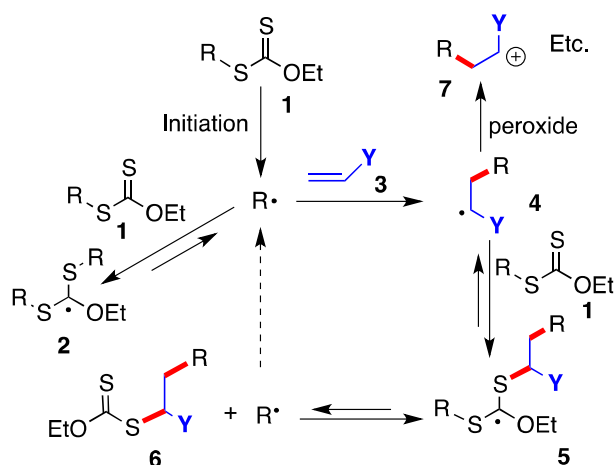
Keywords: pyridines; tetrahydropyridines; 1,5-diketones; xanthates; radical addition.

Introduction

Pyridines constitute perhaps the most important family of heteroaromatics.¹ The pyridine nucleus is indeed ubiquitous and can be found in countless alkaloids,² pharmaceuticals,³ agrochemicals,⁴ ligands for transition metal complexes,⁵ and high-performance new materials.⁶ Not surprisingly, a considerable effort has been devoted over the past decades to the development of efficient, flexible, and practical syntheses of pyridines with well-defined, varied substitution patterns.⁷ The vast number of methods that have been devised so far can be broadly divided into two categories. In the first, the pyridine nucleus is constructed *de novo* from open-chain fragments, whereas in the second an existing pyridine ring is modified regioselectively to provide more substituted structures. In the present brief review, routes based on the unique radical chemistry of xanthates are described.⁸ These, too, can be separated into the same two types of approaches and complement existing methods by furnishing structures not readily accessible otherwise.

General Features of the Degenerative Addition-Transfer of Xanthates

Xanthates **1** can be made to undergo a degenerative addition-transfer to alkenes **3** to give adducts **4** through the radical chain process outlined in simplified form in Scheme 1. This remarkable transformation hinges on the unique ability of xanthates to *store the active radicals*, namely R• and **4**, *in a rather unreactive dormant form*, under the guise of adducts such as **2** and **5**. These adducts are stabilized by three heteroatoms; they are too bulky to react rapidly with other radicals and are unable to disproportionate because they bear no β -hydrogens. They can, however, evolve by β -scission, thereby releasing radicals R• and **4** back into the medium. The continuous regeneration of the active radicals considerably enhances their *effective lifetime*, even in a concentrated medium, while simultaneously diminishing their *absolute concentration* and regulating their *relative concentration*. The actual mechanistic manifold is more complex and exceedingly subtle, and the interested reader is directed to reference 9 for a more comprehensive discussion.⁹



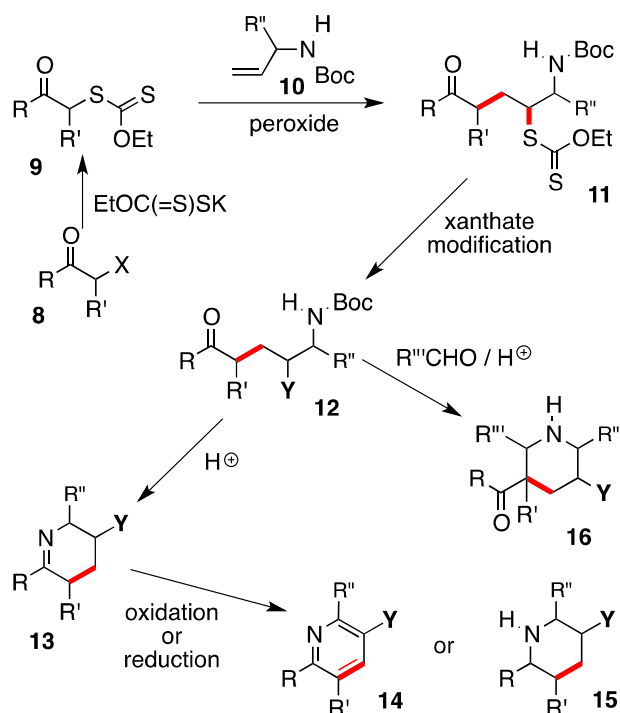
Scheme 1. Addition of a xanthate to an alkene

The sequence furnishes adduct **6**, where a new carbon-carbon bond and a new carbon-sulfur bond are formed. For the addition to be efficient, it is usually necessary to bias the equilibrium between radical **4** and $R\cdot$ in favor of the latter. In other words, the starting $R\cdot$ has to be thermodynamically more stable than adduct radical **4**, neglecting polar effects, which could be important, in a first approximation. This bias drives the desired process forward and limits the formation of oligomers by further addition of radical **4** to alkene **3**. In cases where this constraint is not respected and when the substituent Y on alkene **3** is an electron-donating stabilizing group, it is possible to oxidize adduct radical **4** to the corresponding cation **7**, which then can evolve through various typical ionic pathways. This possibility to cross over from the radical to the ionic manifold can be exploited in many synthetically useful transformations, a few of which will be discussed in the present overview.

The ability of xanthates and their congeners to create new carbon-carbon bonds in an intermolecular setting, starting with both activated and electronically unbiased alkenes, combined with the broad tolerance of radical reactions for many polar and non-polar groups, translate into vast possibilities for organic synthesis. More generally, the increased lifetime of the intermediate radicals through the fast and effective reversible storage in a masked dormant form provides a means for overcoming the energy barrier of elementary steps that have (relatively) slow kinetics and that cannot be easily exploited for synthetic purposes by other methods. In the context of pyridines, the applications of xanthate chemistry can be divided into three categories. The first consists of constructing the pyridine ring by assembling together separate elements. The second hinges on creating a ring through an *intramolecular* addition of a radical to the pyridine nucleus. This ring-closing step could be combined with an intermolecular addition of a xanthate to attain more complex structures. The third, finally, relies on the *intermolecular* addition of a xanthate to the pyridine nucleus, so as to directly introduce extra substituents. Each of these approaches will be discussed in the following sections and illustrated, whenever possible, with examples underscoring flexibility and modularity.

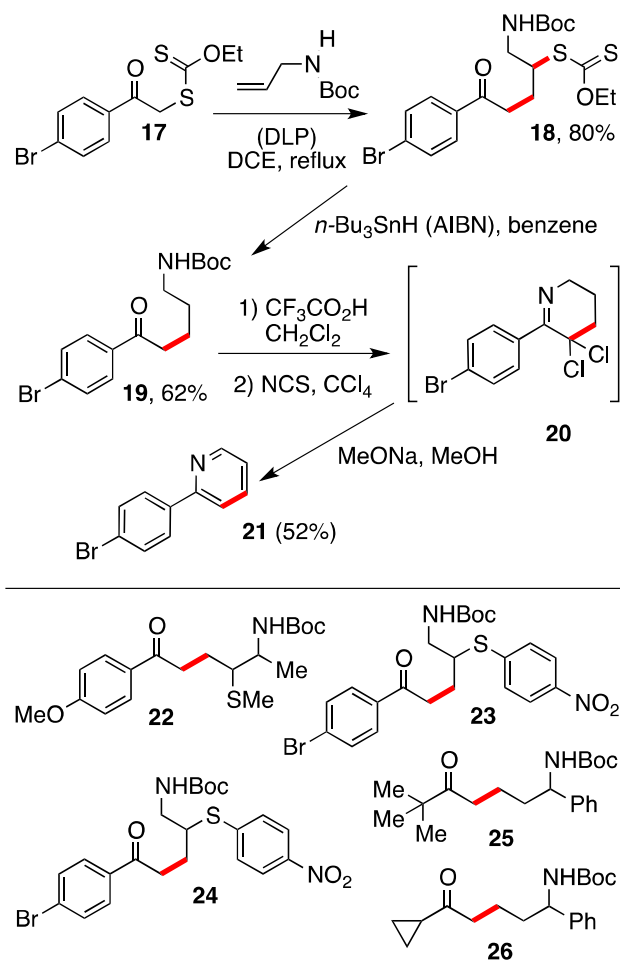
Pyridines by De Novo Ring Construction

One important feature of the xanthate-based process described above is the ease of generating and capturing α -ketonyl radicals.¹⁰ The requisite precursors **9** are accessible by various routes, the simplest and most common of which is through reaction of a ketone bearing an adjacent leaving group (**8**, X = nucleofuge) with potassium *O*-ethyl xanthate (Scheme 2). The xanthate salt is industrially available on very large scale and is exceedingly inexpensive (bulk price around *two* US dollars per kg!); it is also an excellent nucleophile. The radical addition of xanthate **9** to protected allylamine **10** readily furnishes the corresponding adduct **11**, where the ketone and the amine are ideally positioned for ring closure into tetrahydropyridine **13**, after reductive removal or modification of the xanthate moiety and deprotection of the amino group.¹¹ Tetrahydropyridine **13** can then be oxidized into pyridine **14** or reduced into piperidine **15**, if the latter is desired. The chemistry of pyridines and piperidines is intertwined so that in many cases they be interconverted, and access to one often allows access to the other. In this respect, it is interesting to note that intermediate **12** could in principle undergo a Mannich reaction with an aldehyde to give piperidine **16**, which, could be oxidized to the corresponding pyridines (not shown) in cases where R' = H. This approach would be highly modular in that it combines three separate and easily modifiable components. Two other aspects deserve mentioning. The first is that by using protected *homoallyl* amines, the radical sequence ultimately leads to the corresponding azepines. The second is that by replacing the ketone with an ester, the ring-closure step furnishes a piperidone, which could equally be transformed into a pyridine in principle. Seven- and even eight-membered ring lactams can also be made by such an approach.¹²



Scheme 2. Synthesis of piperidines and pyridines

An example of this route to pyridines is displayed in Scheme 3. The addition of *S-p*-bromophenacyl xanthate **17** to Boc-protected allylamine, initiated by dilauroyl peroxide (DLP; also sold under lauroyl peroxide, Laurox[®] or Luperox LP[®]) gives the expected adduct **18** in good yield.¹¹ Reductive removal of the xanthate with stannane, deprotection of the amine, and aromatization using a procedure described by De Kimpe and co-workers¹³ finally provides 2-*p*-bromophenyl pyridine **21** via intermediate dichloride **20**. Tri-*n*-butylstannane is one of many reagents capable of reducing off the xanthate group. Two other reducing systems have been found very useful, namely Barton's hypophosphorous salts¹⁴ and a combination of stoichiometric DLP and isopropanol.¹⁵ Both procedures use inexpensive reagents, are easy to scale up, and avoid completely the use of toxic and ecologically unacceptable heavy metals. One further advantage of the DLP/isopropanol combination is that no obnoxious smells are produced, making it especially suitable for large scale work. Five other Boc-protected δ -aminoketones **22-26** are pictured in the lower half of Scheme 3. They have been prepared by the generic sequence outlined in Scheme 2 and converted into the corresponding tetrahydropyridines or piperidines but not aromatized into pyridines.¹¹



Scheme 3. Pyridine synthesis from δ -aminoketones

Other common protecting groups for the amine moiety are compatible with the radical addition besides the Boc group. Phthalimides **27a-c** in Figure 1 have been prepared and cyclized into tetrahydropyridines in the same study.¹¹ Numerous such protected δ -aminoketones were later prepared for other purposes and which could in principle be transformed into the corresponding pyridines if desired. They are assembled in Figure 1 in order to give an idea of the potential scope of this strategy. Compound **28**,¹⁶ for instance, could act as a precursor to a cyclobutanol substituted pyridine. Heteroaromatics bearing small ring appendages are becoming increasingly important in medicinal chemistry.¹⁷ Protected δ -aminoketones **29** and **30** are readily prepared and contain a masked aldehyde motif.¹⁸

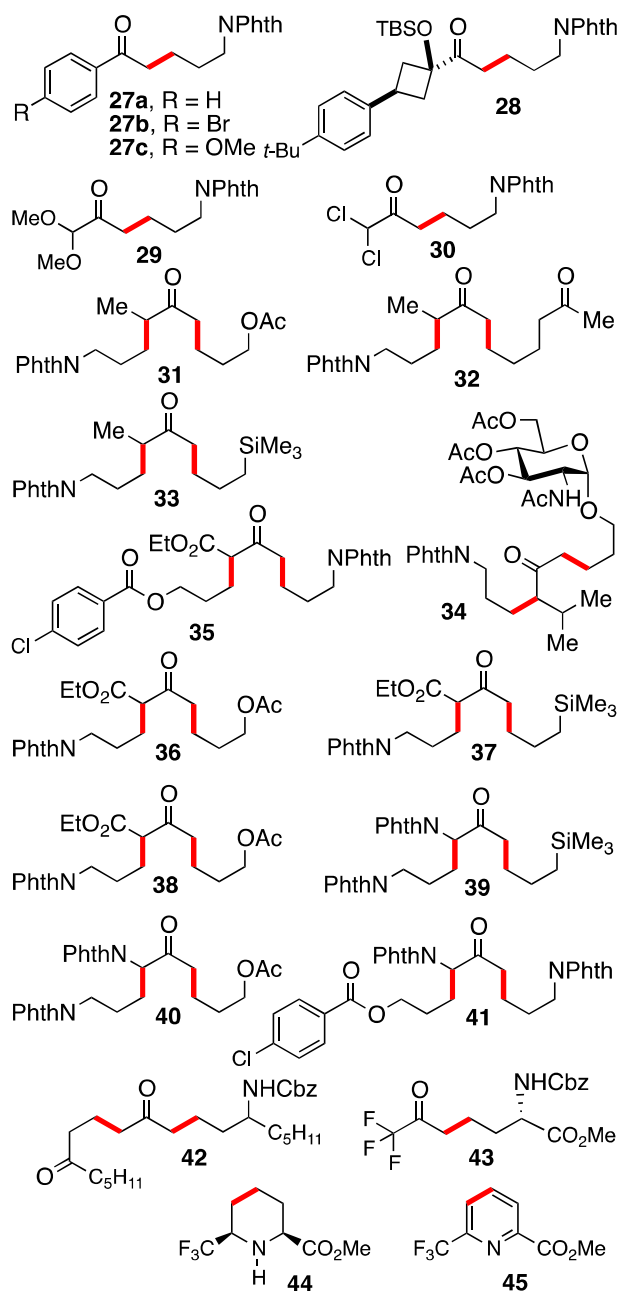
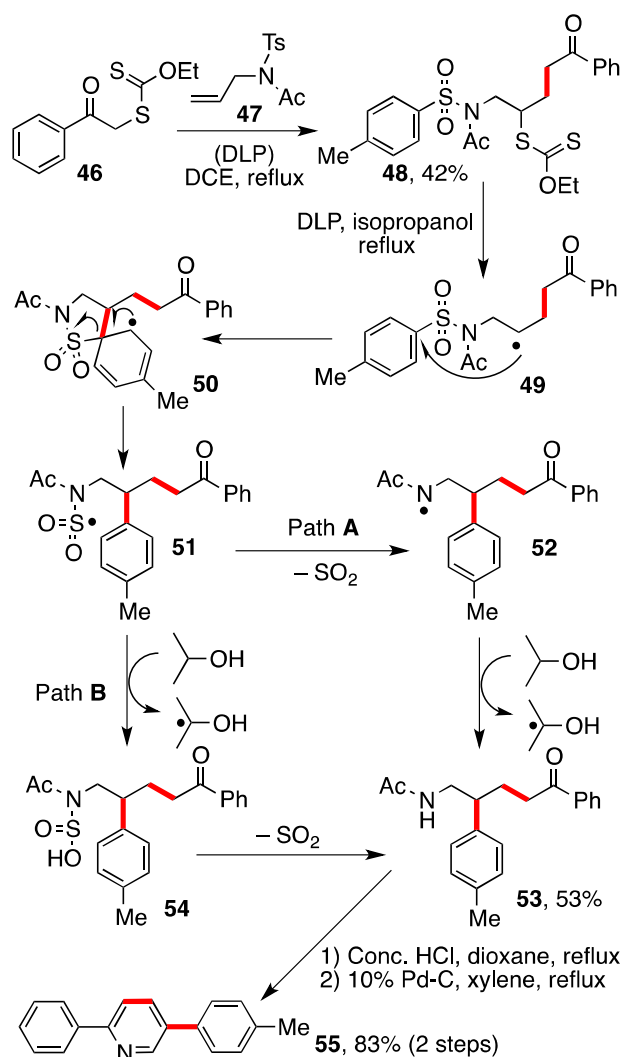


Figure 1. Further examples of δ -aminoketones (NPhth = phthalimide)

The significantly more complex phthalimide protected δ -aminoketones **31-41** were obtained through sequential radical additions to two different alkenes.¹⁹ They could provide substituted pyridines which would be exceedingly tedious to prepare by more conventional routes. Cbz-protected δ -aminoketone **31**,²⁰ a potential precursor for the total synthesis of gephyrotoxin, was also obtained by two sequential radical additions starting from *S*-3-chloroacetyl xanthate. Finally, aminoketone **43** derives from the addition of *S*-3,3,3-trifluoroacetyl xanthate to protected vinyl glycine.²¹ It was easily converted into enantiomerically pure

pipecolate **44** upon catalytic deprotection and reductive cyclization of the resulting amine onto the ketone. In principle, trifluoromethyl picolinate **45** could have been produced under oxidative dehydrogenating conditions.

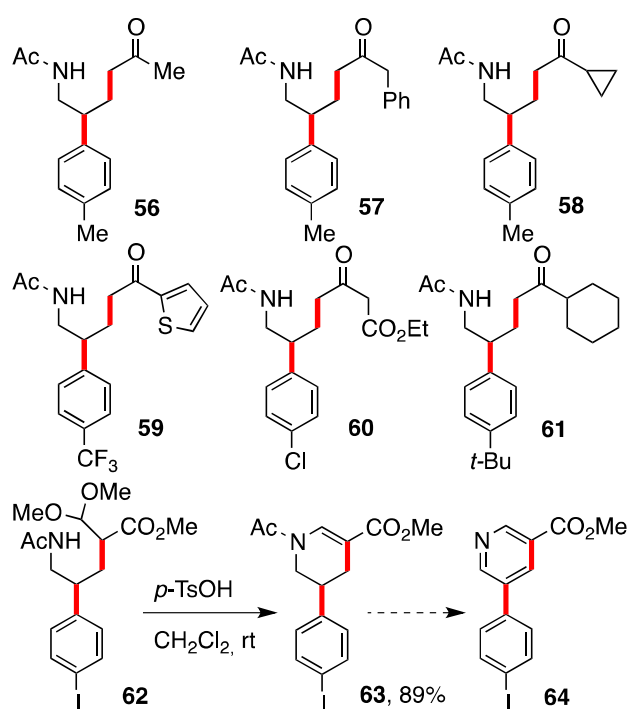
Aryl-substituted pyridines can be crafted in an unusual way by exploiting a radical Smiles rearrangement.²² This is accomplished by using *N*-allyl arylsulfonamides as the olefinic trap, as illustrated by the example depicted in Scheme 5.²³ Thus, exposure of adduct **48**, produced by radical addition of xanthate **46** to sulfonamide **47**, to stoichiometric amounts of DLP in isopropanol triggers a sequence of events leading to *N*-acetyl δ -aminoketone **53**. Radical **49**, generated by the action of the peroxide on xanthate **48**, undergoes an *ipso* substitution to give sulfonyl radical **51** via intermediate spiro intermediate **50**. Two non-mutually exclusive pathways are open to this sulfonyl radical, both of which lead to the desired δ -aminoketone **53**. In path **A**, loss of sulfur dioxide to give amidyl radical **52** precedes hydrogen atom abstraction from isopropanol, whereas in Path **B** hydrogen atom abstraction from the solvent takes place first.



Scheme 5. Synthesis of δ -aminoketones *via* a radical Smiles rearrangement

Hydrogen atom abstraction from isopropanol is sufficiently slow to allow radical **49** to attack the aromatic ring to produce key intermediate **50**. Hydrolysis of the acetamide in product **53** liberates the amino group, which spontaneously cyclizes onto to the ketone to give a cyclic imine (not shown). Dehydrogenation, without prior purification, by heating with 10% Pd/C under air provides the desired pyridine **55** in good yield for the two steps. In this route to pyridines, two new carbon-carbon bonds are created, the first intermolecularly in the addition step and the second during the intramolecular radical Smiles rearrangement.

This modular, three-component strategy, where an aryl moiety is moved within the initial addition product to take the place of the xanthate group through the radical Smiles rearrangement, provides a flexible and fast route to aryl-substituted δ -aminoketones.²³ In Scheme 6 are collected examples of such δ -aminoketones (**56-62**), each of which could in principle be transformed into the corresponding pyridine by hydrolysis of the acetamide and dehydrogenation.

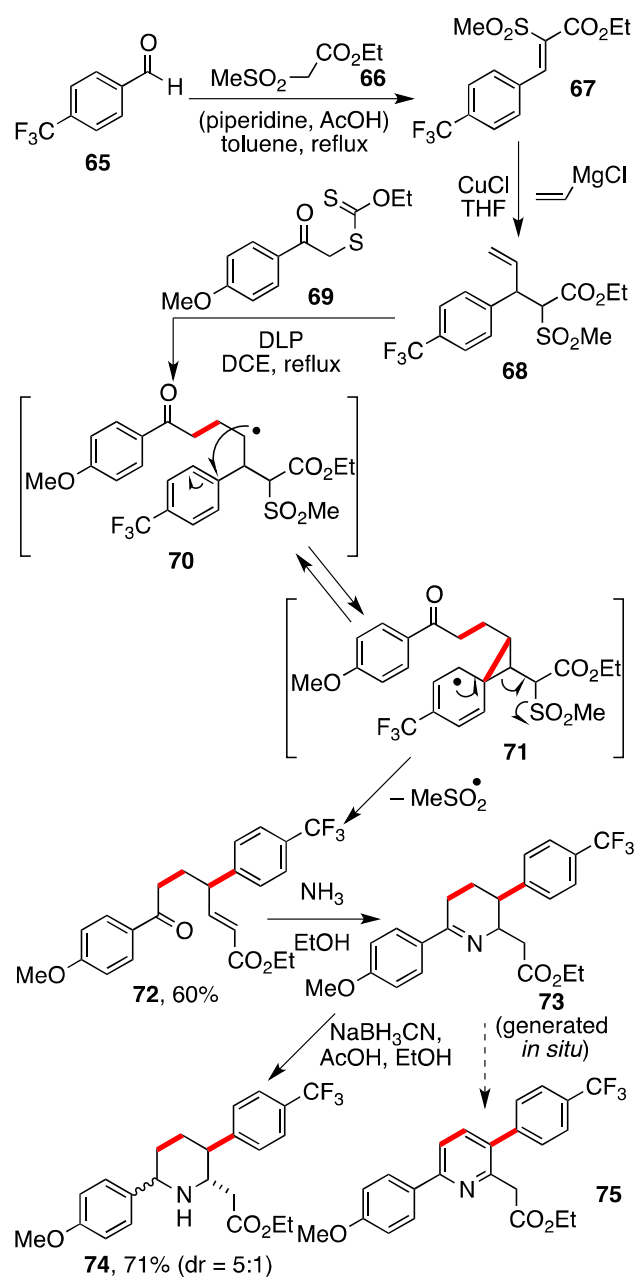


Scheme 6. Further examples of aryl-substituted δ -aminoketones

It was found, interestingly, that the intermolecular radical addition was significantly more efficient when the *N*-allyl sulfonamide was not acetylated (i.e. compound **47** with H instead of Ac), presumably because of a better polarity matching (the α -ketonyl radical has an electrophilic character and reacts faster with electron-rich alkenes). In most of the examples pictured in Scheme 6, the acetylation was performed *after* the radical addition of the xanthate. The acetylation improves the efficiency of the Smiles rearrangement and avoids the formation

of a basic amine following the rearrangement. In the case of compound **62**, the ketone is replaced by a masked aldehyde and the xanthate group is placed geminal to the ester, which provides the corresponding radical with the required stability need to control the process. As discussed in the introductory section in connection with the mechanism (Scheme 1), the initial radical **R•** has to be more stable than adduct radical **4**. Upon treatment with acid, the acetamide readily cyclizes onto the acetal to give tetrahydropyridine **63**, a reasonable precursor to pyridine **64**.

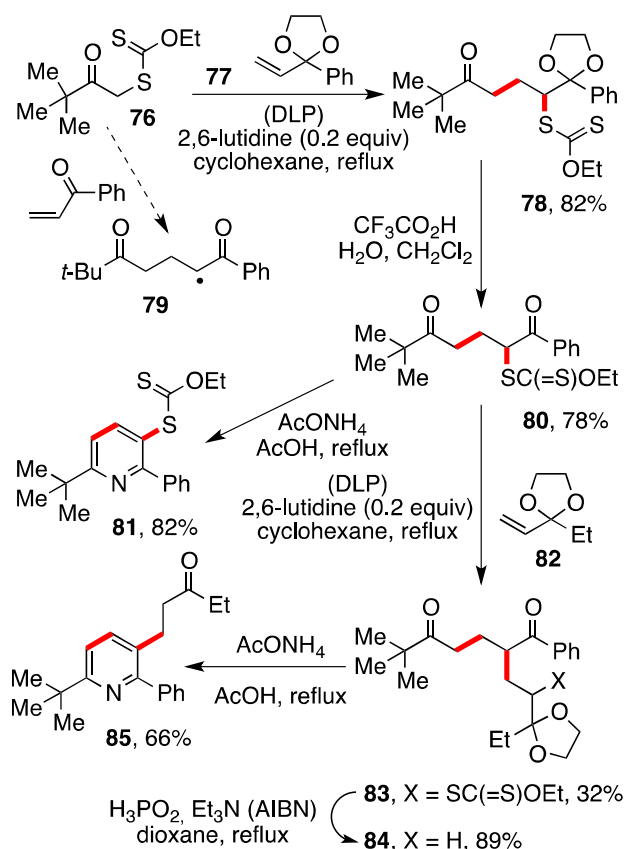
Another approach to introduce an aromatic motif into the δ -aminoketones takes advantage of the well-known but little used radical neophilic rearrangement.²² This conception is illustrated by the transformation in Scheme 7.²³ The requisite alkene precursor **68** is easily obtained by a Knoevenagel condensation of commercially available sulfone **66** with aldehyde **65** to furnish compound **67**, followed by a vinyl cuprate addition to the electrophilic alkene. The addition of xanthate **69** to alkene **68** gives radical **70**, which reacts reversibly with the neighboring aromatic ring to give spiro radical **71**. Ring opening and elimination of methylsulfonyl radical drives the equilibrium towards the formation of unsaturated ester **72**. This compound contains two electrophilic centers, the ketone and the electrophilic alkene, so that exposure to ammonia results in a combination of Michael addition and condensation with the ketone to give cyclic imine **73**. By performing this sequence in the presence of sodium cyanoborohydride and acetic acid, the imine is directly reduced into piperidine **74**, which is the actual isolated product. Oxidative dehydrogenation, instead of reduction, would provide the corresponding pyridine **75**. This potential route to pyridines could prove to be even more powerful than the previous one based on the Smiles rearrangement, simply because of the vastly greater availability of the aldehyde component as compared to the arylsulfonyl chloride and the possibility of replacing the ester in the Knoevenagel reagent **66** with essentially any electrophilic group (e.g. ketone, nitrile, sulfone, phosphonate).



Scheme 7. Synthesis of δ -aminoketones *via* a neophyl rearrangement

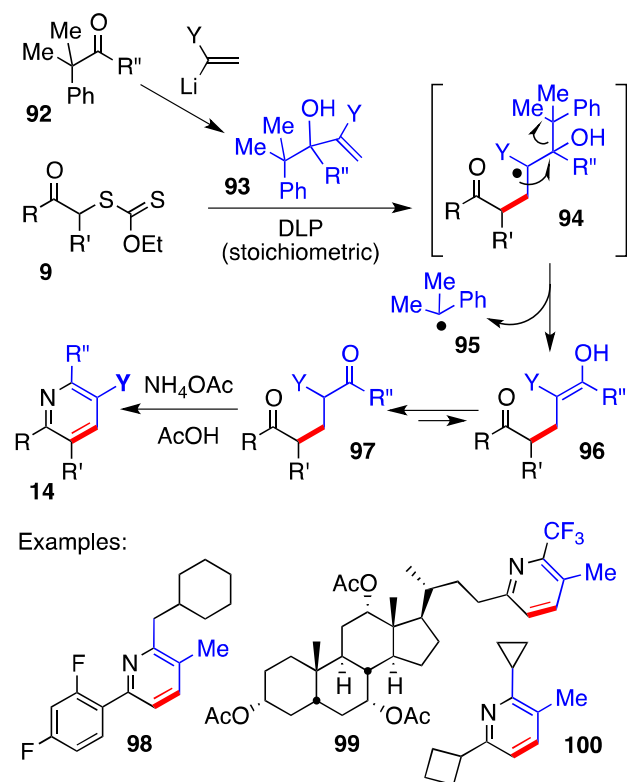
The above transformations derive from studies aimed mostly at the synthesis of piperidines rather than pyridines. Thus, all of the varied δ -aminoketones described so far have been cyclized into the corresponding piperidines, and only a few have been converted into pyridines, even though this could have been accomplished in many cases and would have provided valuable pyridine building blocks. A more focused approach to pyridines was made through the ability of this xanthate chemistry to also provide access to 1,5-diketones and 1,5-ketoaldehydes. These are well-known classical precursors to pyridines by reaction with hydroxylamine or ammonia under mild acidic conditions.²⁴

1,5-Diketones can be prepared by conjugate addition of an enolate or equivalent, such as an enol silyl ether (the Mukaiyama reaction), to an α,β -unsaturated ketone. Boivin and co-workers reported an overall equivalent radical process by adding α -ketonyl xanthates to 2-vinyl dioxolanes.²⁵ Thus, the reaction of xanthate **76** with alkene **77** to give adduct **78** proceeds efficiently in the presence of a small amount of 2,6-lutidine to protect the highly acid labile dioxolane motif (Scheme 8). The direct addition to unprotected phenyl vinyl ketone proceeds poorly because the intermediate adduct radical **79** is stabilized by the ketone and, being secondary, it is more stable than the primary radical (not shown) derived from starting xanthate **76**. This the opposite to the requirement stated above, that the initial radical has to be more stable than the adduct radical, barring any special polar factor. It is therefore necessary to neutralize the stabilizing influence of the ketone by masking it as a dioxolane.



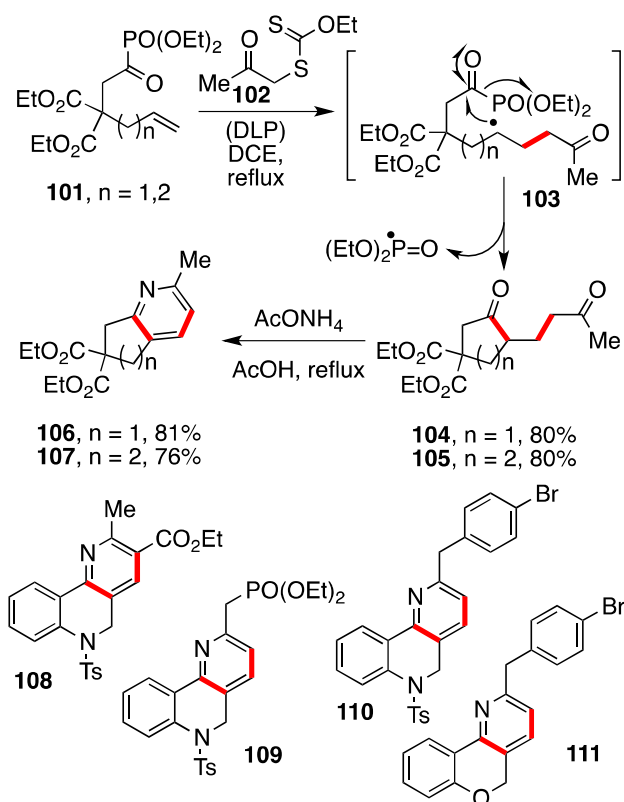
Scheme 8. Synthesis of pyridines from 1,5-diketones

Mild acid hydrolysis of the dioxolane furnishes 1,5-diketone **80** and treatment with ammonium acetate and acetic acid under air gives the expected pyridine **81** in good overall yield. It is noteworthy that the xanthate group survives both steps. Its hydrolysis in the case of compound **81** would provide a 3-mercapto-pyridine (not shown) that would not be easily accessible by other more traditional pyridine syntheses. Furthermore, the radical derived from the xanthate in intermediate **80** is now next to the freed ketone and therefore benefits from its



Scheme 9. An addition-fragmentation route to pyridines

Heating 1,5-dicarbonyl product **97** with ammonium acetate in acetic acid then delivers the corresponding pyridine **14**. This approach is further illustrated by the synthesis of pyridines **98-100**. Bile acid derived pyridine **99** bears a trifluoromethyl appendage, whereas pyridine **100** is substituted by both a cyclobutyl and a cyclopropyl group. A broad diversity of pyridines could be readily attained by modifying the substituents on xanthate **9**, substituent R'' in ketone **92**, and substituent Y in the vinylmetal reagent.



Scheme 10. Acylphosphonate route to pyridines

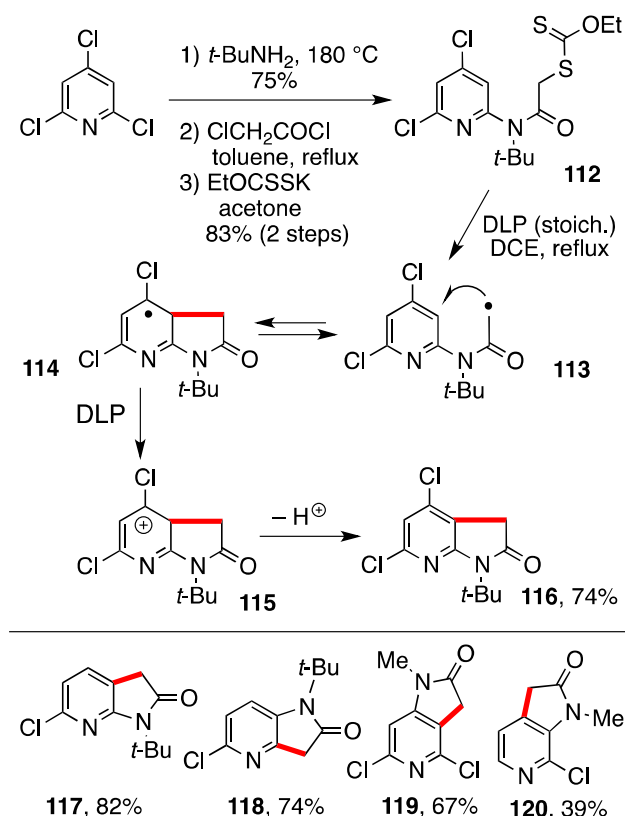
Another counter-intuitive construction of 1,5-dicarbonyl precursors is displayed in Scheme 10.²⁸ Addition of acetyl xanthate **102** to alkene **101** bearing a suitably located α -ketophosphonate motif proceeds *via* adduct **103**. This intermediate undergoes an addition-fragmentation on the carbonyl group to give cyclic ketones **104** or **105** with extrusion of a phosphonyl radical. The usual oxidative condensation with ammonium acetate in acetic acid under air furnishes the desired pyridines **106** and **107**, respectively. Pyridines **108-111** are additional examples of this method.

Modification of the pyridine nucleus by radical ring closure reactions

The radical addition to a pyridine nucleus represents a very useful strategy for obtaining various families of pyridine derivatives. This addition can be intra- or inter-molecular, depending on the type of target structures desired. The former version leads to pyridines fused to five-, six-, and even seven-membered rings; this constitutes the object matter of this section.

Aza-oxindoles can thus be readily obtained by starting with an *N*-substituted aminopyridine which is chloroacetylated and the chlorine substituted by a xanthate group, as shown by the conversion of 1,3,5-trichloropyridine into xanthate **112** (Scheme 11).²⁹ Exposure of this compound to a stoichiometric amount of DLP triggers a sequence of events leading to

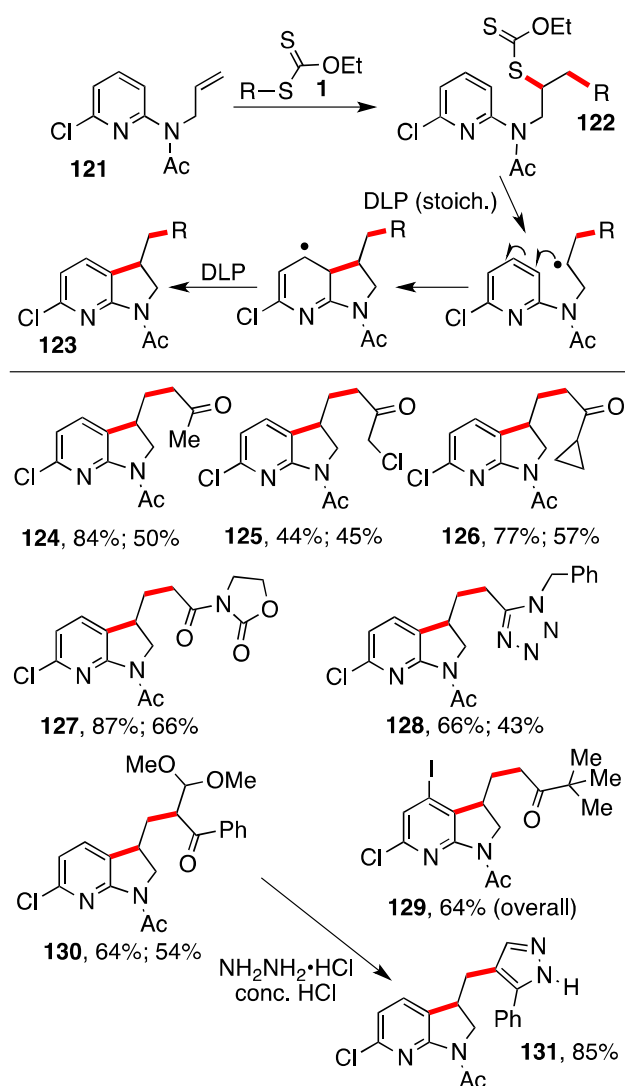
azaoxindole **116**. This transformation proceeds by way of radical **113**, which adds to the pyridine nucleus to give stabilized radical **114**. This step is reversible, but the process is driven forward by conversion of radical **114** into cation **115** through electron transfer to DLP. Loss of a proton restores the aromaticity and provides azaoxindole **116**. This represents a general route to azaoxindoles, as shown by examples **117-120**.²⁹ The extra-nuclear nitrogen can be placed on essentially all positions of the aromatic ring. When two regioisomeric cyclized products are possible one regioisomer generally dominates, as is the case with **118**. The *t*-butyl group can be removed with acid, allowing access to *N*-unsubstituted azaoxindoles, which cannot normally be obtained by direct radical ring-closure. It is usually necessary to sterically block the nucleophilicity of the pyridine nitrogen by placing at least one substituent on the adjacent carbon. A chlorine is particularly suitable, because it can be reductively removed or replaced by a substituent through an organometallic coupling reaction, thus expanding the diversity of accessible pyridines. It is worth mentioning that pyridines are recalcitrant substrates in the Friedel-Crafts reaction and traditional routes to oxindoles cannot be easily extended to the synthesis of azaoxindoles.³⁰



Scheme 11. Synthesis of azaoxindoles

A modular, highly convergent approach to azaindoles **123** can also be implemented through this chemistry.²⁹ The generic route to **123** and a few examples are presented in Scheme 12. The first step is the addition of xanthate **1** to *N*-allylaminopyridine **121** to give the usual

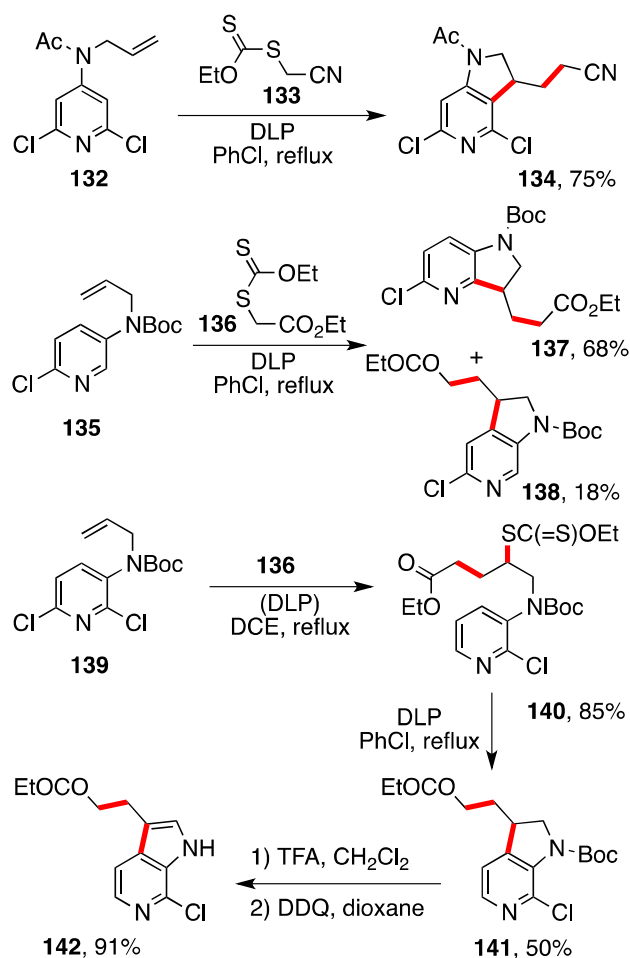
adduct **122**. Exposure to stoichiometric DLP induces ring closure and furnishes the target azaindoline **123**. In examples **124-130**, the yields for these two steps are shown. Numerous different functional groups can be introduced *via* the xanthate partner and the pyridine motif can bear additional substituents, if so desired, as illustrated by iodo derivative **129**. The iodine can be engaged selectively in organometallic reactions, such as the Sonogashira coupling, without complications from the less reactive chlorine. Further diversity can be accessed by modifying the moiety derived from the xanthate. The conversion of azaindoline **130** into pyrazole **131** is one such example.



Scheme 12. Synthesis of azaindolines

As for the azaoxindoles, the extra-nuclear nitrogen can be moved around the pyridine ring. Thus, placing the allylamino group in the 4-position in derivative **132**, and reaction with xanthate **133** leads to azaindoline **134** in good yield (Scheme 13).²⁹ In this case, the two steps

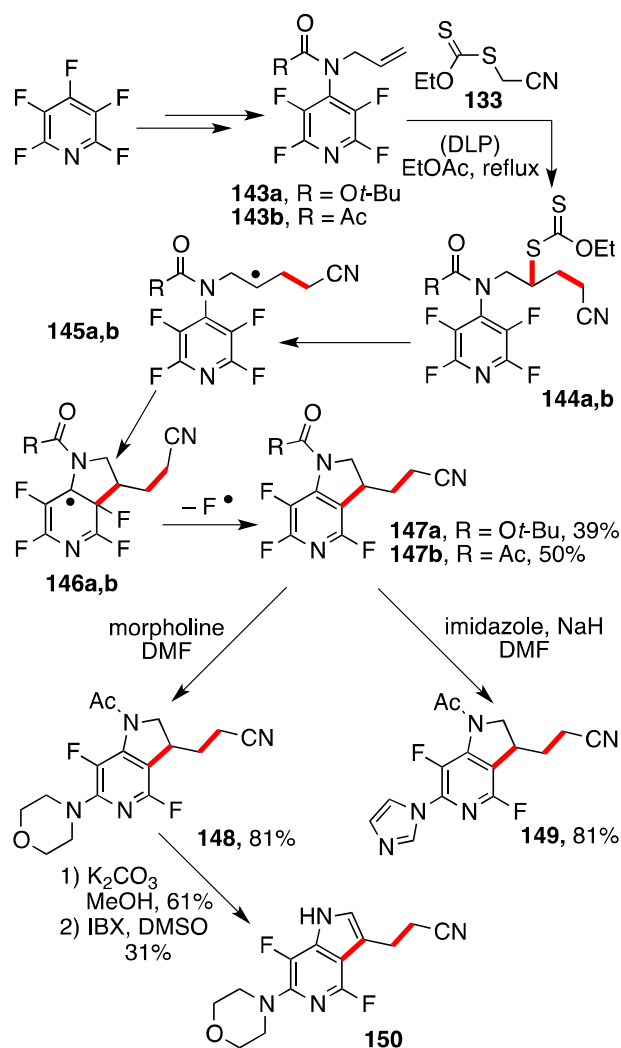
were readily telescoped without the need to isolate the intermediate adduct. Under similar conditions, reaction of xanthate **136** with substrate **135**, bearing the allylamino group in position 5, furnishes two isomeric azaindolines **137** and **138**. The former predominates, in line with the preferred attack on the carbon adjacent to the pyridine nitrogen. By blocking this position with a chlorine atom in the case of substrate **139**, the cyclisation of the corresponding adduct **140** takes place at position 4 to give azaindoline **141** in moderate yield. Removal of the Boc group and oxidation with DDQ furnishes azaindole **142**, further underscoring the flexibility of this technology in allowing access to both azaindolines and azaindoles.²⁹



Scheme 13. Further syntheses of azaindolines

In yet another variation of this strategy, advantage is taken of the particular reactivity of the readily available and inexpensive pentafluoropyridine. Its reaction with allylamine takes place regioselectively on position 4 to give compounds **143a,b** after acylation of the amino group with Boc anhydride and acetic anhydride, respectively (Scheme 14).³¹ Addition of xanthate **133** leads to corresponding adducts **144a,b** which, upon further treatment with DLP,

undergo an *ipso* substitution of a fluorine atom to give trifluoroazaindolines **147a,b** via intermediates **145a,b** and **146a,b** in moderate overall yield. Homolytic fragmentation of a carbon-fluorine bond is extremely rare, making this sequence all the more remarkable, and allows access to a whole family of novel pyridine structures.



Scheme 14. Synthesis of fluoroazaindolines and fluoroazaindoles

The presence of three fluorine atoms offers further avenues for diversification.³¹ For instance, reaction of **147b** with morpholine or the sodium salt of imidazole results in the regioselective substitution of the fluorine in position 2 to give compounds **148** and **149**. The other activated fluorine in position 6 is sterically hindered and remains unaffected. It could possibly be substituted under harsher conditions, but no attempts were made in this direction. In the case of indoline **148**, removal of the acetyl group and oxidation under the vigorous conditions reported by Nicolaou³² provided difluoroazaindole **150**. Trifluoroazaindolines **151-159**

pictured in Figure 3 are further examples of this unusual addition-cyclisation sequence involving a homolytic *ipso* substitution of fluorine.³¹

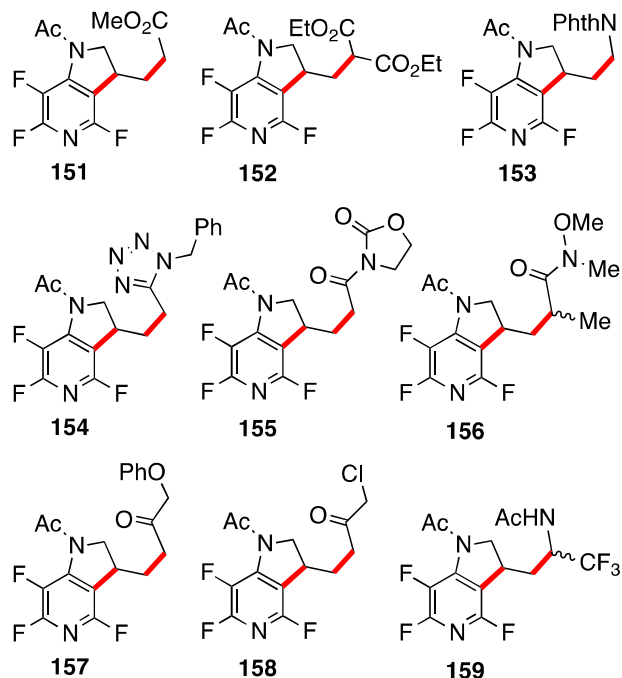
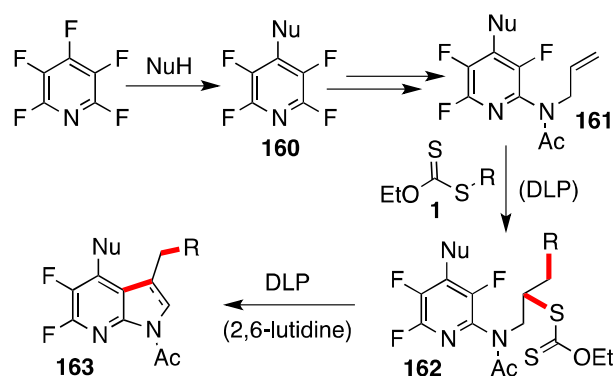


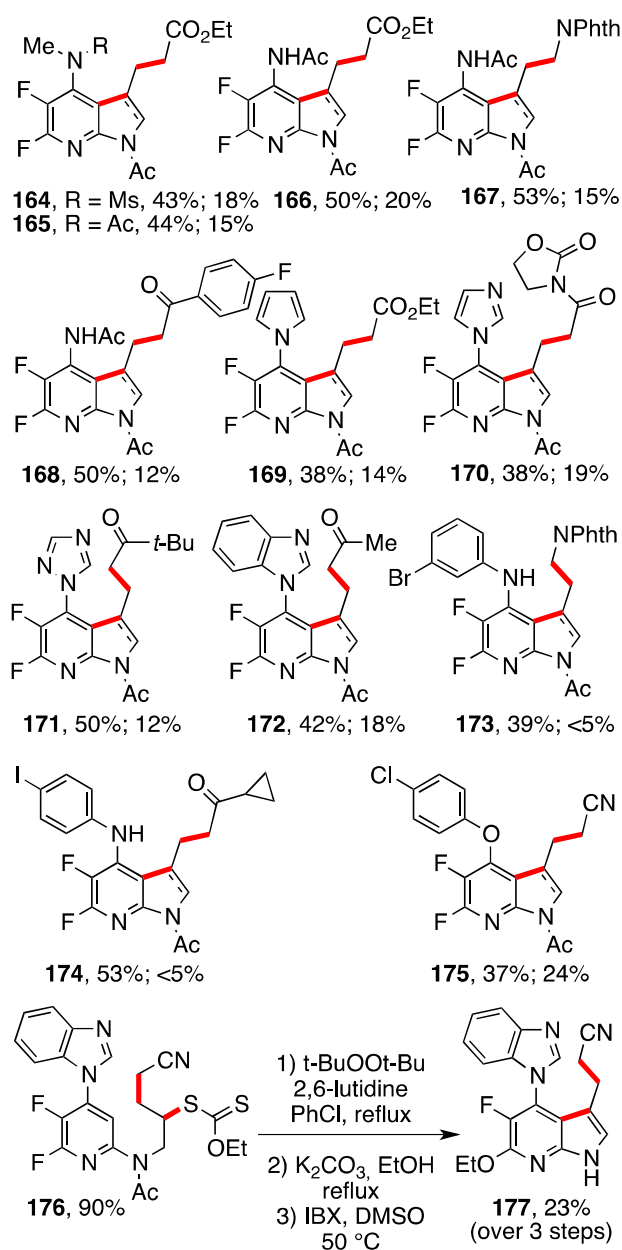
Figure 3. Further examples of fluoroazaindolines

The higher reactivity towards nucleophilic substitution of the 4-fluorine in pentafluoropyridine can be exploited in another way. Reaction with a nucleophile thus furnishes derivative **160**, which now has no choice but to undergo substitution at position 2 upon exposure to allylamine to give compound **161** after acetylation (Scheme 15).³³ Addition of xanthate **1** to the terminal alkene and cyclisation of the resulting adduct **162** provides difluoroazaindoline **163**. In this variation, we noticed the formation of variable amounts of the corresponding indole, presumably derived by further oxidation by the peroxide. We found that addition of 2,6-lutidine to remove any hydrogen fluoride produced in the medium to be beneficial.



Scheme 15. A second route to fluoroazaindolines and fluoroazaindoles

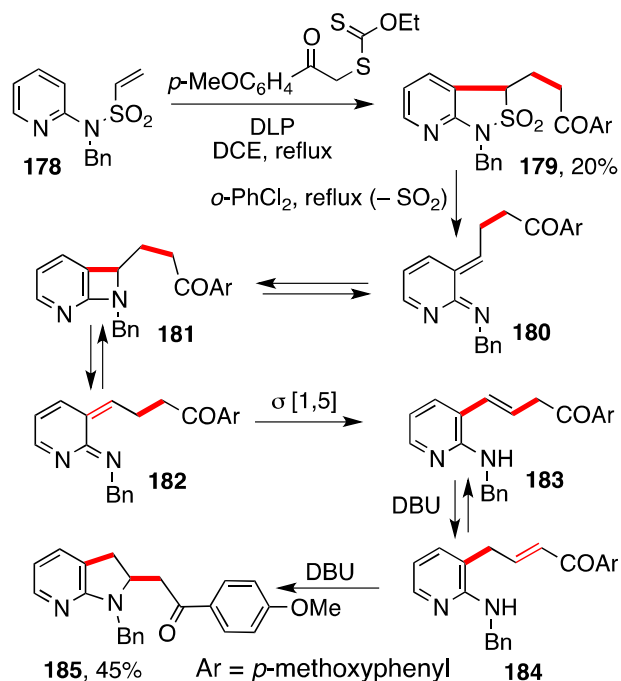
Examples of difluoroazaindolines and difluoroazaindoles obtained by this route are displayed in Scheme 16.³³ Numerous nucleophiles can be used, such as amines or ammonia, that are subsequently mesylated (**164**) or acetylated (**165-168**), pyrrole (**169**), imidazole (**170**), triazole (**171**), benzimidazole (**172**), anilines (**173-174**), and phenol (**175**). Two yields are shown: the first corresponds to that of the major indoline and the second to that of the minor indole. The yield of the latter is variable, being maximum for the phenol derivative **175** and minimum for anilines **173** and **174**. The reasons for these variations are not yet clear. In the case of benzimidazole adduct **176**, the mixture of difluoroindoline and difluoroindole obtained following the radical cyclisation was treated with potassium carbonate in ethanol to remove the acetyl group before oxidizing using Nicolaou's procedure.³² The fluoroazaindole **177** that was finally isolated had its fluorine in position 2 substituted by an ethoxy group, introduced during the deacetylation step. It is evident that other nucleophiles could be used instead of ethanol to further enrich the library of fluoroazaindolines and fluoroazaindoles accessible by this pathway.



Scheme 16. Examples of fluoroazaindoles and fluoroazaindoles

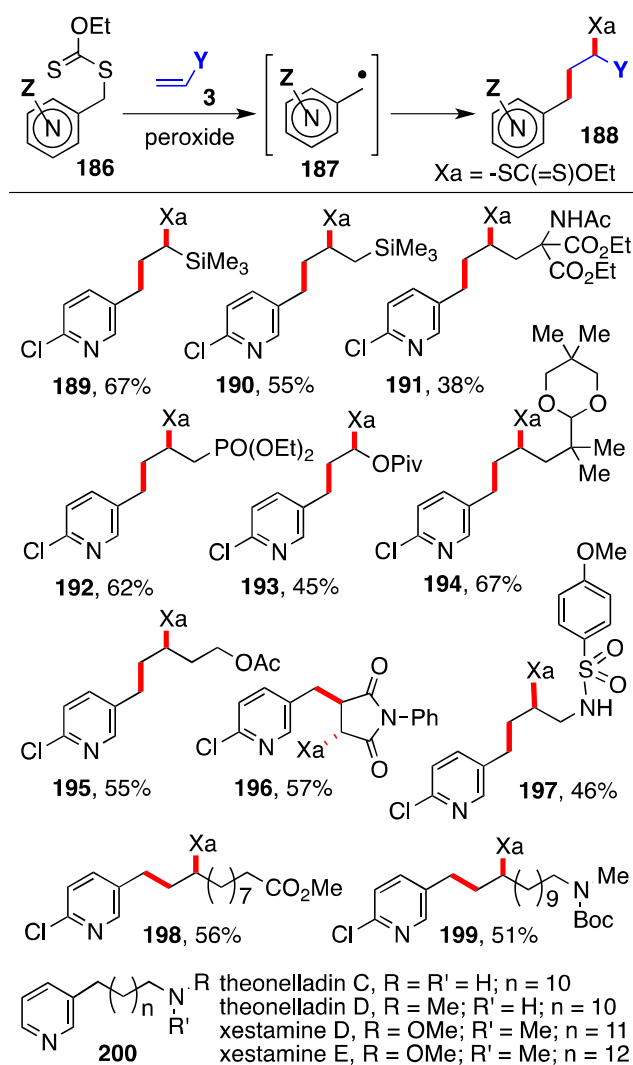
A very different route to azaindoles consists of reacting a vinylsulfonamide such as **178** with a xanthate adjacent to an electron-withdrawing group such as *S*-*p*-methoxyphenacyl xanthate.³⁴ The addition-cyclisation sequence leads to cyclic sulfonamide **179** in modest yield that could certainly be improved. Upon heating, this compound undergoes a series of transformations starting with a cheletropic extrusion of sulfur dioxide to give reactive imine intermediate **180**. This compound is in equilibrium with its geometrical isomer **182** via azetine **181**. Isomer **182**, the less stable of the two, is well-disposed for an irreversible [1,5]-sigmatropic rearrangement giving rise to 3-substituted pyridine **183**. This compound can be

isolated if desired, but its treatment with DBU induces an equilibration with conjugated isomer **184**. This compound is now able to undergo an internal Michael addition to give azaindoline **185** in 45% yield for the two steps. This synthesis illustrates a method to attach a functional side chain adjacent to the amino group, which can be easily varied by simply modifying the xanthate partner, and a route to azaindoline substituted in the 2-position, in contrast to the approaches described in the preceding Schemes, which furnish 3-substituted azaindolines (and azaindoles).



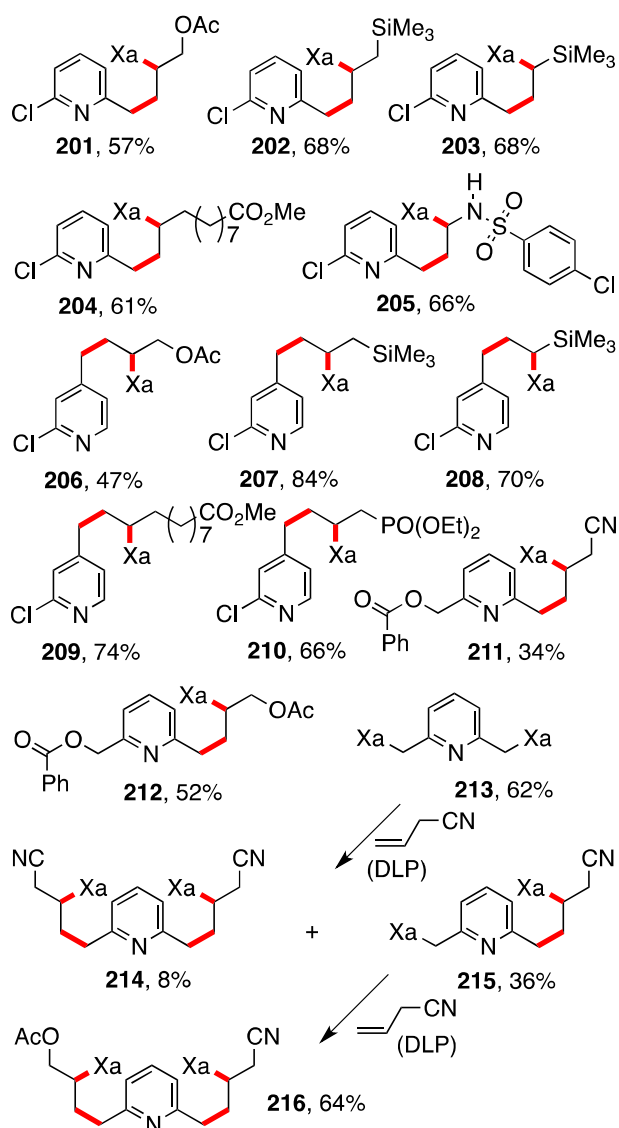
Scheme 17. Synthesis of 2-substituted azaindoline

Modification of the pyridine motif can be accomplished by taking advantage of the mildly electron withdrawing nature of this particular heteroaromatic nucleus. In contrast to benzyl radicals, which were found to be poorly reactive towards unactivated alkenes, pyridylmethyl radicals **187** react with good efficiency (Scheme 18).³⁵ The xanthate precursor **186** thus adds readily to give the usual adducts **188**. The variety of side chains that can be appended is showcased by examples **189-199**. The last product is a close analog (after removal of the xanthate group) to a number of marine alkaloids with general structure **200**.³⁶ Indeed, the ability to create so easily a strategic carbon-carbon bond from readily available fragments makes the total synthesis of these alkaloids almost trivial.



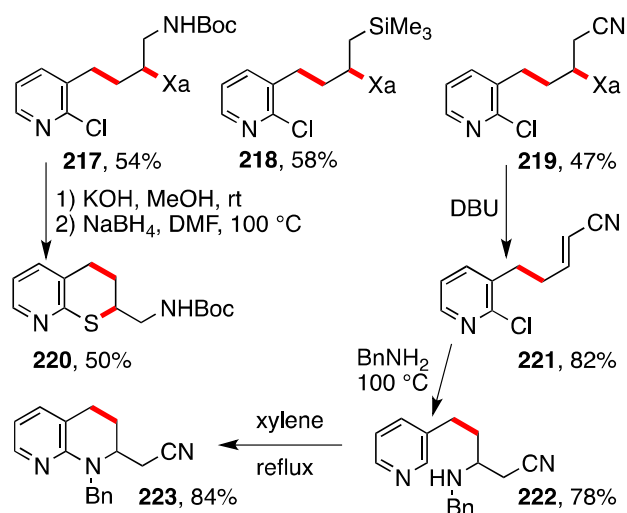
Scheme 18. Additions of pyridylmethyl radicals

Further examples (**201-212** and **214-216**) are displayed in Scheme 19, where the position of the radical with respect to the pyridine nitrogen is varied. Moreover, the chlorine atom is not necessary and can be replaced by another group (e.g. **211**, **212**, **214-216**), so as to sterically shield the pyridine nitrogen and decrease its propensity to ionically cleave the xanthate function by nucleophilic attack. In the case of bis-xanthate **213**, the mono-addition product **215** dominated strongly over symmetrical bis-adduct **214**. This provided a simple pathway to unsymmetrical bis-adducts, since it proved possible to perform a second addition to a different alkene to give compound **216**.³⁵



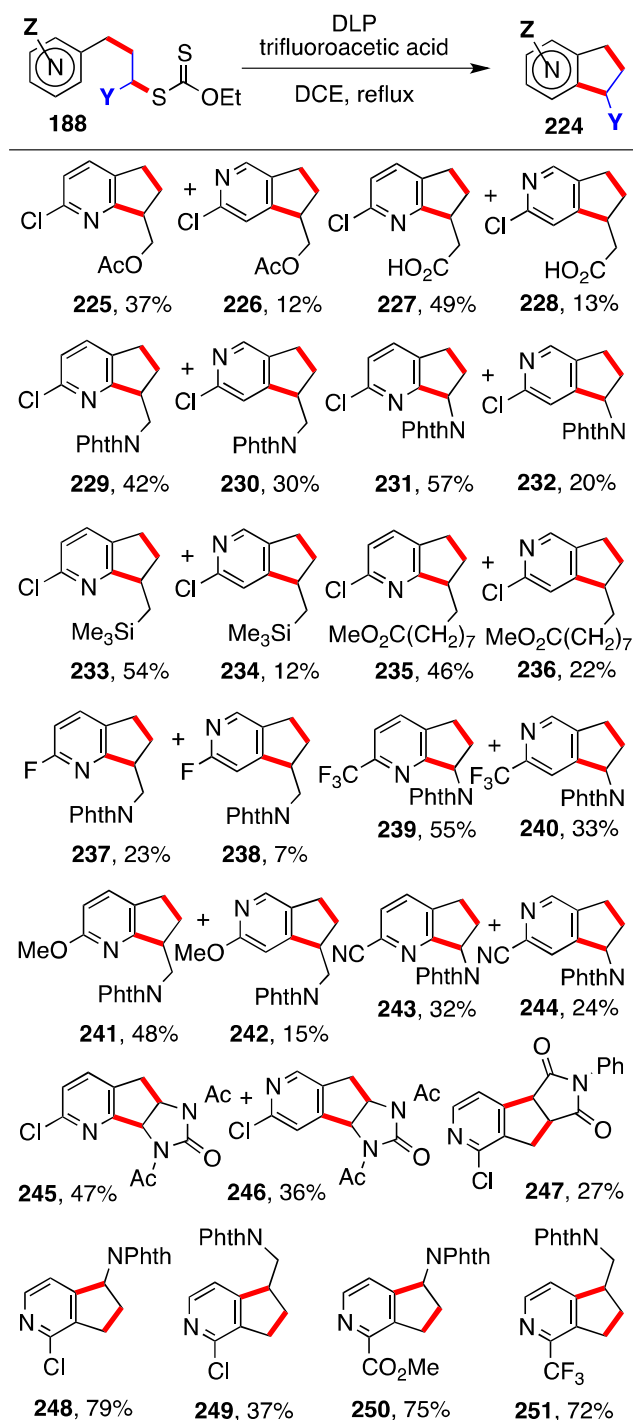
Scheme 19. Further additions of pyridylmethyl radicals

Access to such pyridines would be quite tedious by more classical strategies. Furthermore, additional rings can be constructed by placing the chlorine atom in the adjacent position to the alkyl chain, as in adducts **217-219** (Scheme 20).³⁵ Cleavage of the xanthate in **217** and heating with borohydride (to reduce any disulfide that may form) induces substitution of the chlorine to give azathiochromane **220**. In the case of adduct **219**, the xanthate is in the β -position to the cyanide and exposure to base causes its elimination to give unsaturated nitrile **221**. Conjugate addition of benzylamine furnishes compound **222** and heating in xylene induces ring closure to give tetrahydronaphthyridine **223**.³⁵



Scheme 20. Additions of pyridylmethyl radicals and further ionic reactions

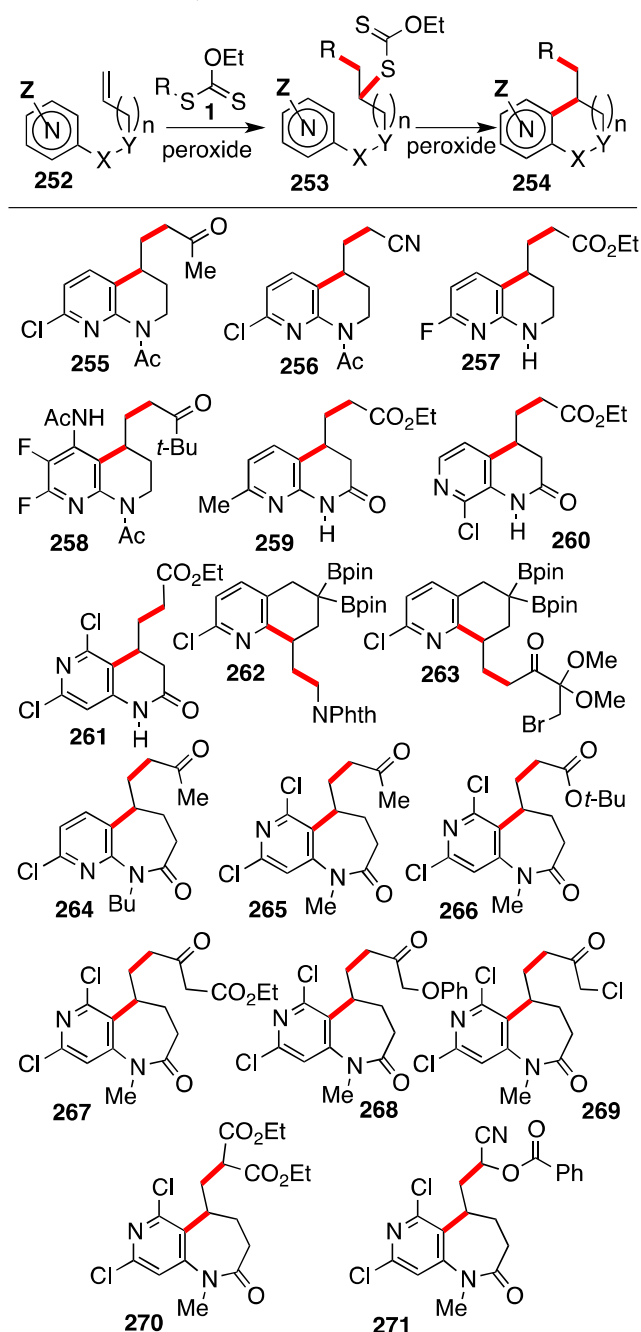
Adducts **188**, arising from the addition of pyridylmethyl xanthates **186** to alkenes, can moreover be converted into azaindanes **224** by cyclisation of the corresponding radical onto the pyridine ring (Scheme 21).³⁷ However, for this to take place with some efficiency it proved necessary to activate the pyridine nucleus by protonation, as was shown many years ago by Minisci.³⁸ Numerous azaindanes could be prepared by this approach.³⁷ Many different substituents on the pyridine ring and on the alkene partner are tolerated, providing a quick, convenient access to azaindanes not readily available by previous methods. Indeed, azaindanes have been relatively difficult to obtain in the past, requiring in most cases the construction of the pyridine nucleus itself.³⁹ The activation of the pyridine ring causes a lowering of the regioselectivity when two cyclisation modes are possible, and pairs of isomers are isolated (**224-246**) in usually good combined yield. In the case of azaindanes **247-251**, only one regioisomer is formed.



Scheme 21. Synthesis of azaindanes

Six- and seven-membered ring can also be fused to the pyridine ring. An initial intermolecular addition of xanthate **1** to an appropriate alkene **252** provides adduct **253**, where the xanthate group occupies the correct position for engaging in a second radical sequence to give the desired bicyclic product **254** (Scheme 22). This strategy could readily be

put to practice, as shown by the varied examples given. In the case of six membered rings, saturated chains could be formed (**255-258**),^{29,33} as well as lactams (**259-261**).^{29,33} Interestingly, the extra-nuclear nitrogen does not need to be substituted, as illustrated by products **257**⁴⁰ and **259-261**,^{29,33} unlike the situation with ring-closures forming five-membered rings discussed earlier. Examples **262** and **263**, bearing a very unusual geminal diboronate motif, show that even all carbon chains can undergo the cyclisation successfully.⁴¹

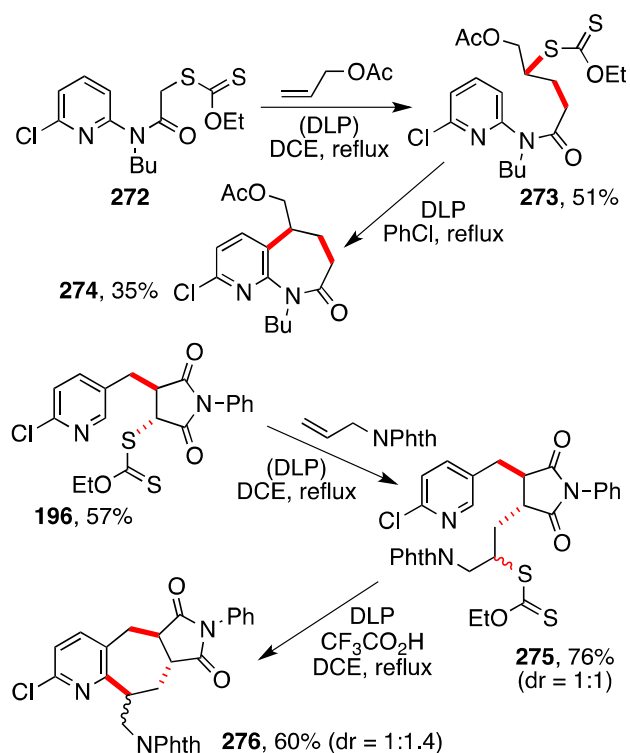


Scheme 22. Fusing six- and seven-membered rings to pyridines

Addition of one carbon to the alkenyl side chain in **252** ($n = 2$) allows the synthesis of pyridines fused to a seven-membered lactam. This is highlighted by examples **264-271** in Scheme 22.^{29,33,42} Note that the extra-nuclear nitrogen needs to be substituted for the cyclisation to take place. The case of the six-membered ring formation, where the extra-nuclear nitrogen may or may not be substituted, is thus somewhat of an anomaly for reasons that are not completely clear at the present time.^{9a} In the examples pictured in Scheme 22, the extra-nuclear nitrogen can be moved around the ring providing an entry to numerous families of bicyclic pyridine derivatives.

There is another particularly versatile route to pyridines fused to seven-membered rings. It exploits the fact that even intramolecular radical additions to (hetero)aromatic nuclei leading to 5-membered rings are relatively slow and oftentimes reversible. It is therefore in many instances possible to capture the radical by an intermolecular addition to an external alkene before cyclisation to the (hetero)aromatic ring has occurred. This is illustrated by the behavior of xanthate **272** (Scheme 23).²⁹ In the absence of an olefinic trap, such xanthates furnish azaoxindoles upon treatment with stoichiometric amounts of peroxide (see transformations in Scheme 11); however, in the presence of allyl acetate, the intermolecular adduct **273** prevails. The xanthate group is now in the same position as in structure **253**, with $n = 2$, and exposure to further peroxide causes cyclisation into pyridoazepinone **274** in modest yield. In this example, and in all the examples in Scheme 22, no activation of the pyridine by salt formation was necessary, even if, in a few cases, the addition of acid could have improved the yields.

The beneficial effect of acid can be seen in the second transformation in Scheme 23.³⁷ Adduct **196** (see Scheme 18) can be cyclized by the action of peroxide in the presence of trifluoroacetic acid. However, in the absence of acid, the ring closure onto the unprotonated pyridine nucleus is too slow and the corresponding radical can be captured by *N*-allyl phthalimide to efficiently give the normal addition product **275**. Subjecting this compound to stoichiometric amounts of peroxide in the presence of trifluoroacetic acid now causes ring closure to give highly functionalized cycloheptane **276** in synthetically useful yield.



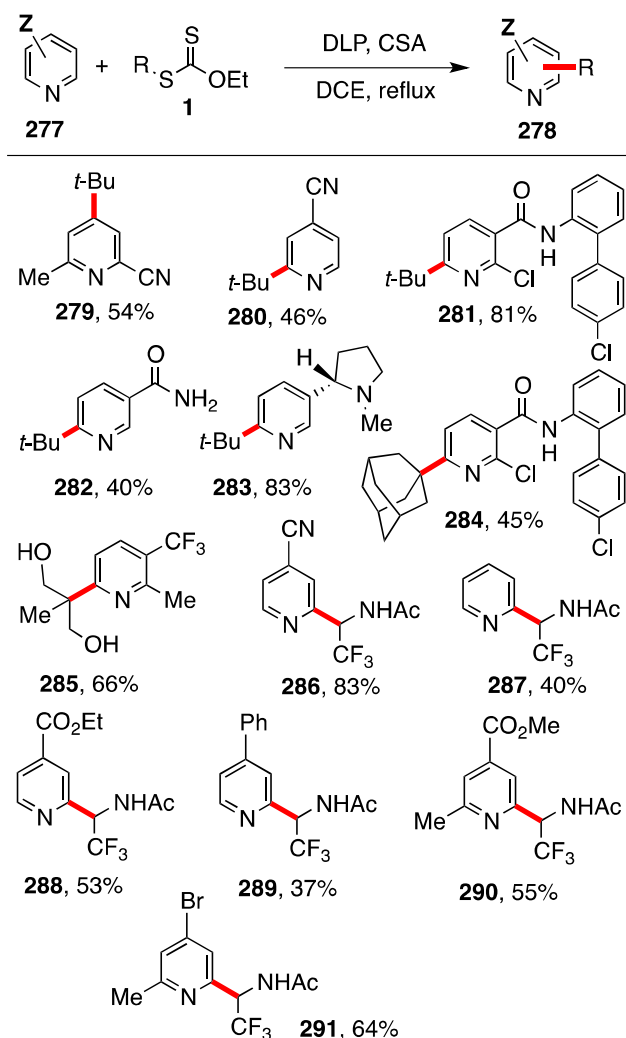
Scheme 23. Further examples of seven-membered rings fused to pyridines

Modification of the pyridine nucleus by intermolecular radical addition

One final route to pyridine derivatives that holds much promise for accessing a large diversity of structures is the direct addition of xanthates to pyridinium salts, an approach inspired by the pioneering work of Minisci, who studied the radical addition to protonated pyridines and quinolines nearly a half century ago.³⁸ Indeed, the Minisci reaction and its variants have been revived in recent times by the need of the pharmaceutical and agrochemical industries for the late stage modification of lead structures and optimization of their pharmacological profile.⁴³ The attachment of a substituent on the heteroaromatic portion of a bioactive molecule can be used to alter its shape, polarity, solubility, bioavailability, biodegradability, and indeed its potency and all the properties required for the development of a drug substance or an active ingredient for crop protection.

The examples assembled in Scheme 24 give an idea of the possibilities offered by the reaction of xanthates with various protonated pyridines. Camphorsulfonic acid was used because the resulting pyridinium salts are generally well soluble in organic media. Tertiary hydrophobic groups such as *t*-butyl and adamantyl are readily appended (**279-284**).⁴⁴ Polar hydrophilic groups can be introduced, such as the 1,1-bis(hydroxymethyl)ethyl motif attached to the pyridine core in compound **285**. In this case, the xanthate precursor was not the free alcohol, but the cyclic acetonide. The last examples, **286-291**, illustrate the introduction of a 1-acetamido-2,2,2-trifluoroethylamino unit.⁴⁵ 2,2,2-Trifluoro-ethylamino motifs have been

proposed to be amide isosteres and are pharmaceutically relevant.⁴⁶ The regiochemistry is in line with previous studies on the radical addition to pyridines and indeed other heteroaromatics that are outside the scope of the present overview.⁴⁷



Scheme 24. Direct radical alkylation of pyridines

Concluding remarks

Various strategies to access pyridines have been briefly described. They take advantage of the remarkable properties of this radical chemistry of xanthates, most importantly the ability to allow inter- and intramolecular additions to activated and electronically unbiased alkenes, to pyridines, and to many other heteroarenes such as pyrroles, indoles, furans, thiophenes, pyrimidines, pyrazines, and quinolines. Practical features are low cost, experimental simplicity, ease of scale-up, versatility, modularity, and compatibility with numerous

functionalities, especially polar groups that are not easily handled by other methods based on ionic and organometallic reactions.

Pyridines and numerous other heterocycles can be assembled from scratch by bringing the requisite functional groups together through the intermolecular radical addition. The vast number (literally hundreds) of readily available xanthate partners translates into a very large variety of pyridines that can be prepared by concise, convergent approaches. The ability to manipulate fluorine substituted pyridines opens further unique opportunities for the synthesis of medicinally relevant structures.

The scope of most approaches discussed herein has not been completely delineated and much remains to be done. For instance, only one example of the 2-substituted azaindoline has been reported (**185**, Scheme 17), yet this synthesis has obviously a greater potential, especially after optimization of the yields. There are further possibilities that have not been tested, in particular regarding routes to fluorinated pyridines that are especially prized by medicinal chemists.⁴⁸

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