Recent advances in the synthesis of 2,3-dihydropyrroles

Dong Wang, Yu Fan, Peng Yu, Laurent Désaubry

REVIEW

Recent advances in the synthesis of 2,3-dihydropyrroles

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The 2,3-dihydropyrrole unit is a privileged heterocyclic found in many pharmacologically active natural products. Significant recent advances in the synthesis of this heterocycle have led to intense interest in the development of new drug candidates. The aim of this review is to summarize advances accomplished in this stimulating field with an emphasis on recent developments or important seminal contributions.

1. Introduction

2,3-Dihydropyrroles, also called 2-pyrrolines, are structural components of a large number of biologically active natural compounds (Figure 1). For example, isolated from the fungus *Aspergillus fumigatus*, Spirotryprostatin B (**1**), inhibits cell cycle progression in mammalian cells.[2] Meropenem(SM-7338) (**2**),[3] is a broad-spectrum antibiotic active against Gram-positive and negative bacteria. Recently, in combination with vaborbactam, it was approved by FDA for the treatment of adult patients with complicated urinary tract infections.[4] The pyrrolobenzodiazepines Anthramycin (**3**) and Sibiromycin (**4**) produced by actinomycetes are potent DNA alkylating agents with impressive antineoplastic activity.[5]

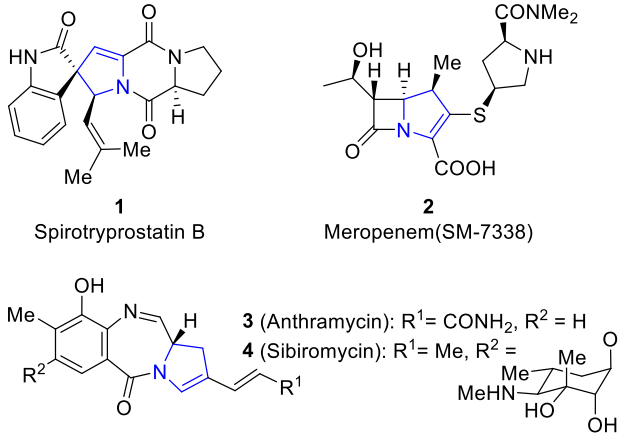


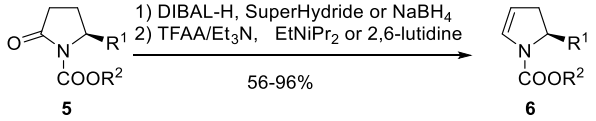
Figure 1. Representative 2,3-dihydropyrrole natural products.

Many methods have been developed to prepare 2,3-dihydropyrroles, however there can be restrictions according to their substitutions pattern, particularly on the nitrogen. For convenience, these methods have been classified into functional group manipulation of preexisting pyrrolidones or pyrrolidines, and ring closure of acyclic precursors. Finally, several examples of the use of 2,3-dihydropyrroles as intermediates in the total synthesis of natural products will be discussed. This topic has been reviewed by Jubault, Leclerc, and Quirion in 2007, but remarkable progress has been achieved over the last 13 years.[6]

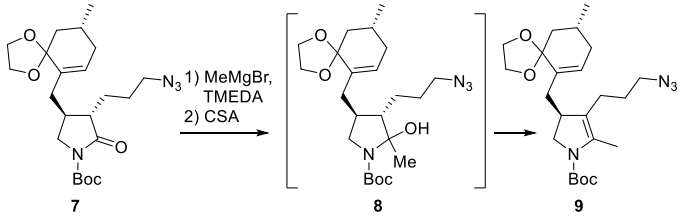
2. Functional group manipulation with pyrrolidones or pyrrolidines

2.1. Reduction of 2-pyrrolidones and reaction with Grignard or lithiated reagents

Reduction of *N*-protected 2-pyrrolidones **5** by DIBAL-H, Super-Hydride or $NaBH_4$ followed by dehydration induced by TFAA in the presence of a base remains a convenient approach to prepare *N*-protected 2-pyrrolidones non-substituted in positions 2 and 3 (Scheme 1).[7]



Scheme 1. Reduction and dehydration of *N*-protected 2-pyrrolidones.[7]



Scheme 2. Selected example of addition of an organometallic reagent to a *N*-protected 2-pyrrolidone followed by dehydration.[8]

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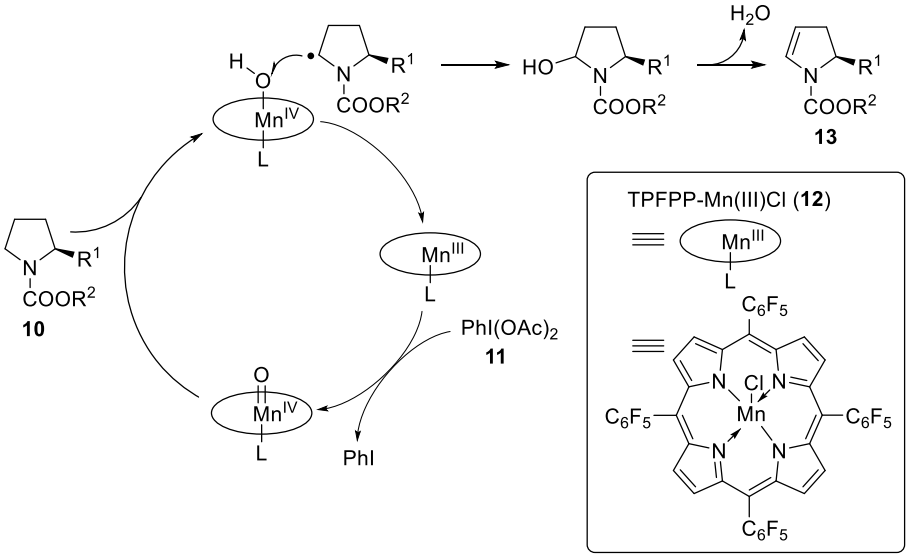


Scheme 3. TPFPP-Mn(III)Cl catalyzed oxidation of *N*-protected pyrrolidines (**10**) by PIDA (**11**).[1]

Addition of Grignard or lithiated reagents with *N*-protected 2-pyrrolidones also afford after dehydration substituted 2,3-dihydropyrroles with a new substituent in position 2 (Scheme 2).[8]

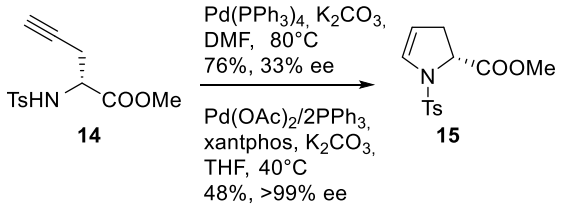
3.2. Oxidation of pyrrolidines

2,3-Dihydropyrroles can also be generated by a controlled oxidation of pyrrolidines. For instance, Groves' team recently developed a desaturation of *N*-protected pyrrolidines **10** using PIDA (**11**) and the catalyst Mn(TPFPP)Cl (**12**) (Scheme 3).[1]

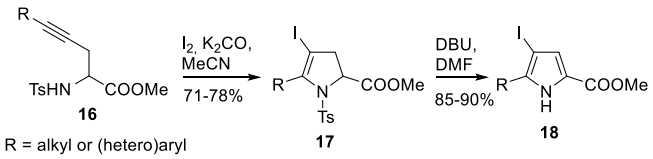
3. Cyclization

3.1. 5-Endo-dig cyclization of homopropargylamines

In 1998, Rutjes' group reported the Pd-catalyzed 5-endo-dig cyclization of protected propargylglycine **14** into dihydropyrrole **15**, with an enantiomeric excess of 33% (Scheme 4).[9] Further studies from this team showed that the use of xantphos as a ligand allows this reaction to be performed without racemization.[10]



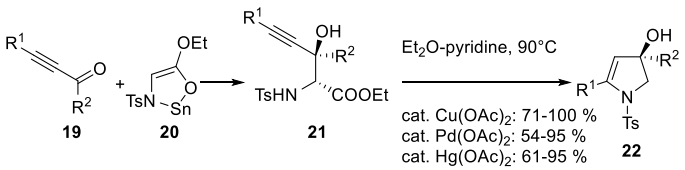
Scheme 4. 5-Endo-dig cyclization of protected propargylglycine **14**.[9, 10]



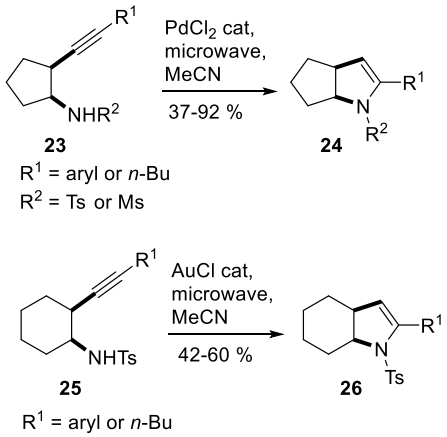
Scheme 5. Iodocyclisation of homopropargylic sulfonamides **16** and base-catalyzed elimination of sulfinate.[10, 11]

The same year, Knight's group disclosed the iodocyclization of homopropargylic sulfonamides **16** to give with excellent yields the iododihydropyrroles **17**, which can be readily transformed into pyrroles **18** upon treatment DBU (Scheme 5).[10]

The same group also prepared functionalized 3-hydroxy-2,3-dihydropyrroles starting from the diastereoselective condensation of ynones **19** and the tin(II) enolate of glycinate **20**, to afford the β-hydroxy-α-amino esters **21** with a good diastereoslectivity (ca. 9:1) (Scheme 6).[12] Upon treatment with copper(II), palladium(II) and mercury(II) salts these adducts afforded the hydroxy-dihydropyrroles **22**. The best yields were observed with $Cu(OAc)_2$.



Scheme 6. Synthesis of ynoates **21** and conversion into hydroxy-dihydropyrroles **22**.[12]

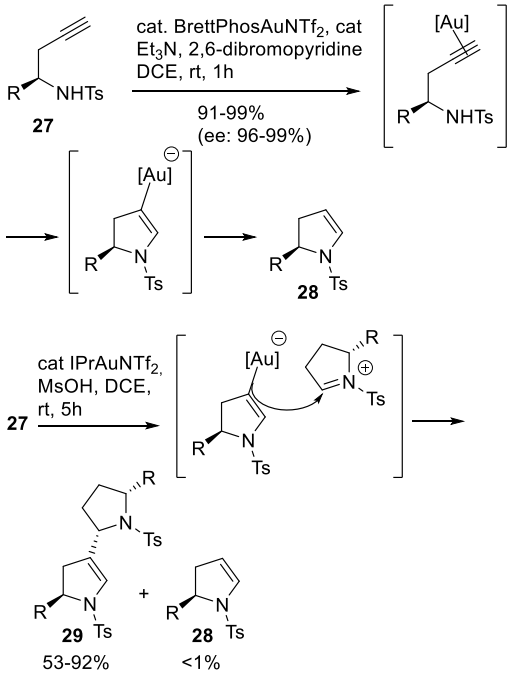


Scheme 7. Intramolecular cyclization catalyzed by $PdCl_2$ or AuCl to generate 2,3-dihydropyrroles **24** and **26**.[13]

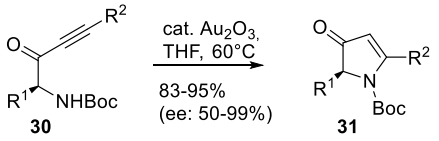
Hou group performed a similar reaction with cyclic substrates to furnish dihydropyrroles cyclopentane- and cyclohexane-fused 2,3-dihydropyrroles **24** and **26** using respectively $PdCl_2$ or AuCl as catalyst under microwave conditions (Scheme 7).[13]

Gold has been found to catalyze also the 5-endo-dig cyclization of homopropargyl sulfonamides **27** in presence of triethylamine and 2,6-dibromopyridine (Scheme 8).[14] In absence of these additives, the formation of a dimer **29** was observed.[14, 15]

Gold(III) oxide also catalyzes the cyclization of α-amino-ynones **30** into pyrrolin-4-ones **31** in high yields with a moderate to total stereocontrol (Scheme 9).[16]

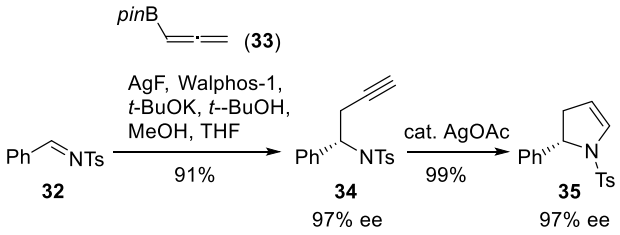


Scheme 8. Gold-catalyzed cyclization of homopropargyl sulfonamides **27**.[15,14]



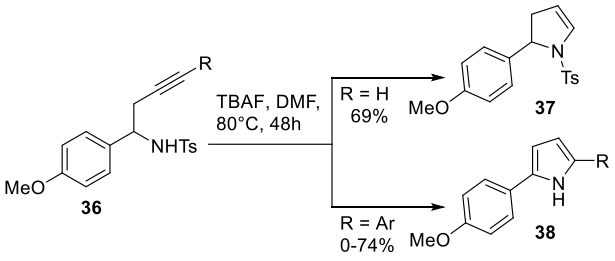
Scheme 9. Gold- catalyzed cyclization of α-amino-ynones into pyrrolin-4-ones **30**.[16]

Recently, an enantioselective homopropargylamines **34** has been devised using an allenyl boronic acid pinacol ester (**33**) in presence of silver fluoride and the chiral ligand Walphos-1 (Scheme 10).[17] These adducts undergo a ring closure in presence of silver acetate.



Scheme 10. Enantioselective silver-catalyzed propargylation of *N*-tosylimine **32** and cyclization into 2,3-dihydropyrrole **35**.[17]

Interestingly, Hill and co-workers found that TBAF can catalyze the 5-endo-dig cyclization of N-tosyl homopropargylamines in absence of transition metal to generate a 2,3-dihydropyrrole or a pyrrole according whether the alkyne is terminal or disubstituted (Scheme 11).[18]

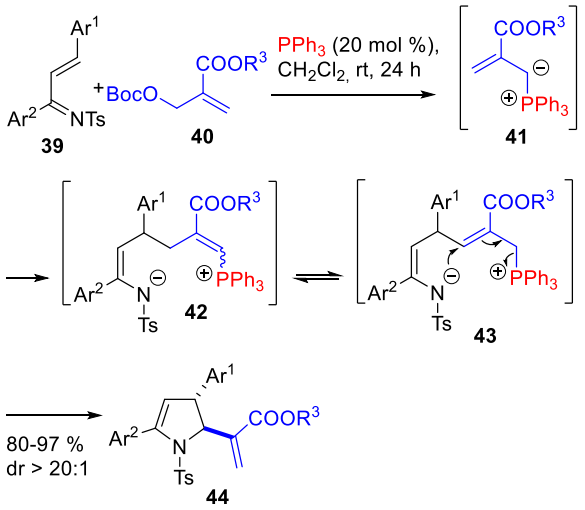


Scheme 11. TBAF-catalyzed cyclization of homopropargyl sulfonamides.[18]

3.2. Cascade reactions

3.2.1. Cascade Michael addition/annulation

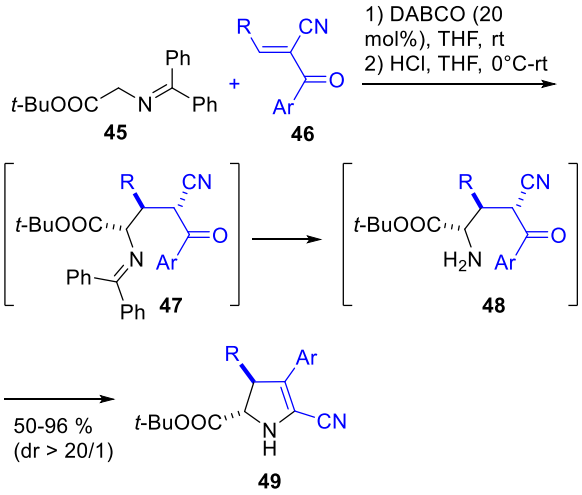
Domino reactions, which enable the one-pot sequential formation of several chemical bonds, represent an extremely efficient process for rapid synthesis of complex molecules.[19] Thus, He's group developed a catalytic [4 + 1] cyclization of α,β-unsaturated imines with allylic carbonates **40** to diastereoselectively prepare trisubstituted *N*-tosyl dihydropyrroles **44** in high yields via phosphorus ylide intermediates **41**-**43** (Scheme 12).[20] Similarly to many of the previous synthesis, this method gives access to 2,3-



Scheme 12. PPh_3-catalyzed [4 + 1] annulation between α,β-unsaturated *N*-tosylimines **39** and allylic carbonates **40**.[20]

2,3-dihydropyrroles protected by a tosyl, which cannot be deprotected without generating a pyrrole.

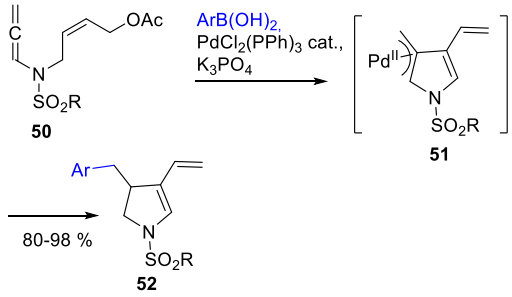
Lattanzi group reported synthesis of unprotected 2,3-dihydropyrroles that relies on a sequential one-pot DABCO-catalyzed Michael addition/deprotection/ cyclization/ tautomerization approach starting from readily accessible glycine imine esters **45** and Knoevenagel reagent **46**. This efficient method provides dihydropyrroles in good yield and high diastereoselectivity.[21] In contrast with the previous method, it also has the advantage to avoid the requirement to protect the imine with a tosyl that cannot be easily removed subsequently.



Scheme 13. Condensation of glycine imine derived esters **45** to trans-2-aryl-3-acrylonitriles **46**.[21]

3.2.2. Cascade metallo-ene/Suzuki coupling reaction

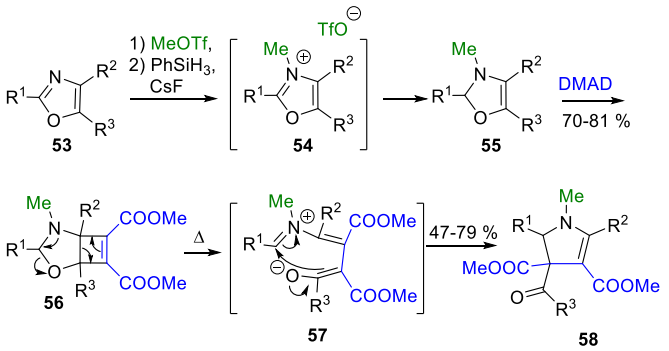
Liu group developed an original tandem metallo-ene/Suzuki coupling reaction between allenamides **50** and boronic acids catalyzed by palladium (Scheme 14).[22] Unfortunately the preparation of the substrates is not straightforward, which limits the interest of this reaction.



Scheme 14. Palladium-catalyzed metallo-ene/Suzuki coupling reaction of allenamides **44**.[22]

3.2.3. Cascade [2+2] cycloaddition/rearrangement

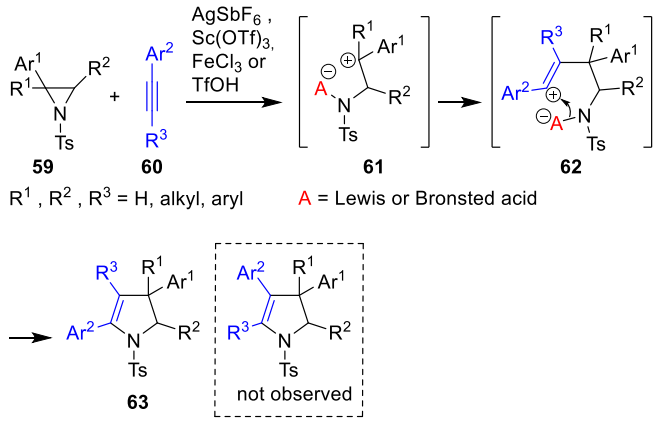
Vedejs' group reported the controlled reduction of oxazolium salts **54** to afford the nucleophilic dehydro-oxazolines **55** that can undergo a [2+2] cycloaddition with dimethyl acetylenedicarboxylate (DMAD) to give the cyclobutenes **56** (Scheme 15).[23] These unstable intermediates spontaneously afford 2,3-disubstituted dihydropyrroles **58**, probably through intermediate **57**.



Sheme 15. Vedejs' 4-oxazoline route to 2,3-disubstituted dihydropyrroles **58**.[23]

3.3. Carboamination of alkynes with aziridines

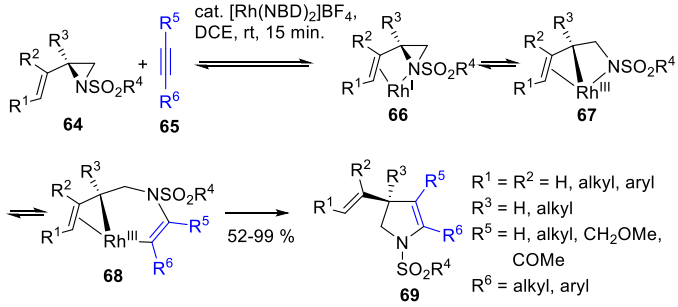
Wender's group was the first to report in 2009 the use of Lewis and Brønsted acids to catalyze the condensation of *N*-tosylaziridines **59** with alkynes **60** to afford polysubstituted dihydropyrroles **63** in a regiospecific manner under mild reaction conditions (Scheme 16).[24] Afterward, Wang group found that $FeCl_3$ also catalyzes this reaction.[25]



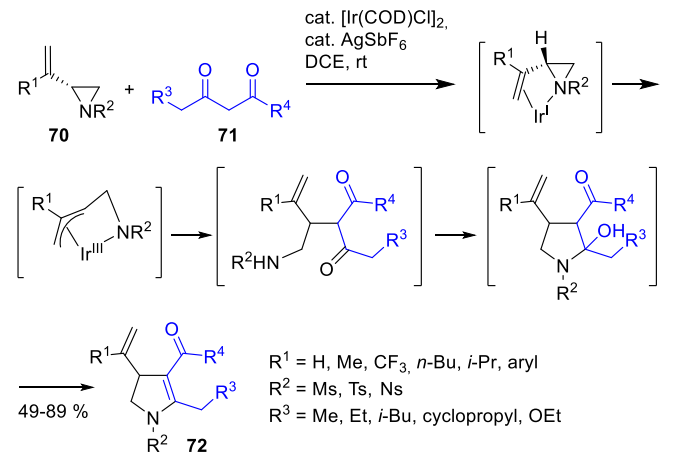
Scheme 16. Acid-catalyzed condensations of *N*-tosyl arylaziridines **59** with alkynes **60**.[24, 25]

Zhang group developed a similar cycloaddition of vinylaziridines **64** with alkynes **65** through a different mechanism catalyzed by $[Rh(NBD)_2]BF_4$ with broad substrate scope and high stereoselectivity under mild reaction conditions (Scheme 17).[26] Subsequently, the same group developed an iridium-catalyzed domino-ring-opening cyclization of vinylaziridines **70** with β-ketocarbonyls **71** (Scheme 18).[27]

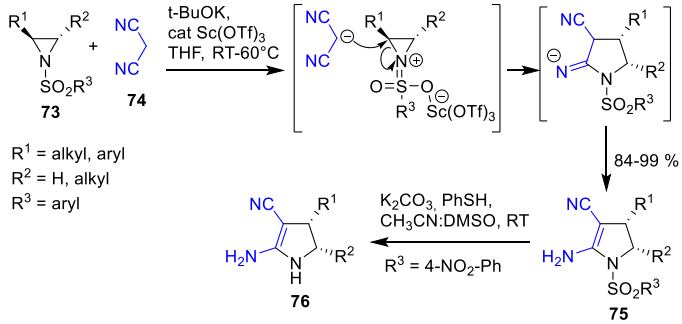
Ghorai group developed a domino ring-opening condensation of substituted *N*-sulfonyl aziridines **73** with malononitrile **74** to provide



Scheme 17. Condensation of *N*- sulfonyl-vinylaziridines **64** with alkynes **65**.[26]



Scheme 18. Condensations of *N*- sulfonyl vinylylaziridines **70** with β-ketocarbonyls **71**.[27]



Scheme 19. Condensations of *N*- sulfonyl arylaziridines **73** with malononitrile **74**.[28]

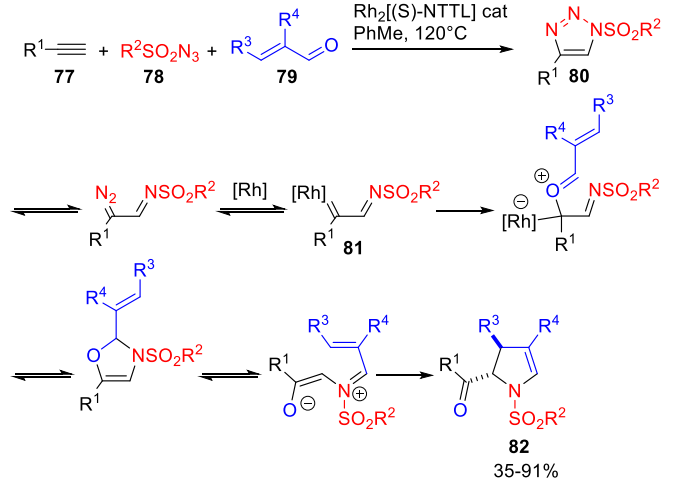
corresponding dihydropyroles **75** in good yields and with a high stereoselectivity (Scheme 19).[28] Importantly, the adducts protected by a nosyl could easily be removed in good yield to provide *N*-unsubstituted dihydropyroles **76**.

3.4. Multicomponent reactions

Multicomponent reactions are one-pot reactions that use several reagents to generate a single product containing most of the reagent atoms.[29, 30] As such, they are extremely valuable in medicinal chemistry to generate complex molecules in only one step.[31-33]

3.4.1. Rhodium catalyzed three component synthesis

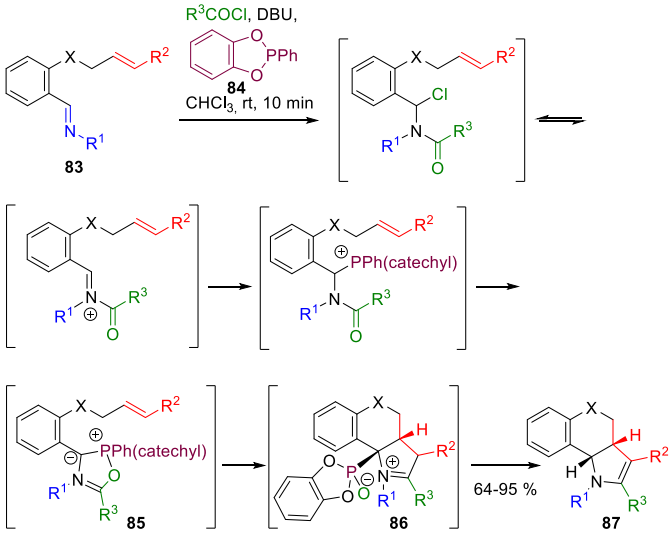
An interesting three component reaction to prepare *N*- sulfonyl 2,3-dihydropyrroles was reported by Murakami and co-workers (Scheme 20).[34] Condensation of a terminal alkyne **77** with a *N*-sulfonyl-azide **78** to provide a 1,2,3-triazole **80** that generates *in situ* an α-imino rhodium carbene complex **81**, which reacts with a α,β-unsaturated aldehyde **79** to produce a trans-2,3-disubstituted dihydropyrrole **82**.



Scheme 20. Rhodium catalyzed three component synthesis of trans-2,3-disubstituted dihydropyrroles **82**.[34]

3.4.2. Phosphonite mediated three component reaction

Another three component reaction, based on the phosphonite PhP(2-catechyl) (**84**) induced coupling of alkene-tethered imines **83** with acid chlorides, has been reported by Arndtsen and co-workers.[35] This reaction involves phosphorus-containing 1,3-dipoles **85** that undergo an intramolecular 1,3-dipolar cycloaddition with high stereo- and regioselectivity to generate the intermediate **86**. Then loss of phosphine oxide and deprotonation of the iminium provides the 2,3-dihydropyrroles **87**.

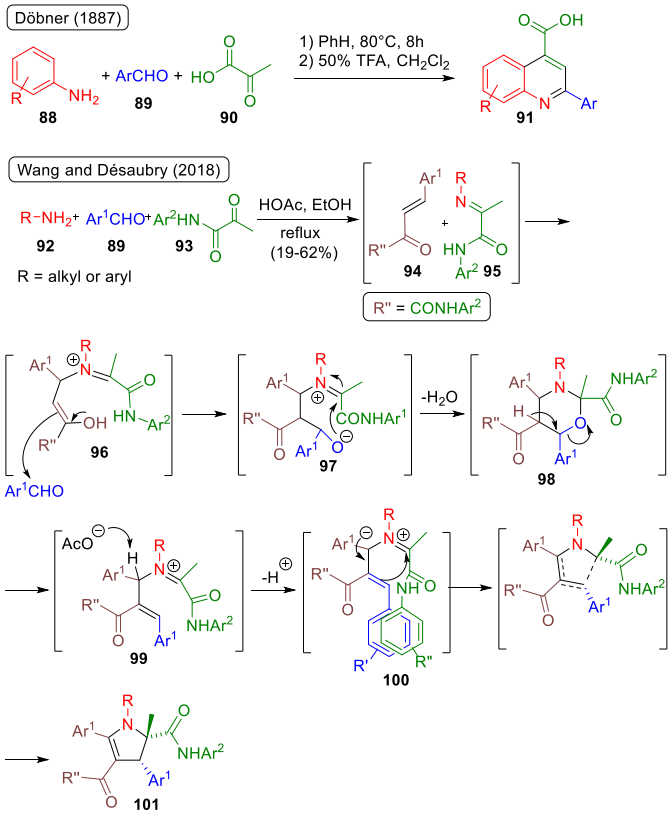


X = CH_2, O, S, nothing, R^1 = H, Me, Ph, COOEt, R^2 = alkyl or benzyl, R^3 = (hetero)aryl or *t*-Bu

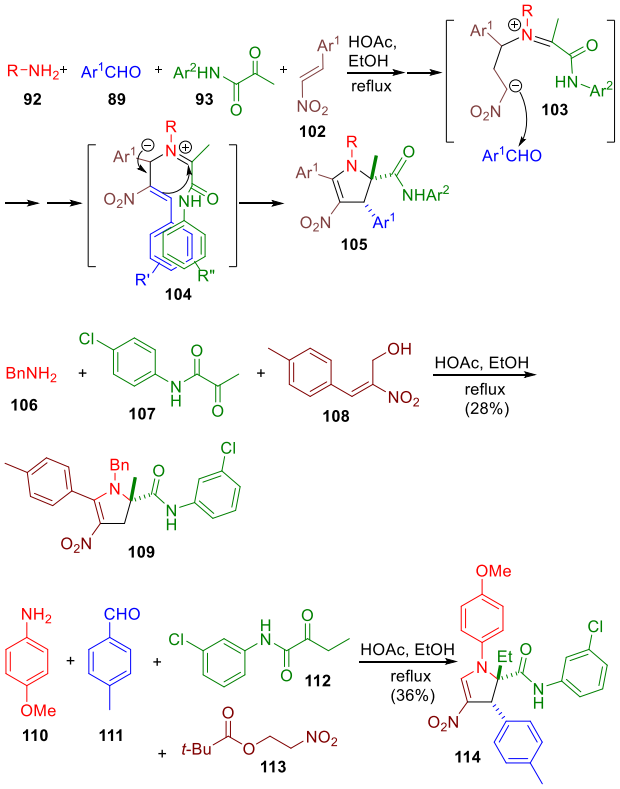
Scheme 21. Coupling of alkene-tethered imines **83** and acid chlorides.[35]

3.4.3. Multicomponent reaction using α-ketoamides

In 1887 Oskar Döbner reported that the condensation of an aniline (**88**) with an aromatic aldehyde (**89**) and pyruvic acid (**90**) generates a quinoline (**91**) (Scheme 22).[36, 37] More than 130 years later, the replacement of pyruvic acid (**90**) with a pyruvic amide (**93**) was found to lead to the stereoselective formation of a polysubstituted 2,3-dihydropyrrole (**101**) instead of the expected quinolines.[38] The mechanism of this reaction was proposed to involve the condensation of enone **94** with imine **95** to produce intermediate **96** that reacts with aldehyde **89**, leading to 3-oxazine **98**. Successive dehydration and deprotonation then generate the azomethine ylide **100** that undergoes an intramolecular 1,5-dipolar cycloaddition to afford the 2,3-dihydropyrrole **101**. This reaction does not require a *N*-protection by a tosyl difficult to remove and generates five new bonds (~90% average yield per bond formation) in one step. It was applied to the synthesis of potent α-glucosidase inhibitors.[39] Thereafter the scope of this reaction was extended by adding β-nitroalkene **102** and **108** or β-pivaloxy-nitroalkane **113** to generate 2,3-dihydro-4-nitropyrroles functionalized in every position (Scheme 23).[39]



Scheme 22. Döbner reaction and formation of dihydropyrroles **101** with pyruvic amides **93**.[38]

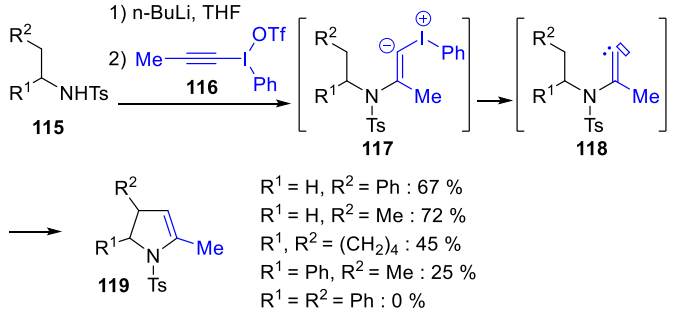


Scheme 23. Multicomponent synthesis of 2,3-dihydro-4-nitropyrroles.[39]

3.5. Miscellaneous

3.5.1. Condensation of hypervalent alkynyliodonium salts with aliphatic amines

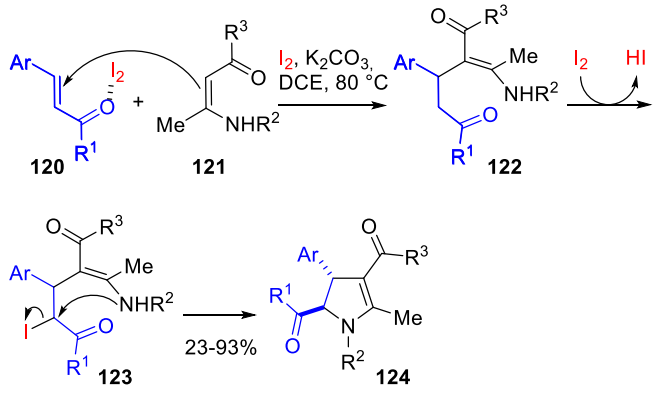
Feldman group discovered that the condensation of tosylamide anions **115** with alkynyliodonium triflates **116** generates alkylidene carbenes **118** that undergo a C-H insertion to afford 2,3-dihydropyrroles **119** (Scheme 24).[40] This reaction occurs with lower yields when the amine is substituted by a protecting group other than a tosyl. Another limitations of this reaction is the instability of the adduct in acidic medium, which requires silica gel to be pretreated with Et_3N before to be used for flash chromatography purification.



Scheme 24. Synthesis of 2,3-dihydropyrroles by condensation of lithiated sulfonamides with alkynyliodonium triflates **116**.[40]

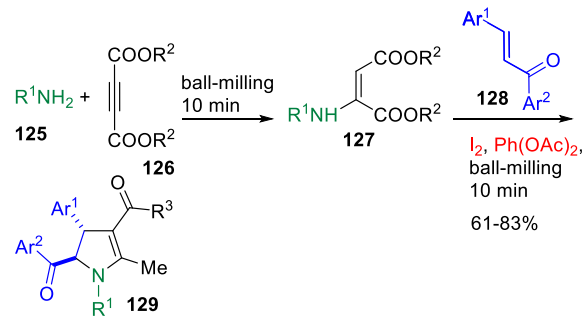
3.5.2. Iodine-promoted synthesis of polysubstituted 2,3-dihydropyrroles

Gao's group developed a convenient synthesis of polysubstituted trans-2,3-dihydropyrroles **124** from chalcones **120** and β-enaminocarbonyls **121** via an iodine promoted Michael addition followed by an iodination and an annulation step (Scheme 25).[41] Subsequently Wang's group performed this reaction in absence of solvent and generated the β-enaminocarbonyls *in situ* by condensation of amines with alkyne esters (Scheme 26).[42]



R1 = (hetero)aryl, Me; R2 = alkyl, aryl; R3 = Me, OEt

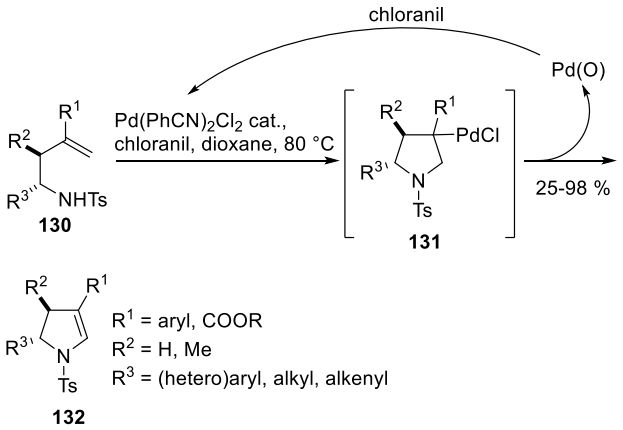
Scheme 25. Iodine-promoted synthesis of dihydropyrroles **124** from chalcones **120** and β-enaminocarbonyls **121**.[41]



Scheme 26. Mechanosynthesis of trans-2,3-dihydropyrroles **129** from amines, alkyne esters, and chalcones.[42]

3.5.3. Intramolecular Pd(II)-catalyzed annulation

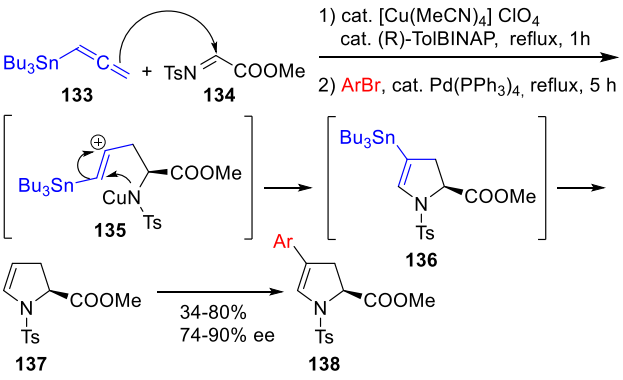
In line with the former approach, Loh's group reported a palladium-catalyzed 5-endo-trig cyclization of *N*-tosyl homoallylamines in presence of chloranil as oxidant (Scheme 27).[43]



Scheme 27. Palladium-catalyzed cyclization of *N*-sulfonyl homoallylamines **130**.[43]

3.5.4. [2+3] annulation of allenylstannanes with α-imino esters

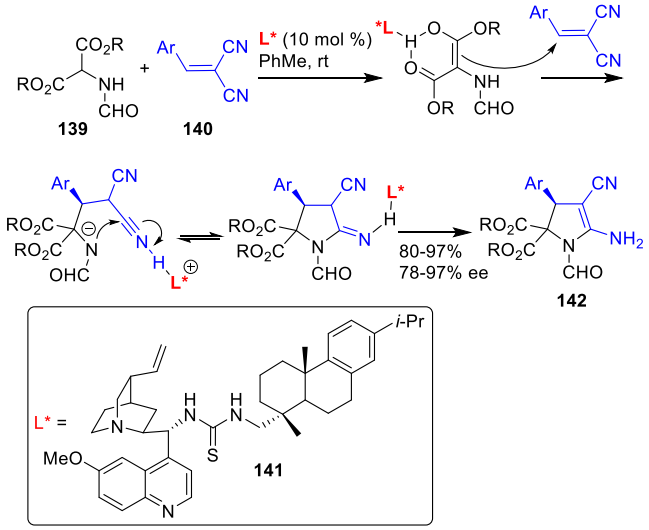
Takahiko and coworkers described the copper-catalyzed enantioselective [2+3] annulation of allenylstannane **133** with α-imino ester **134** followed by a Stille reaction to afford *N*-tosyl-dihydropyrroles (Scheme 28).[44]



Scheme 28. Condensation of allenylstannane **133** and α-imino ester **134** followed by a Stille reaction.[44]

3.5.5. Organocatalytic synthesis of chiral *N*-formyl- 2,3-dihydropyrroles

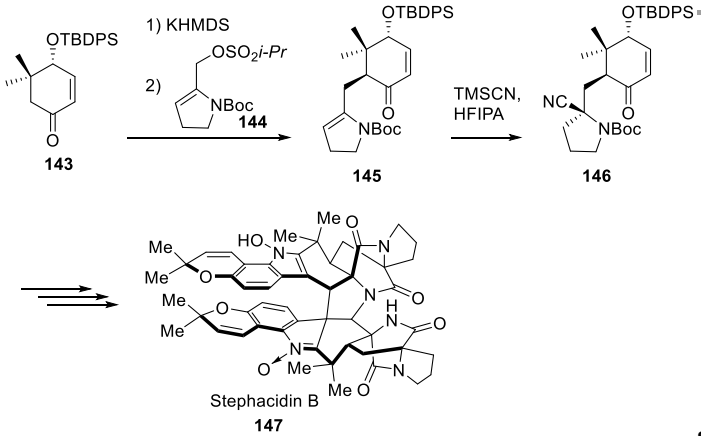
A convenient asymmetric tandem Michael addition/cyclization between formylaminomalonates **139** and aromatic dicyanoolefins **140** catalyzed by the novel chiral thiourea **141** furnishes *N*-formyl-2,3-dihydropyrroles **142** with high yields and good enantioselectivities in only one step (Scheme 29).[45]



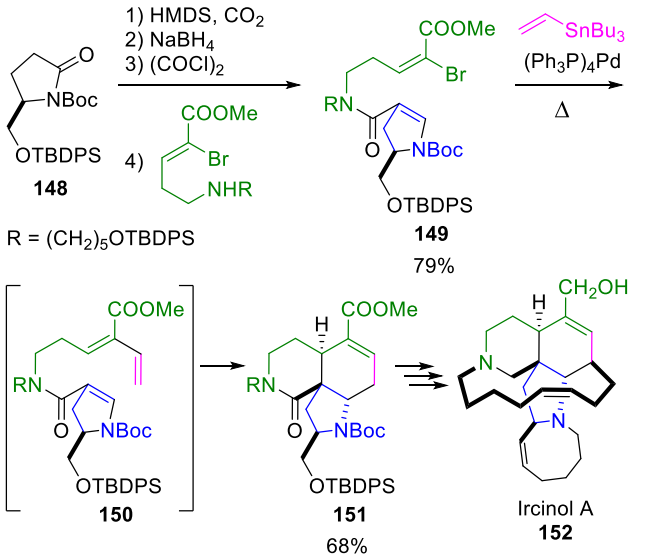
Scheme 29. Organocatalytic synthesis of chiral *N*-formyl- 2,3-dihydropyrroles **142**.[45]

4. 2,3-Dihydropyrroles as intermediates in the total synthesis of natural products

2,3-Dihydropyrroles have been used as critical intermediates in the synthesis of natural products. For instance, deprotonation of ketone **143** and alkylation with sulfonate **144** stereospecifically afforded the dihydropyrrole **145**, which underwent Strecker-like reaction with TMSCN generating **146**, en route toward the total synthesis of Stephacidin B described by Myers' group (Scheme 30).[46]



Scheme 30. Use of 2,3-dihydropyrrole **145** as an intermediate in Myers' enantioselective total synthesis of Stephacidin B.[46]

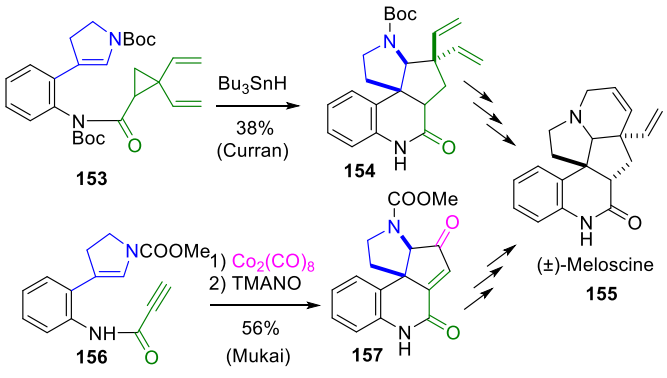


Scheme 31. Synthesis of the tricyclic core of Ircinol A (**152**) by Martin and co-workers.[47]

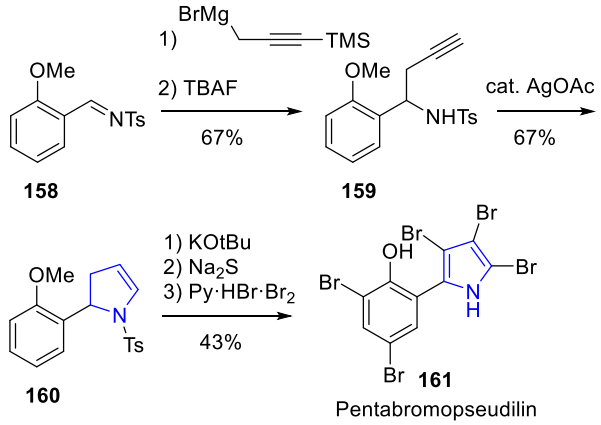
The approach of Martin and co-workers to fashion the scaffold of the complex manzamine alkaloids relies on the readily accessible chiral dihydropyrrole **149** that was converted in one step to the key tricyclic intermediate **151** through a tandem Stille/Diels-Alder reaction (Scheme 31).[47]

The *Melodinus* alkaloid (±)-Meloscine **155** has been prepared in 2011 by the groups of Curran and Mukai using in both cases a dihydropyrrole (**153** or **156**) to assemble the core structure of this complex alkaloid exploiting an elegant radical-initiated cyclization and an intramolecular Pauson-Khand reaction (Scheme 32). [48, 49]

Knölker and colleagues developed a silver(I)- catalyzed 5-endo-dig cyclization of homopropargylamines **159** into 2,3-dihydropyrrole **160** that was applied to the synthesis of the natural myosin ATPase inhibitor pentabromopseudilin (**161**), a polyhalogenated pyrrole synthesized by *Pseudomonas bromoutilis* and *Chromobacteria* (Scheme 33).[50]



Scheme 32. Curran and Mukai's syntheses of the tetracyclic skeleton (±)-Meloscine (**155**).[48, 49]



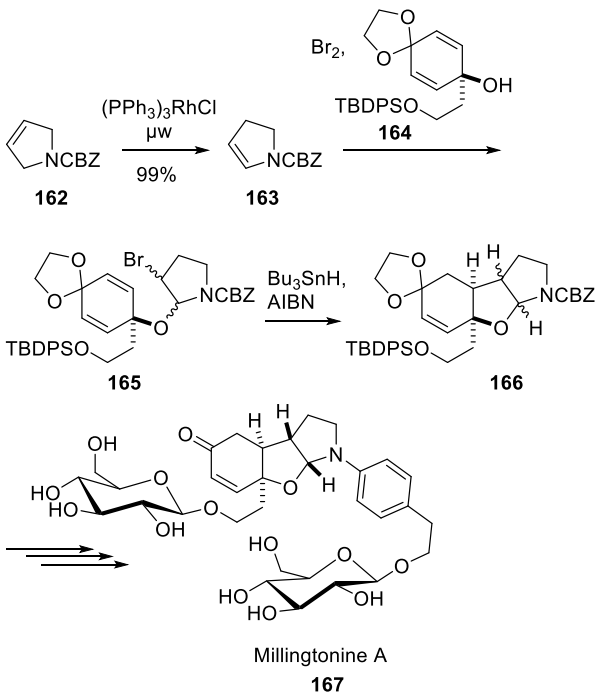
Scheme 33. Knölker's synthesis of pentabromopseudilin. [50]

Millingtonine A (**167**) is a glycosidal alkaloid extracted from the Asian medicinal plant *Millingtonia hortensis*. Baxendale and co-workers' approach to assemble the core of this complex heterocycle began with the isomerization of the protected 1,2-dihydropyrrole **162** into 2,3-dihydropyrrole **163** with Wilkinson's catalyst (Scheme 34).[51] Engagement of this protected enamine into a Ueno-Stork cyclization with the allylic alcohol **164** furnished the key intermediate **165** that was converted in few steps to millingtonine A (**167**).

5. Conclusion

From the endo-dig cyclization of homopropargylamines to the cascade or multicomponent reactions, methods to prepare these heterocycles span the breadth of functional groups, and classical and modern reactions. Even if some of them suffer from the necessity to use a tosyl, which is difficult to deprotect, the synthetic studies towards 2,3-dihydropyrroles has been rich in intellectual excitement and has already been applied to several natural products and bioactive compounds. While we tried our very best to be comprehensive, it is possible that we have inadvertently missed some important reports, for which we express our regret here in advance.

Last but not least, we hope that this review will be useful for the design and synthesis of functionally active molecules, especially for biological applications.



Scheme 34. Baxendale's total synthesis of millingtonine A(**167**).[51]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The acknowledgements come at the end of an article after the conclusions and before the notes and references.

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