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Strategies for the Synthesis of Spiropiperidines – A Review of the Last 10 Years

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Spiropiperidines have gained in popularity in drug discovery programmes as medicinal chemists explore new areas of three-dimensional chemical space. This review focuses on the methodology used for the construction of 2-, 3- and 4-spiropiperidines, covering the literature from the last 10 years. It classifies the synthesis of each of the types of spiropiperidine by synthetic strategy: the formation of the spiro-ring on a preformed piperidine ring, and the formation of the piperidine ring on a preformed carbo- or heterocyclic ring. While 3- and 4-spiropiperidines are predominantly synthesised for drug discovery projects, 2-spiropiperidines are synthesised en route to natural products. The lack of 2-spiropiperidines in drug discovery is presumably due to limited general procedures for their synthesis.

1. Introduction

The identification and generation of high quality lead compounds are imperative in the initial stages of drug discovery. With a greater understanding of chemical and biological space, there has been a much greater emphasis on the exploration and exploitation of a molecule's three-dimensional nature.[1] Spirocycles are frequently used as scaffolds and pharmacophores in drug discovery as a consequence of their structural complexity and rigidity, and their ability to be elaborated along well-defined vectors.[2] Owing to the frequency of nitrogen containing heterocycles in drug discovery and the growing desire to explore three-dimensional space, aza-spirocycles are fast becoming highly desirable targets for synthesis. For example, the 2-spiropiperidine-containing natural product histrionicotoxin was identified as an acetylcholine receptor inhibitor,[3] a 3-spiropiperidine was reported by Novartis as a ghrelin receptor agonist in patent US 20120302540,[4] and GlaxoSmithKline have reported a 4-spiropiperidine as a fatty acid synthase inhibitor in patent WO 2013177253.[5] n 2009 Troin reviewed the synthesis of spirocyclic piperidines as important building blocks in medicinal chemistry.[6] The review highlighted the diverse approaches made towards the synthesis of 3- and 4-spiropiperidines. In this review, we present a summary of the past 10 years literature on the synthesis of spiropiperidines, including the relatively under-explored synthesis of 2-spiropiperidines, which were not covered in Troin's review. In each case, we will discuss two approaches towards the synthesis of the spirocycle; firstly, the formation of the spirocycle on a preformed piperidine ring, and secondly, the formation of the spirocycle on a preformed carbocyclic/heterocyclic ring.

2. 2-Spiropiperidines

2.1 2-Spiropiperidine formation on a preformed piperidine ring.

The synthesis of 2-spiropiperidines from a preformed piperidine ring is an under explored method for their synthesis. The two presented methods proceed via a reductive lithiation and a 1,3-dipolar cycloaddition. It is clear from the lack of literature precedent that new methods for the synthesis of 2-spiropiperidines from a preformed piperidine ring is a relatively novel approach.

A new route to tertiary α-amino stereocentres was developed by Rychnovsky in 2008, which in turn allows the synthesis of 2-spiropiperidines.[7] α-Amino nitrile **1** was alkylated to give substituted piperidine **2**, which then underwent a reductive cyclisation onto the alkene to yield 2-spiropiperidine **3** in good yield and high diastereoselectivity (Scheme 1). The reaction has been demonstrated to give 2-spiropiperidines with five and six membered carbocyclic rings with a range of tethers, in moderate to good yield.

Ryan and co-workers synthesised (–)-perhydrohistrionicotoxin **6** on gram-scale in batch, as well as through flow. The natural product contains a 2-spiropiperidine core, which was accessed through isoxazolidine **4** (Scheme 2).[8] Under microwave irradiation at 184 °C, isoxazolidine **4** underwent a retro [3+2] cycloaddition followed by 1,3-dipolar cycloaddition to give 2-spiropiperidine **5** in good yield. The *N-O* bond was then reductively cleaved to give the natural product 2-spiropiperidine **6** in high yield.

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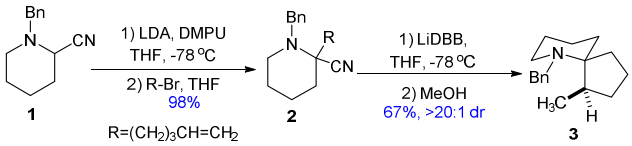
2.2 2-Spiropiperidine formation on a preformed carbocyclic/heterocyclic ring.

The formation of a 2-spiropiperidine from a preformed carbocyclic or heterocyclic ring is the most common strategy for the synthesis of 2-spiropiperidines. Methods include [6+3], [3+2], and 1,3-dipolar cycloadditions, ring closing metathesis, and the use of commercially available SnAP reagents.

A 1,3-dipolar cycloaddition approach was reported by Coldham in 2017 for the synthesis of spirocyclic amines.[9] Condensation of hydroxylamine with an open chain ketone **7** followed by displacement of the chlorine gave the 1,3-dipole **8**, which underwent cycloaddition in PhMe under reflux to give tricycle **9** (Scheme 3). The *N-O* bond was then reductively cleaved with Zn/AcOH to yield 2- spiropiperidine **10** in excellent yield.

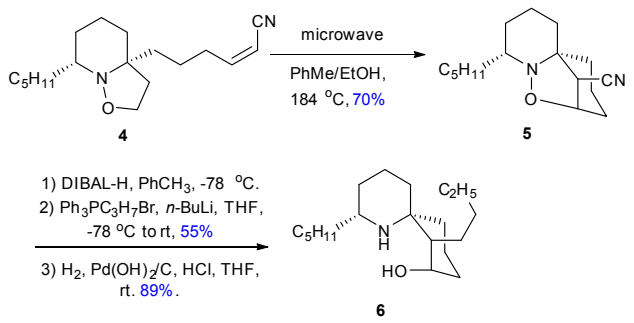


Scheme 1 Rychnovsky's synthesis of 2-spiropiperidines through alkylation and reductive cyclisation.

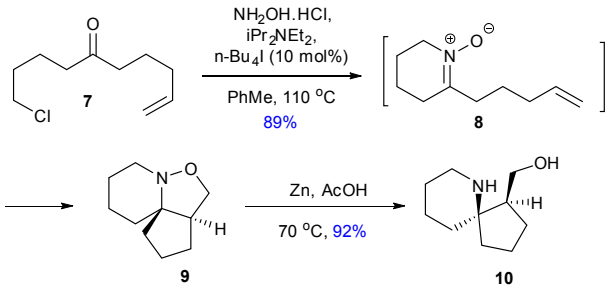
Samuel Griggs was born in London, United Kingdom in 1992. He received his MChem from the University of Nottingham in 2010, undertaking a 12-month placement at Sygnature Discovery and working in the laboratory of Professor Robert Stockman as part of his degree. In 2014 he began pursuing his PhD in the group of Dr Paul Clarke at the University of York, working towards the synthesis of 2-spiropiperidines. He is funded by the University of York and receives CASE funding from GlaxoSmithKline.

Dr Daniel Tape was born in Plymouth and obtained his MChem from the University of Southampton in 2001. After graduating, he joined GlaxoSmithKline (GSK) as a synthetic and medicinal chemist working in the field of respiratory disease. During his time at GSK he obtained his PhD in conjunction with the University of Strathclyde under the tutelage of Dr Craig Jamieson and Dr Diane Coe in the field of Toll Like receptor agonists. Daniel currently works in the Flexible Discovery Unit working on several projects across the GSK portfolio.

Dr Paul Clarke obtained his B.Sc(Hons) in 1993 from the University of Bath. He remained at Bath to study for a PhD in the group of Alan Armstrong, graduating in 1996. Postdoctoral research at Florida State University with Robert A. Holton was followed by postdoctoral research at the University of Exeter with Christopher J. Moody. Paul was appointment to a lectureship in organic chemistry at the University of Nottingham in 1999. In 2006 he moved to the University of York. In 2009 Paul was admitted as a Fellow of the Royal Society of Chemistry. Paul has research interests in the synthesis of tetrahydropyrans, total synthesis, medicinal chemistry, and the origins of life. Paul is currently on the editorial board of the journal Life and is a synthetic chemistry consultant for the pharmaceutical industry.



Scheme 2 Retro [3+2] followed by a 1,3-dipolar cycloaddition to afford the 2-spiropiperidine core of (–)-perhydrohistrionicotoxin.



Scheme 3 1,3-Dipolar cycloaddition to yield a tricyclic precursor to 2-spiropiperidines

Tricyclic, bridged 2-spiropiperidines have been synthesized by means of a silver-catalysed diastereoselective [6+3] cycloaddition in a reaction developed by Guo and coworkers.[10] Tropone **11** is treated with an azomethine ylide, generated from precursor **12** which is derived from homoserine lactone (Scheme 4). A range of silver catalysts were screened with different bases, with AgOAc (10 mol%) and DBU (20 mol%) yielding the best results. The 1,3-dipolar cycloaddition proceeded under mild conditions, giving a range of tricyclic 2-

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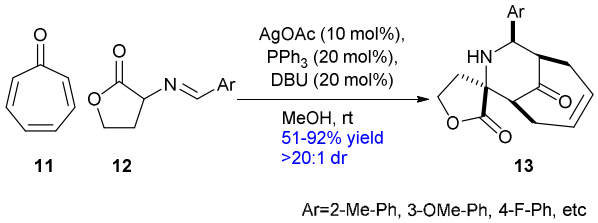
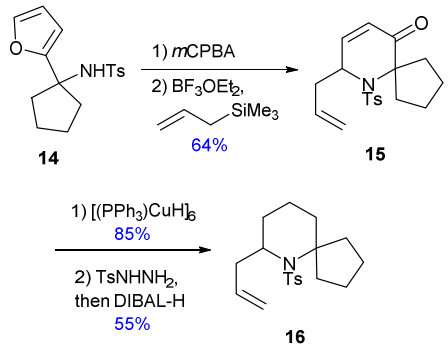
spiropiperidines **13** in moderate to excellent yields, with diastereoselectivities >20:1.



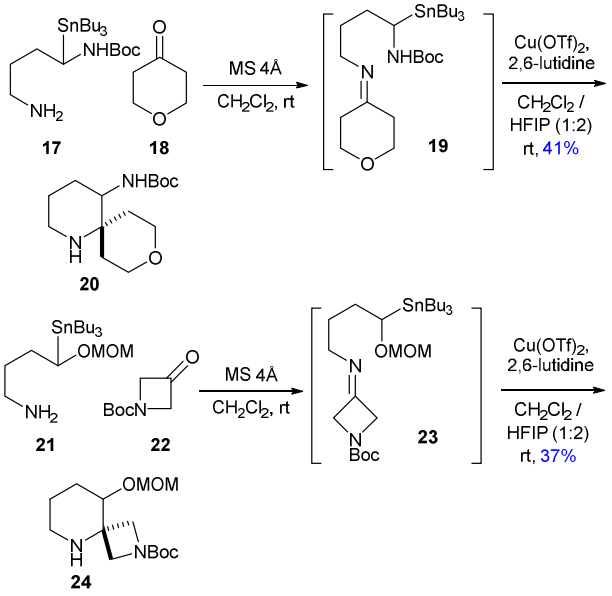
Scheme 4 [6+3] Cycloaddition of tropone to homoserine lactone derived azomethine ylides.



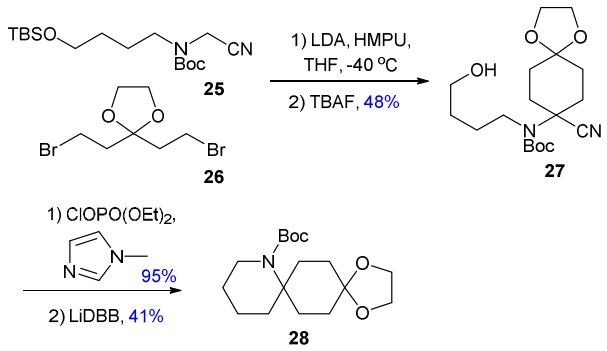
Scheme 5 Aza-Achmatowicz rearrangement to afford the 2-spiropiperidine core of pinnaic acid.

Marquez efficiently accessed the 2-spiropiperidine core of the natural product pinnaic acid via an aza-Achmatowicz rearrangement (Scheme 5).[11] Upon oxidation of the furan and subsequent rearrangement of amine **14**, the hemi-aminal was allylated under Lewis acidic conditions to give 2-spiropiperidin-3-one **15** in good yield. Selective 1,4-reduction was achieved using Stryker's reagent and deoxygenation occurred with tosylhydrazine and DIBAL-H to give 2-spiropiperidine **16** in moderate yield.

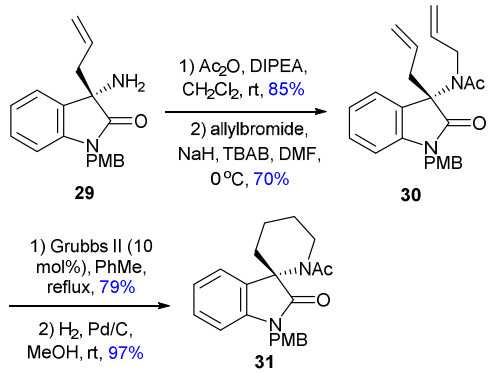
SnAP (tin amine protocol) reagents are a series of commercially available reagents developed by Bode.[12] Treatment of SnAP reagents **17** and **21** with ketones gave rise to imines **19** and **23**, which underwent homolytic cleavage of the C-Sn bond and a radical addition to the imine upon addition of $Cu(OTf)_2$, giving spirocyclic heterocycles **20** and **24** respectively (Scheme 6).[13] This robust procedure allows efficient access to a range of substituted spiropiperidines and does not require protection of the piperidine nitrogen, however, it does involve the use of potentially toxic organotin reagents.



Scheme 6 Synthesis of 2-spirospiperidines using SnAP reagents.



Scheme 7 Trianion synthon approach to the synthesis of 2-spiropiperidines.



Scheme 8 Ring closing metathesis to form the 2-spiropiperidine – a type II β-turn peptide isostere.

Rychnovsky's approach to the synthesis of spirocyclic heterocycles was reversed in later studies, forming the carbocyclic ring prior to the heterocyclic ring.[14] Just one example of a 2-spiropiperidine is reported utilising this approach. The α-amino nitrile **25** was utilised as a trianion

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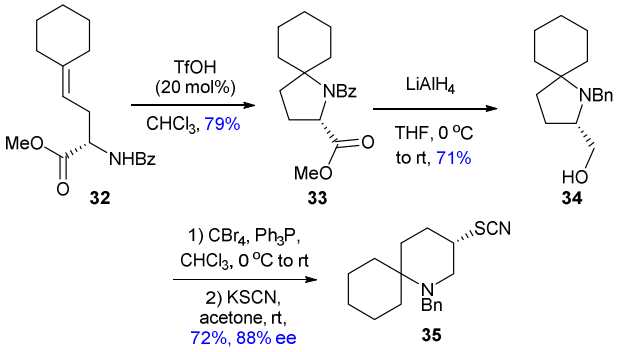
synthon – first to perform a double alkylation with dibromo ketal **26** to form the carbocyclic ring of **27**, followed by a reductive cyclisation to give 2-spiropiperidine **28** (Scheme 7).

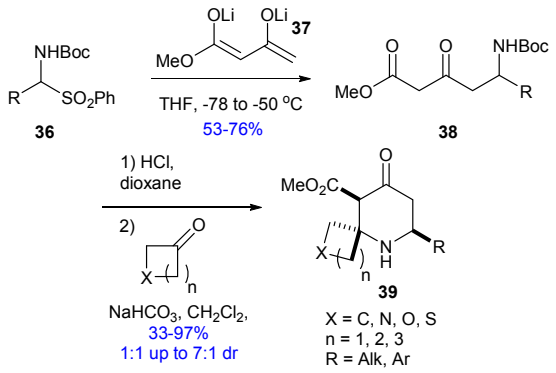
A ring closing metathesis was reported by Silvani for the synthesis of a spiropiperidine-3,3'-oxindole scaffold as a type II β-turn peptide isostere in 2010.[15] Oxindole **29**, synthesised from isatine via Grignard addition into an imine,[16] underwent *N*-acylation followed by *N*-allylation to give diene **30** (Scheme 8). 2-Spiropiperidine **31** was formed in high yield through a ring closing metathesis of **30** with Grubbs II catalyst, followed by hydrogenation of the double bond.

Robinson and co-workers developed a route to enantiopure 2-azaspirocycles in 2013.[17] A cross-metathesis between *N*-protected allylglycine and methylenecyclohexane gave enantiopure cyclisation precursor **32**, which then underwent acid mediated cyclisation with TfOH to give 2-spiropyrrolidine **33** in good yield (Scheme 9). To access the 2-spiropiperidine, the ester was first reduced to alcohol **34** with $LiAlH_4$, followed by treatment under Appel conditions to access the bromide. Ring expansion occurred through formation of an aziridinium intermediate and trapping with the bromide. The bromide was found to be silica unstable, so it was converted to the thiocyanate analogue **35** in good yield, though with a slight erosion of %ee.

A two-step synthesis of 2-spiropiperidines (Scheme 10) was recently presented by Clarke.[18] δ-Amino-β-ketoesters **38** were formed through Mannich addition of the dianion of methyl acetoacetate **37** onto *N*-Boc imines, which were formed *in situ* from *N*-Boc sulfone precursor **36**. The *N*-Boc-δ-amino-β-ketoesters were deprotected with HCl in dioxane and the HCl salts of δ-amino-β-ketoesters **38** were then 'cracked' in the presence of a cyclic ketone to give highly functionalised 2-spiropiperidines **39**. The synthesis has been shown to proceed with aliphatic, aromatic and heteroaromatic C-6 substituents, with examples of carbocyclic and heterocyclic spirocycles at C-2. 2-Spiropiperidines are formed in good to excellent yields with moderate diastereoselectivities. The 2-spiropiperidines were further functionalised to generate a small library of medicinally relevant molecules.

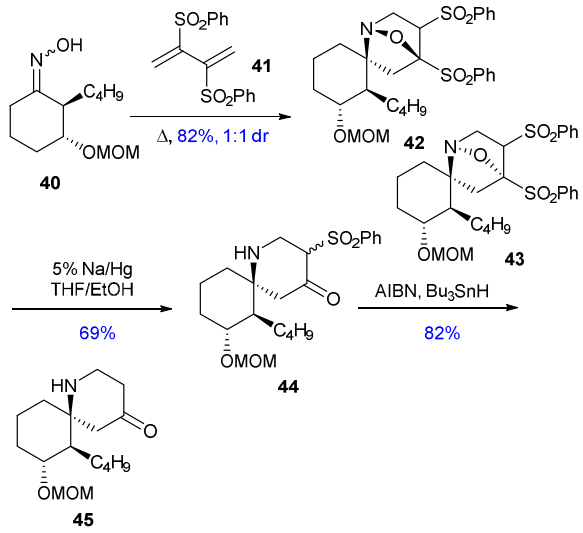


Scheme 9 Ring expansion of 2-spiropyrrolidines to afford 2-spiropiperidines with high enantiomeric excess.



Scheme 10 Two-step synthesis of 2-spiropiperidines from a δ-amino-β-ketoester.

Padwa reported an alternative route to access the 2-spiropiperidine core of (±)-2,7,8-*epi*-perhydrohistrionicotoxin, and in turn a new approach for the synthesis of 2-spiropiperidines.[19] Oxime **40** underwent addition to diene **41** followed by a [3+2] annulation to afford cycloadducts **42** and **43** in high yield and a 1:1 ratio (Scheme 11). The ratio of products was insignificant as the only stereochemical difference was the oxo bridge, which was subsequently destroyed through reductive cleavage with Na/Hg amalgam to give spiropiperidine **44**. The sulfone was then reduced using AIBN/Bu_3SnH to yield 2-spiropiperidine **45** in excellent yield.



Scheme 11 [3+2] annulation followed by reductive cleavage *en route* to (±)-2,7,8-*epi*-perhydrohistrionicotoxin.

Nankakurines are lycopodium alkaloids that contain a 2-spiropiperidine motif that are isolated from mosses. Over the last ten years there have been multiple syntheses of the nankakurines, some of which are presented below.

Overman and co-workers presented an intramolecular azomethine imine cycloaddition with hydrazide **46** to give tetracyclic pyrazolidine **47** in high yield (Scheme 12).[20] The *N*-*N* bond was subsequently cleaved with SmI_2, and selective reductive amination gave cyclisation precursor **48**. Hydrogenation followed by reduction gave diamine alcohol **49**,

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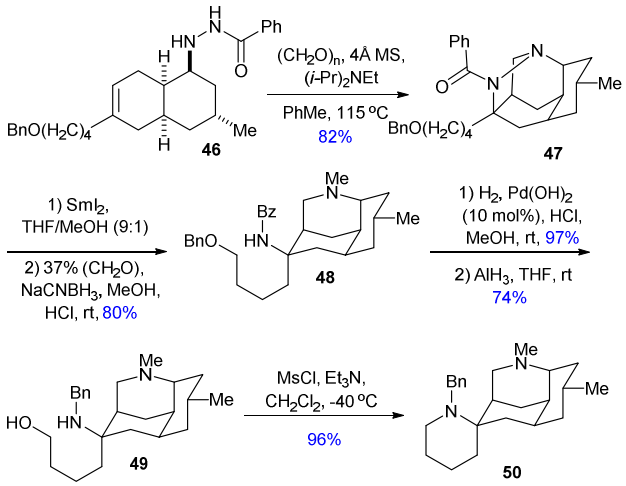
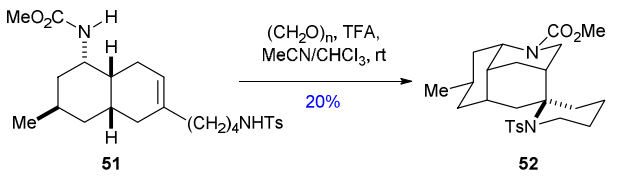
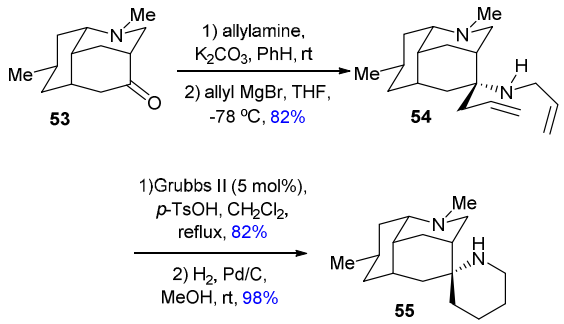
and selective *O*-mesylation allowed cyclisation to proceed, giving 2-spiropiperidine **50** in excellent yield. Overman also demonstrated the use of a sulfonamide-terminated aza-Prins cyclisation with carbamate **51** and 1 equivalent of formaldehyde (Scheme 13).[21] Whilst the reaction proceeded in low yield, it enabled fast access to 2-spiropiperidine **52**, just two steps from the natural product.



Scheme 12 Nankakurine via a SmI_2 mediated *N-N* bond cleavage and S_N2 cyclisation.



Scheme 13 Sulfonamide-terminated aza-Prins cyclisation onto an iminium.



Scheme 14 Waters' ring closing metathesis to form the nankakurine core.

Waters' approach to the nankakurine core was via a ring closing metathesis.[22] Sequential addition of allylamine and allyl magnesium bromide into ketone **53** furnished diene **54** in high yield (Scheme 14). The spiropiperidine was formed through ring closing metathesis of diene **54** and subsequent hydrogenation to give core **55** in excellent yield.

3. 3-Spiropiperidines

3.1 3-Spiropiperidine formation on a preformed piperidine ring.

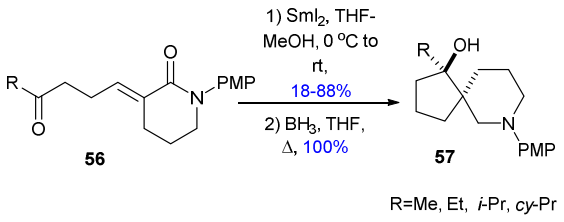
The synthesis of 3-spiropiperidines is represented by an equal number of the two synthetic strategies. Methodology used to form the carbocyclic or heterocyclic ring on to the piperidine ring includes radical cyclisations with SmI_2, organolanthanide addition to ketones, and palladium-mediated intramolecular cyclisations.

Procter developed a samarium(II)-mediated stereoselective cyclisation for the synthesis of aza-spirocycles.[23] Unsaturated ketolactam **56** underwent a sequential conjugate-reduction-aldol cyclisation when treated with SmI_2 to give a spirocyclic lactam, which was reduced with BH_3 to give 3-spiropiperidine **57** in excellent yield (Scheme 15). The cyclisation has been demonstrated to give a range of substituted spirocyclic cyclopentane rings.

An intramolecular Mitsunobu reaction was the strategy employed by Micheli and co-workers to give 3-spiropiperidines.[24] Michael addition of ester **58** on to ethyl acrylate and complete reduction of the glutarimide ring and esters gave diol **59** (Scheme 16). Treatment of diol **59** under Mitsunobu conditions initiated cyclisation to form the pyran ring and consequently a 3-spiropiperidine **60**. The chemistry has also been demonstrated with the synthesis of tetrahydrofuran and oxetane spirocycles.

Enolate chemistry of ester functionalised piperidine **61** was utilised to access the 3-spiropiperidine precursor **62** in a report by Su in 2011.[25] Monotosylation of diol **62** followed by intramolecular cyclisation gave 3-spiropiperidine **63** in moderate yield (Scheme 17). A synthesis of a 4-spiropiperidine bearing an oxetane is also presented using the same method.[25]

Pfefferkorn developed an intramolecular palladium-catalysed α-arylation reaction for the synthesis of a 3-spiropiperidine.[26] Oxidative addition occurs with bromide **64** and palladium, and subsequent reaction with the amide enolate furnished 3-spiropiperidine **65** in moderate yield (Scheme 18), for use as a scaffold in drug discovery.



Scheme 15 Samarium(II)-mediated stereoselective cyclisation for the formation of 3-spiropiperidines.

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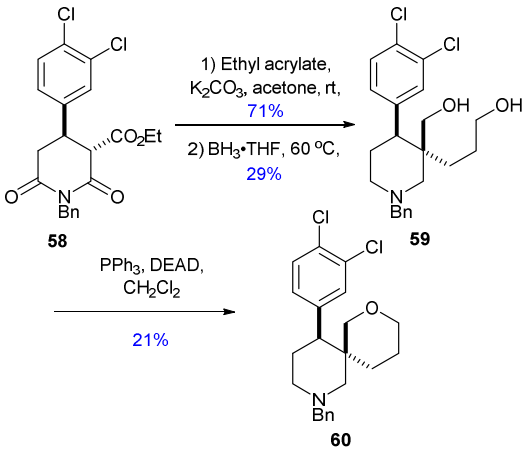
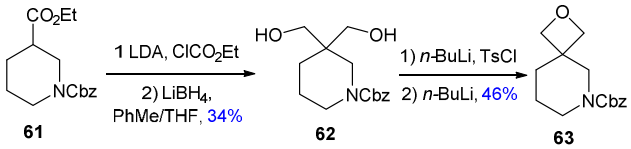
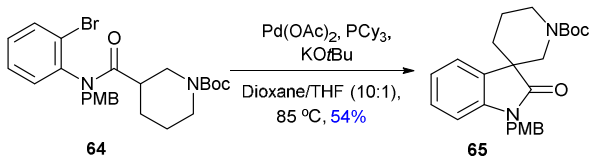


Scheme 16 Intramolecular Mitsunobu to access 3-spiropiperidines.

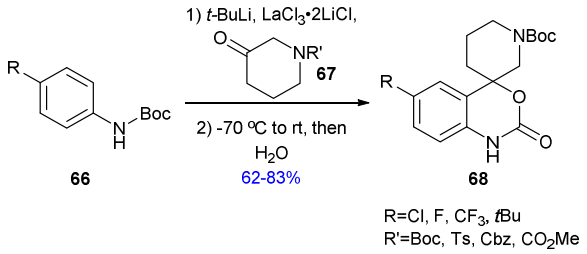


Scheme 17 Monotosylation and deprotonation to initiate cyclisation to form a 3-spiropiperidine bearing an oxetane ring.



Scheme 18 Intramolecular arylation of a functionalised amide enolate.

Nicolau and co-workers introduced a new route to 3-spiropiperidines from *N*-Boc anilines **66** (Scheme 19).[27] A directed lithiation of aniline **66** with *t*-BuLi, metal exchange with $LaCl_3$ and addition to *N*-protected piperidone **67** gave rise to 3-spiropiperidine **68** in good yield. The 3-spiropiperidines presented are derived from a range of *p*-substituted anilines and are compatible with Boc-, Cbz-, Ts- and methyl carbamate protected 3-piperidones.

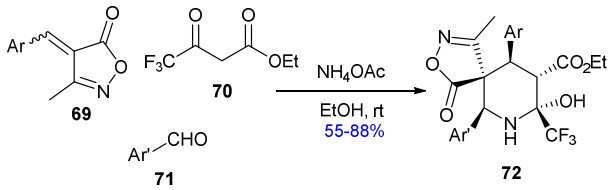


Scheme 19 Lithium-Lanthanum exchange and subsequent addition to *N*-protected piperidone to yield 3-spiropiperidines.

3.2 3-Spiropiperidine formation on a preformed carbocyclic/heterocyclic ring.

Approaches to 3-spiropiperidines by the formation of the piperidine ring on a preformed carbocyclic or heterocyclic ring employ a diverse range of chemistry. Palladium-mediated cyclisations, asymmetric Michael additions, cycloadditions, and multicomponent reactions are representative strategies that give rise to 3-spiropiperidines.

A one-pot multicomponent synthesis of trifluoromethylated 3-spiropiperidines was reported by Song and co-workers in 2016 (Scheme 20).[28] The four-component reaction proceeded at room temperature under catalyst-free conditions to give 3-spiropiperidines **72** in high yields. Michael-addition of β-ketoester **70** to isoxazolone **69**, followed by addition into the imine derived from condensation of NH_4OAc with aldehyde **71**, gave an open chain amine. Subsequent intramolecular cyclisation by aminal formation gave the 3-spiropiperidine **72**. The synthesis has been demonstrated with a range of aromatic aldehydes and isoxazol-5-ones.



Scheme 20 One-pot, four component synthesis of trifluoromethylated 3-spiropiperidines.

A TfOH catalyst was used for a tandem semi-pinacol rearrangement/alkyne-aldehyde metathesis, in the synthesis of 3-spiropiperidines bearing a cyclopentanone spirocycle in a report by Yeh in 2011.[29] Epoxide **73** was treated with TfOH, which underwent the cyclisation cascade to give the hydroxy 3-spiropiperidine, which was oxidised with IBX to 3-spiropiperidine **74** (Scheme 21). The substituent on the alkyne was varied to different substituted aromatics, although the resultant spirocycle formed remained unchanged throughout the study. The ketone of the spirocycle provides a handle for further elaboration.

Reddy and co-workers presented one example of the synthesis of 3-spiropiperidines with a Prins/ene cascade process.[30] The reaction proceeded under mild conditions between diene **75** and an aromatic aldehyde **76** to give 3-spiropiperidine **77** in good yield (Scheme 22).

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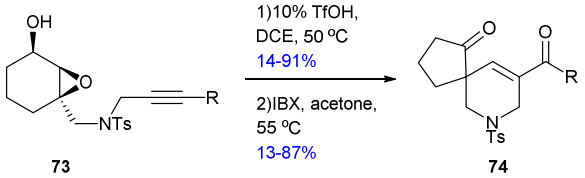
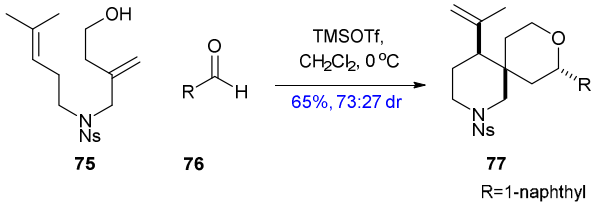


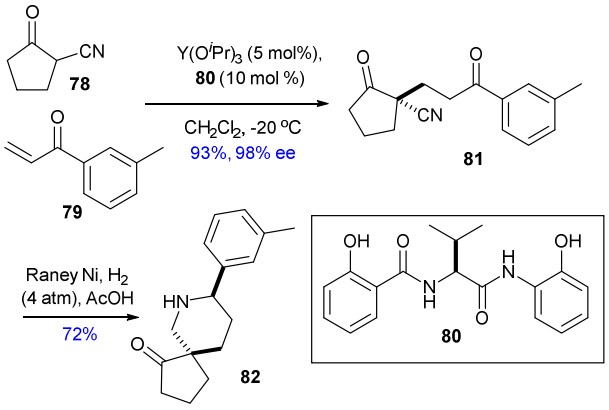
Scheme 21 Tandem semi-pinacol rearrangement/alkyne-aldehyde metathesis to furnish 3-spiropiperidines.



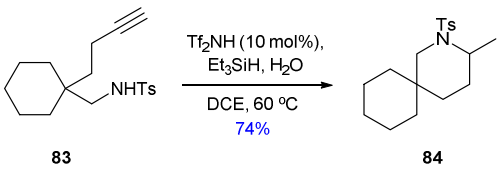
Scheme 22 Tandem Prins cyclisation strategy for the synthesis of 3-spiropiperidines

A catalytic asymmetric conjugate addition of α-cyanoketones to vinyl ketones to generate new quaternary stereogenic centres was reported by Shibasaki in 2010.[31] The conjugate addition between ketone **78** and Michael acceptor **79**, using $Y(O^iPr)_3$ with an amide ligand **80**, proceeded in high yield and excellent enantioselectivity (Scheme 23). Nitrile **81** was reduced with Raney Ni in AcOH under a H_2 atmosphere, which induced an intramolecular condensation to form a cyclic imine, which was then further reduced to give 3-spiropiperidine **82** in good yield.

Described by Shibuya in 2017, a Brønsted acid-catalysed intramolecular hydroalkylation/reduction of unactivated alkynes gave rise to one example of a 3-spiropiperidine synthesis.[32] Treatment of alkyne **83** with catalytic Tf_2NH followed by reduction of the enamine with Et_3SiH gave 3-spiropiperidine **84** in good yield (Scheme 24).

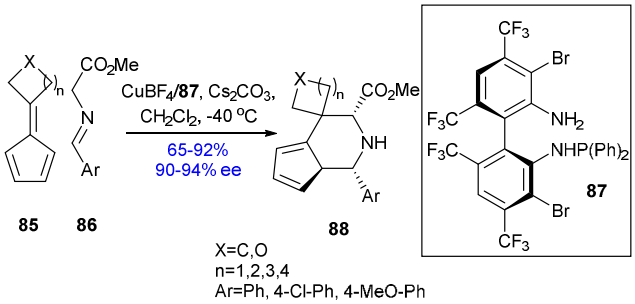


Scheme 23 Conjugate addition of an α-cyanoketone to a vinyl ketone to give a 3-spiropiperidine precursor.



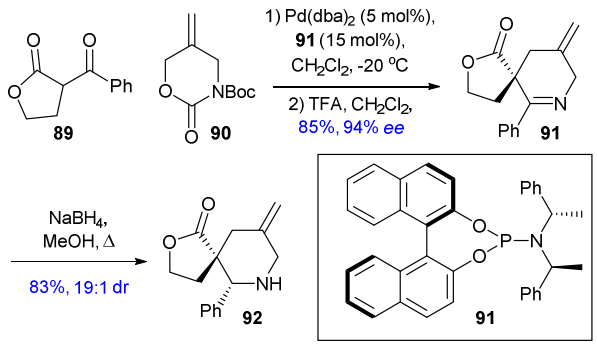
Scheme 24 Sequential hydroalkylation and silane reduction of unactivated alkynes to give a 3-spiropiperidine.

Wang demonstrated the use of substituted fulvenes **85** as 6π dipolarophiles in a [6+3] cycloaddition with azomethine ylides generated from precursor **86** (Scheme 25).[30] Catalysed by Cu(I) with chiral ligand **87**, the enantioselective reaction allowed the synthesis of 3-spiropiperidines **88** in good to high yields with high enantioselectivity. The reaction was reported with a range of fulvene derivatives which consequently accessed different sized carbocyclic spirocycles.



Scheme 25 Enantioselective [6+3] cycloaddition of substituted fulvenes with azomethine ylides.

Harrity and co-workers introduced in 2016, a new palladium-catalysed method for the synthesis of functionalised piperidines.[34] Upon treatment with palladium, cyclic carbamate **90** underwent loss of CO_2 and a formal [4+2] cycloaddition comprising of an allylation-condensation sequence. Use of a 1,3-dicarbonyl with a cyclic lactone **89**, where the ketone substituent can be either aliphatic or aromatic, gave spirocyclic imine **91** in high yield and excellent %ee (Scheme 26). The imine was then reduced to give 3-spiropiperidine **92**.



Scheme 26 Sequential allylation-condensation between a cyclic carbamate and a 1,3-dicarbonyl for 3-spiropiperidine synthesis.

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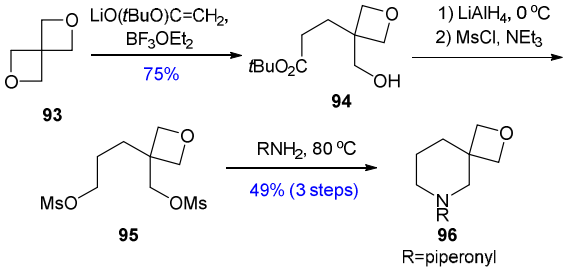
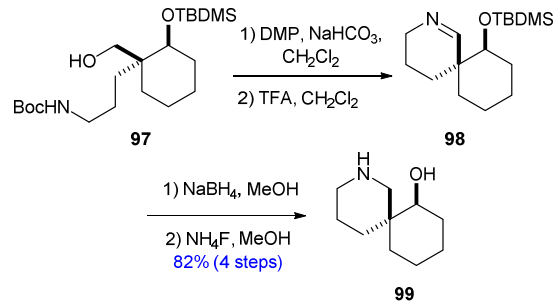
The SpiroChem library[35] was utilised by Carreira for the synthesis of 3-spiropiperidines, starting with spiro building block **93**.[36] Ring opening of one oxetane ring of **93** with a lithium-enolate furnished **94**, which after reduction, gave a diol which underwent double mesylation to give **95** (Scheme 27). Heating **95** in the presence of piperonylamine induced double displacement to give 3- spiropiperidine **96** in good yield over 3 steps.



Scheme 27 Double displacement of a diol generated from ring opening of 2,6-dioxaspiro[3.3]heptane.

Diastereoselective ring-rearrangement metathesis was reported by Lee in 2012.[37] Alcohol **97** was oxidised to the aldehyde, and subsequent amine deprotection with TFA gave the aminal, which eliminated to give imine **98**. Reduction of the imine with $NaBH_4$ gave the 3-spiropiperidine, which was deprotected with ammonium fluoride to give **99** (Scheme 28).



Scheme 28 Aminal formation and elimination followed by reduction to give the 3-spiropiperidine core of nitramine.

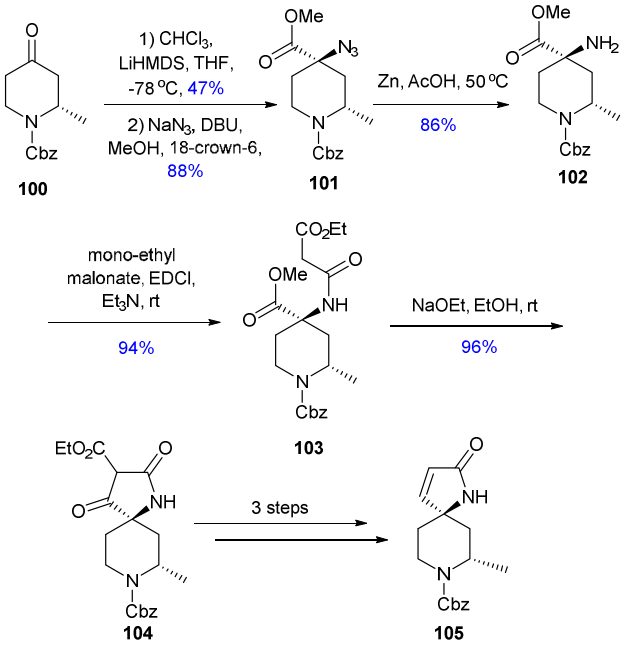
4. 4-Spiropiperidines

4.1 4-Spiropiperidine formation on a preformed piperidine ring

All the reported syntheses of 4-spiropiperidines arise from the formation of a carbocyclic or heterocyclic ring on a preformed piperidine ring. Where the methods involve intramolecular cyclisations via displacement, lactamisation, or ring closing metathesis, the key bond forming step is the construction of the fully substituted spiro-centre. Other methods for the formation of the 4-spiropiperidine include Rh(III) catalysed C-H activation, Fischer-indole syntheses, and acid-mediated cyclisations.

Lee and co-workers developed a stereoselective synthesis of 4-spiropiperidines for use in studies as BACE-1 aspartyl protease inhibitors in 2013.[38] Base-mediated addition of chloroform to optically active **100** followed by a modified Corey-Link reaction[39] furnished azide **101** with the correct stereochemistry, which was then reduced with Zn/AcOH to amine **102** (Scheme 29). Acylation of amine **102** with mono-ethyl malonate gave malonamide **103** and intramolecular Dieckmann cyclisation gave 4-spiropiperidine **104** in excellent yield. The target 4-spiropiperidine **105** was reached in 3 further steps – decarboxylation, reduction and elimination. An alternative approach to a similar compound was reported by Henegar in 2013[40] via a stereospecific Jocic reaction,[41] whereby trichloromethylcarbinol **107** was converted to the α-amino ester **108**, followed by amidation with ethyl malonyl chloride (Scheme 30). Subsequent Dieckmann cyclisation and decarboxylation gave the 3-spiropiperidine **110** in good yield over 3 steps.

SnAP reagents were also used for the synthesis of a 4-spiropiperidine.[42] Under the same conditions as presented in Scheme 6,[13] use of piperidin-4-one **112** enabled the synthesis of 4-spiropiperidine **114** with a heterocyclic spirocycle (Scheme 31). The protocol yields spirocyclic morpholines and piperazines bearing different nitrogen containing heterocycles at the spiro-centre.



Scheme 29 Corey-Link reaction followed by intramolecular Dieckmann cyclisation.

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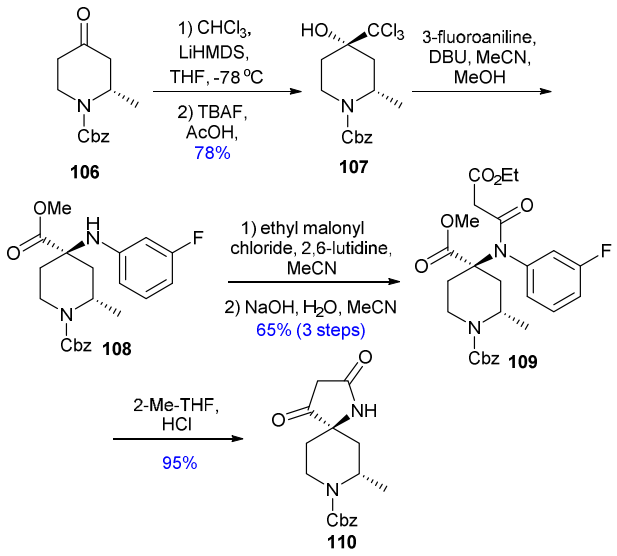
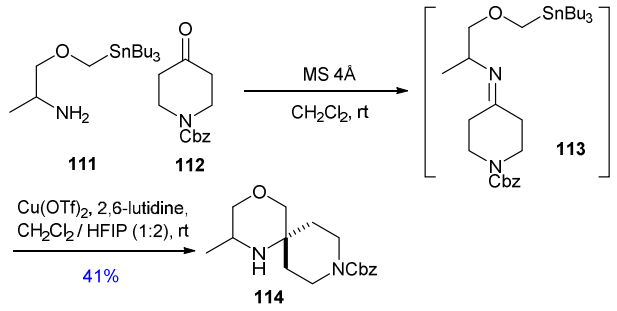
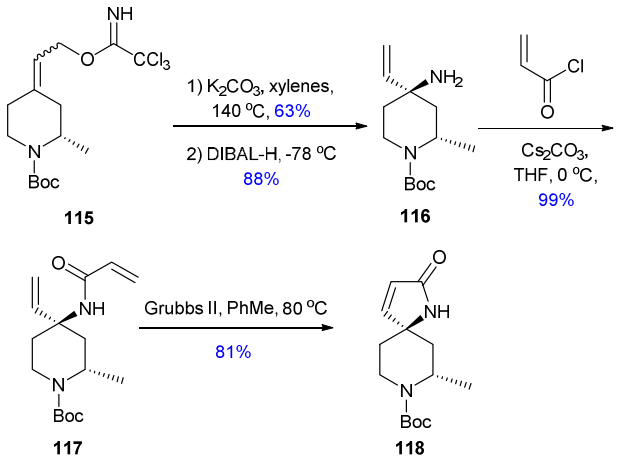


Scheme 30 Stereospecific Jocic reaction for the conversion of a trichloromethylcarbinol to an α-amino ester.



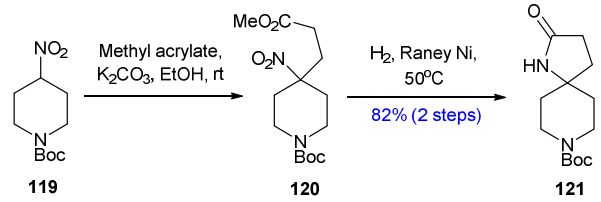
Scheme 31 SnAP reagents for the synthesis of spirocyclic morpholines and piperazines.

An alternative approach to the 4-spiropiperidine BACE-1 aspartyl protease target **118** was reported by Martinez-Alsina in 2017.[43] Amine **116** was accessed through a diastereoselective Overman rearrangement of trichloroacetimidate **115** followed by DIBAL-H reduction of the resultant trichloroacetamide (Scheme 32). Acylation of amine **116** with acroloyl chloride gave diene **117** which underwent ring closing metathesis to give 4-spiropiperidine **118** in high yield. The synthesis was employed to generate novel spirocyclic sultams and lactams for SAR studies.

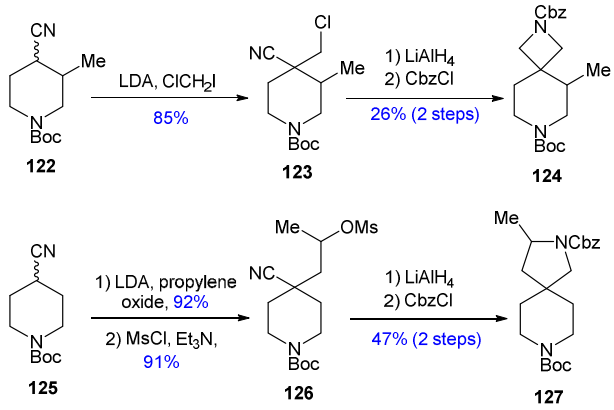


Scheme 32 Ring closing metathesis on a precursor generated from an Overman rearrangement.

Miel presented the synthesis of a spiropiperidine analogue of the eastern part of the anti-HIV drug maraviroc, utilising the first reported synthesis of nitro piperidine **119**.[44] Michael addition of nitro piperidine **119** to methyl acrylate gave nitro ester **120**, which was reduced by catalytic hydrogenation (Scheme 33). The reduced amino intermediate underwent spontaneous lactamisation to give 4-spiropiperidine **121** in high yield over two steps. Smith and co-workers employed a similar strategy of obtaining the spirocycle as Miel by reduction and spontaneous cyclisation in 2016.[45] The anion of cyano-piperidine **122** formed with LDA was quenched with $ClCH_2I$ to give alkylated piperidine **123** (Scheme 34). Reduction of the nitrile gave the amine, which cyclised to form the azetidine. Subsequent protection gave 4-spiropiperidine **124** in moderate yield. The same strategy was employed to form the pyrrolidine of **127** from cyano-piperidine **125**.



Scheme 33 Nitro group reduction and lactamisation to form the spiro-γ-lactam.



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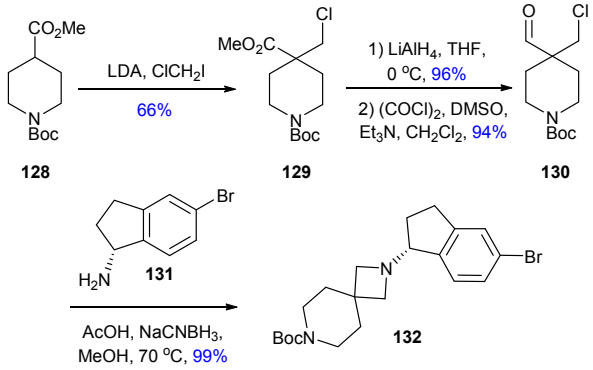
Scheme 34 Spriocycle formation by nitrile reduction and subsequent cyclisation by displacement.

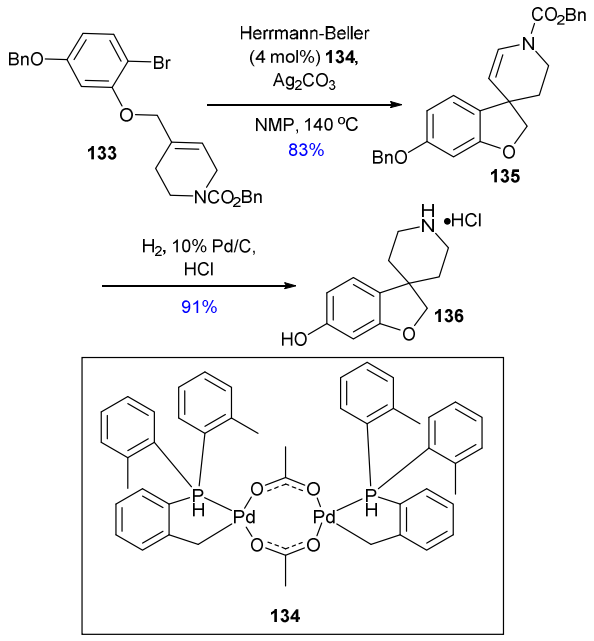
Potent, selective CNS-targeted inverse agonists of the ghrelin receptor, each bearing a 4-spiropiperidine core were reported by McClure and coworkers.[46] The general synthesis of the analogues began with addition of ester **128** into $ClCH_2I$ to give chloride **129**, and reduction of the ester and subsequent oxidation gave aldehyde **130** (Scheme 35). Reductive amination with aminoindane **131** followed by intramolecular cyclisation to displace the chloride formed oxetane **132** in excellent yield.



Scheme 35 Reductive amination and chlorine displacement to form the azetidine of the 4-spiropiperidine.

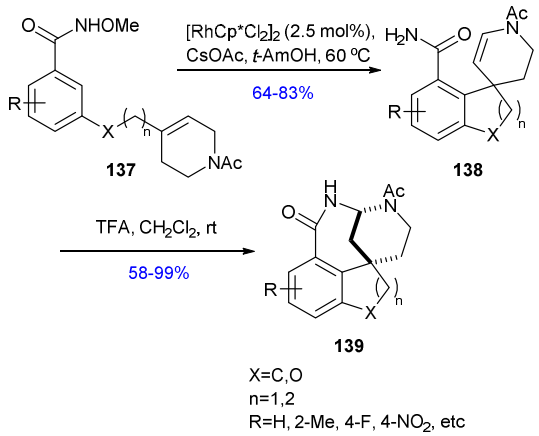
The synthesis of spirocyclic benzofurans bearing a 4-spiropiperidine through an intramolecular Heck cyclisation was developed by Leflemme.[47] Bromide **133** was treated with Herrmann-Beller catalyst **134** which underwent intramolecular cyclisation to give benzofuran **135** in high yield (Scheme 36). The cyclisation was demonstrated with different benzyl alcohol substitution around the phenyl ring. Enamine **135** then underwent reduction and global deprotection to give 4-spiropiperidinyl benzofuran **136** in excellent yield. Chabaud and co-workers reported the synthesis of similar spirocyclic substituted benzofurans, as well as indanes and benzopyrans through rhodium(III)-catalysed C-H activation (Scheme 37).[48] Direction from the methoxy-amide **137** formed the indane ring and enamine **138** in good yield. The enamine **138** was treated with catalytic TFA to induce cyclisation to form the tetracyclic piperidine **139**. The same method has also been utilised for the synthesis of 3-spiropiperidines.[48]

Clayden described an electrophile-induced dearomatizing spirocyclisation of *N*-arylisonicotinamides in 2008.[49] Treatment of pyridine **140** with Tf_2O induced an intramolecular spirocyclisation to give dihydropyridine **141** in excellent yield (Scheme 38). High pressure hydrogenation of **141** gave 4-spiropiperidine **142**. The procedure presented generates 4-spiropiperidines bearing a substituted oxindole as the spirocycle. This work was developed further in 2013 demonstrate the robustness with the use of substituted *N*-alkenyl pyrdinecarboxamides.[50]



Scheme 36 Intramolecular Heck cyclisation for synthesis of spirocyclic benzofurans.

Yang and co-workers reported the discovery of $P2Y_1$ antagonists as novel antiplatelet agents, with analogues bearing a 4-spiropiperidine unit in 2014.[51] Spiroindole **145** was synthesised via a Fischer indole synthesis between hydrazine **143** and aldehyde **144** under acidic conditions (Scheme 39). The resultant indolenine was reduced with $NaBH_4$ to give 4-spiropiperidine **145**. The bromide was then used as a handle for Suzuki couplings to generate aromatic analogues.



Scheme 37 Rhodium catalysed C-H activation for the synthesis of spiropiperidine derivatives.

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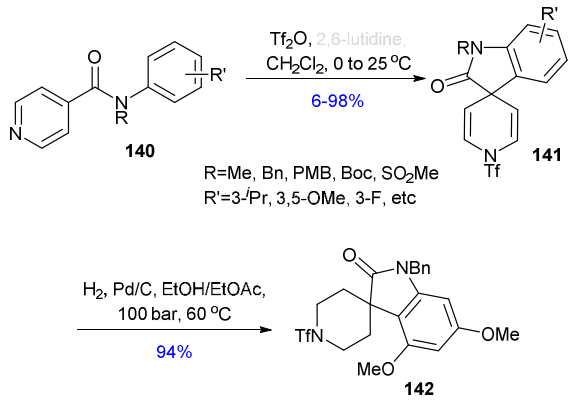
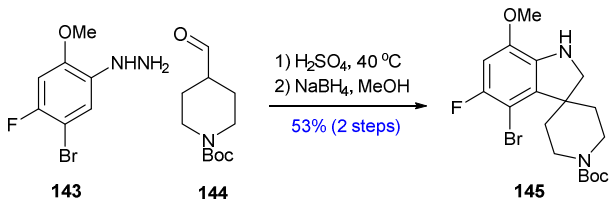
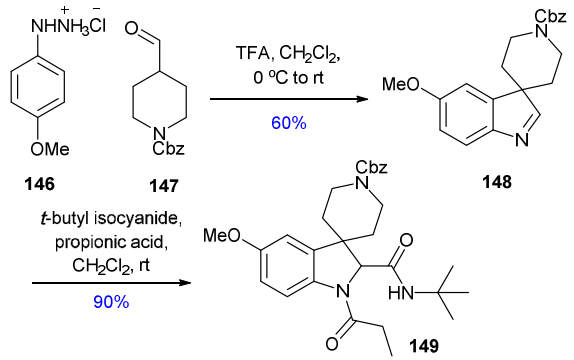


Scheme 38 Intramolecular dearomatizing spirocyclisation for synthesis of dihydropyridines.



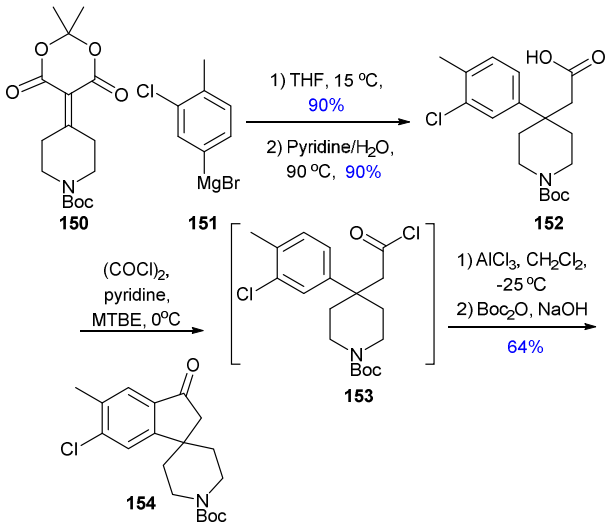
Scheme 39 Fischer indole to introduce the spiroindolenine.

A Fischer indole approach was also reported by Ruijter in 2016 for use in Ugi-type reactions to generate spirocyclic indolenines (Scheme 40).[52] The indolenine **148** was not reduced, instead, addition of an isocyanide and trapping with a carboxylic acid generated the 4-spiropiperidine Ugi product **149** in good to excellent yields. Substituents on the aromatic ring of the resultant indole have been varied, along with different isocyanides and carboxylic acids, however, substitution on the piperidine ring has not been reported.



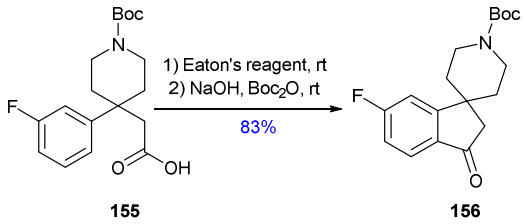
Scheme 40 Fischer indole synthesis followed by Ugi reaction.

A novel rhodium-catalysed asymmetric hydrogenation of a spirocyclic indone was reported by Limanto for the synthesis of a tertiary carbinamide.[53] Addition of Grignard **151** into Michael acceptor **150**, formed from the condensation of *N*-Boc piperidone with Meldrum's acid, followed by hydrolysis gave carboxylic acid **152** in high yield (Scheme 41). Formation of the acid chloride **153** with oxalyl chloride allowed for $AlCl_3$-mediated intramolecular Friedel-Crafts cyclisation to occur. The acidic conditions deprotected the amine, which was re-protected to give indone **154** bearing a non-substituted 4-spiropiperidine in good yield. Bandarage demonstrated a similar strategy, using Eaton's reagent[54] to perform the cyclisation directly onto the acid **155** to form the indane ring of **156** (Scheme 42).[55]

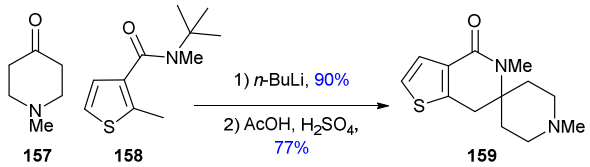


Scheme 41 Ring closing Friedel-Crafts acylation for 4-spiropiperidine synthesis.

Stanetty reported the synthesis of benzo- and thieno-fused spirolactams in 2009. Lithiation of thiophene **158** and addition to *N*-methyl piperidone **157** followed by acid mediated cyclisation gave 4-spiropiperidine **159** in high yield (Scheme 43).[56]



Scheme 42 Intramolecular cyclization utilizing Eaton's reagent



Scheme 43 Acid mediated cyclisation for thiophene-fused spirocycles.

A synthesis of substituted spiro-chromanones as histone deacetylase inhibitors was presented by Thaler.[57,58] *N*-Phenyl piperidone **160** was treated with hydroxy ketone **161** in the presence of pyrrolidine to give 4-spiropiperidine **162** in

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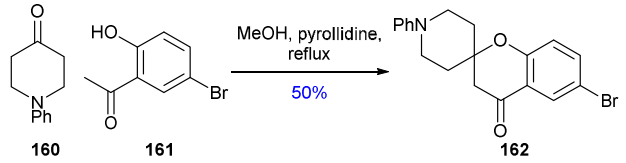
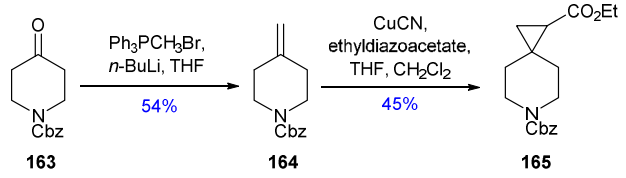
moderate yield (Scheme 44). The aromatic bromide was then used as a handle for elaboration through cross couplings.

Brown reported the discovery of spirofused piperazine and diazepine amides as selective histamine-3 antagonists bearing 4-spiropiperidines.[59] Wittig methylenation of *N*-Cbz piperidone **163** furnished exocyclic methylene **164** and cyclopropanation was achieved with CuCN and ethyldiazoacetate to give 4-spiropiperidine **165** in moderate yield (Scheme 45). The ester was then hydrolysed to the carboxylic acid for a series of amide couplings. The synthesis of 4-spiropiperidines bearing cyclobutane, azetidine and pyrrolidine and piperidine rings are also presented for assay screening.

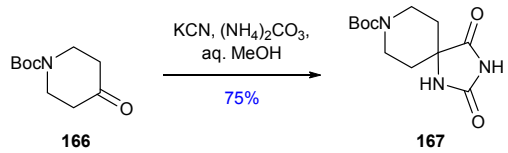


Scheme 44 Spirocyclic chromanone synthesis from *N*-phenyl piperidone.



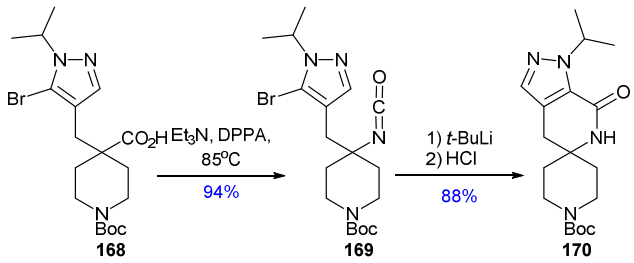
Scheme 45 Cyclopropanation of an exocyclic double for spirocycle synthesis.

The use of spiropiperidine hydantoins as a novel class of antimalarial agents was evaluated by Meyers in 2015.[60] The hydantoin was installed on *N*-Boc piperidone **166** with KCN and $(NH_4)_2CO_3$ to give spirocyclic hydantoin **167** in good yield (Scheme 46). The hydantoin was further substituted and the piperidine nitrogen was elaborated with different aromatic systems.

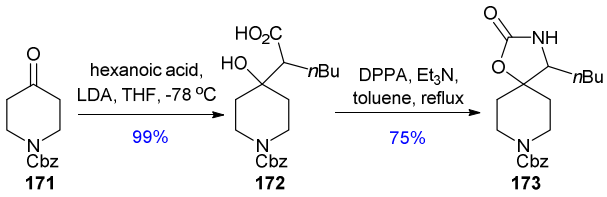


Scheme 46 Spiropiperidine hydantoin synthesis.

The synthesis of spiropiperidine lactam acetyl-CoA carboxylase inhibitors was developed by Menhaji-Klotz and coworkers.[61] For analogue synthesis, *N*-Boc piperidone **168** was synthesised via enolate chemistry into the respective halo-pyrazole (Scheme 47). Treatment of **168** with DPPA induced a Curtius rearrangement to isocyanate **169**, which was quenched through addition of the lithiated pyrazole to give spirolactam **170** in excellent yield. A similar strategy was employed by Rotstein and co-workers for their synthesis of CCR5 antagonists.[62] *N*-Cbz piperidone **172** underwent a Curtius rearrangement, and the subsequent isocyanate was trapped intramolecularly by the alcohol, furnishing the spirocyclic carbonate **173** in high yield (Scheme 48). The synthesis of both five and six membered cyclic carbonates are presented.



Scheme 47 Lithiated pyrazole addition into an isocyanate to form a spirocyclic lactam.



Scheme 48 Alcohol-mediated attack into an isocyanate for spirocyclic carbamate synthesis.

4.2 4-Spiropiperidine formation on a preformed carbocyclic/heterocyclic ring.

Interestingly, at the time of writing we were unable to find a literature example where the 4-spiropiperidine was formed as a result of the synthesis of the piperidine ring. Few examples of the preformed carbocyclic ring are described in Troin's review in 2009.[3]

Conclusions

We have presented an overview of the past 10 years of the synthesis of 2-, 3- and 4-spiropiperidines. Whilst the syntheses of 2-spiropiperidines are mainly for methodology purposes and natural product synthesis, 3- and 4-spiropiperidines have held their place as useful scaffolds in drug discovery. It is interesting to note the trend in how the spirocycles are formed; 2-spiropiperidines tend to arise from annulation of a preformed carbocyclic ring, 4-spiropiperidines arise exclusively from annulation of a preformed piperidine ring, and 3-spiropiperidines are represented by an approximate 1:1 ratio of the two approaches. The majority of 2-spiropiperidine syntheses arise from piperidine formation, presumably a consequence of the difficulty of achieving double substitution

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directly on the carbon alpha to the nitrogen. New methods for achieving double substitution of this carbon atom to install spirocycles would be a novel approach. The presented examples of 4-spiropiperidine syntheses all require a preformed piperidine ring. Often, the key challenge for these syntheses lie in the formation of the spiro-centre, not the subsequent ring forming reaction. Methods for the enantioselective synthesis of 4-spiropiperidines are required. Additionally, nearly all the examples of 4-spiropiperidine syntheses show unsubstituted piperidines, highlighting the opportunity for the development of methods to access 4-spiropiperidines which are substituted on the piperidine ring. 3-Spiropiperidines are represented by a very diverse range of chemistry, including enantioselective syntheses, furnishing substituted piperidines and spirocycles which have been well explored.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

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