Stereoselective synthesis and applications of spirocyclic oxindoles

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The development of novel synthetic strategies to form new chemical entities in a stereoselective manner is an ongoing significant objective in organic and medicinal chemistry. This review analyses the development of new stereoselective approaches to spirocyclic oxindoles with spiro-3- to 8-membered rings. It highlights the importance of these structures for applications in medicinal chemistry, as intermediates or final products in total synthesis and as model compounds for the development of enantioselective catalytic methodologies.

Introduction

The application of spirocyclic structures in drug discovery has seen a dramatic increase in attention in recent years, alongside major developments in their synthetic chemistry. Defined as a bicycle connected by a single fully-substituted carbon atom, which is not connected by an adjacent atom, spirocycles are inherently highly 3-dimensional structures. The shared tetrahedral sp3-carbon atom positions the planes of the 2 rings orthogonally, despite the torsional strain this may impose on the substituents of the rings. Spiro cyclic compounds can improve certain physicochemical properties such as lipophilicity, aqueous solubility and metabolic stability, in comparison to the respective monocyclic structure. Furthermore, they access relatively underexplored chemical space and novel intellectual property (IP) space. Saturated spirocycles provide a dense, rigid scaffold, with the potential to append more substituents, and so occupy an increased number of defined vectors compared to flat aromatic compounds. All of these factors have contributed to a greater uptake in medicinal chemistry and have demanded significant advances in organic synthesis to provide spirocycles in a controlled and stereoselective manner.

This review focuses specifically on spirocyclic oxindoles (spirooxindoles or spiroindolones). These are a widespread...
motif within modern organic synthesis, drug discovery and natural product chemistry. Stereoselective synthetic methods towards this privileged class of spirocycles have seen enormous development in recent years. This review aims to combine the analysis of recent synthetic strategies with an overview of the importance of these scaffolds for medicinal chemistry and in natural product synthesis. Since 1950 there have been 6896 publications containing spirooxindoles, 3283 of these publications have appeared since 2012.15 Oxindoles are often used as rigid scaffolds for testing new asymmetric synthetic methodology and due to the demand of discovery chemistry for controlled and modular syntheses, and with the plethora of publications in this area, we will focus on stereoselective processes. This review examines spirocyclic oxindoles containing a spiro(3 to 8)-membered ring, in turn, analysing carbocyclic then monoheteroatom nitrogen-containing and oxygen-containing spirocycles. The review will cover recent developments from 2013, following major work by Singh and Desta,6 until April 2020. Specific bioactivity and applications of each ring system will be discussed at the start of the relevant section and provide a reference work for the preparation of different spirocyclic patterns. Within each section, the discussion is split by the reaction type employed to construct the spirocycle.

Fig. 1 shows a representative set of each ring system, which will be covered in this review, as they feature in medicinal or natural products.7 Notable biological activity is indicated, including use as anti-cancer agents,8 and anti-viral agents.9 Some ring types are not represented in these bioactive compounds, i.e. aziridines, likely due to their instability relative to larger ring sizes, but will nonetheless be featured in the review.

Given the importance of this structural class, spirocyclic oxindoles have been featured in other reviews discussing their synthesis,10 including asymmetric synthesis,11 use of isatin starting materials12 or the synthesis of target product scaffolds.13 General reviews on spirocyclic compounds (i.e. spiroindolones) also often contain spirocyclic oxindoles without specifically focusing on these.14 We expect the analysis presented in this review of the structural types, synthesis and applications to lead to further studies, and aid in the identification of future opportunities to expand the applications of this fascinating class of compounds.

Frequency analysis of spirooxindoles

To quantify the importance of spiroindolones in the medicinal chemistry and organic synthesis literature, we analysed publications which feature spiroindolones containing up to one heteroatom in the spirocycle between 1970–2020 (Fig. 2).15 The number of publications in which these structures feature has grown significantly over the last 50 years and has consistently reached numbers above 400 per year since 2013. Even accounting for the generalised increase in publications, this represents an extensive level of attention. The number of publications on 5- and 6-membered rings (silver and gold in Fig. 2) dominates the contribution to this total. However, in the last decade the relative contribution of 3-, 4- and 7-membered spirocycles (dark/light blues and orange) has increased.

We also analysed the frequency of the different types of rings which feature in this review (Fig. 3). Considering 3-membered spirocycles, we can see that cyclopropane rings are much more common than their aziridine or epoxide analogues. Similarly, cyclobutanes far outnumber azetidines or oxetanes. Notably the number of oxetanes is surprisingly low, especially, when compared to azetidines. The position of the heteroatom has a significant influence on the frequency of a certain ring. This may generally correlate with ease of synthesis or lower complexity, i.e. 3,4′-spirotetrahydropyran oxindoles far outnumber the 3,2′- or 3,3′-analogues. 7-Membered rings are generally underrepresented when bridged examples are discounted (these will generally have been counted in the numbers for other ring sizes as these are a less significant contribution). There is only one example of a non-bridged monoheteroatom containing 8-membered spirooxindole in the literature (synthesised as an analogue of cipargamin).16

Although there will be a clear correlation between the number of publications for each ring size, we have tried to discuss each ring type on an equal basis, though inevitably the 5-membered nitrogen section is largest.

Three-membered rings

Spirocyclopropyl oxindoles

Three-membered ring containing spiroindolones feature in pharmaceutical compounds as well as being used as reactive intermediates, i.e. in ring opening reactions.17 These ring opening reactions can often be coupled with ring closing reactions to form spirocycles of larger ring size. There has recently been an excellent review on the catalytic enantioselective synthesis of polysubstituted spirocyclopropyl oxindoles by Cao and Zhou,18 as well as a review of transition metal-free strategies by Ashfeld.19

Applications. Spirocyclopropyl oxindoles are featured in a wide variety of reports showing their bioactivity (see Fig. 1 for examples). These bioactivities include examples of antitumour agents,20 pain treatment,21 treatment of CNS disorders,22 antivirals,23 among others.24

Direct methylene cyclopropanation. Direct cyclopropanation methodology with unprotected oxindoles has been a synthetic challenge which has seen many recent advances (Scheme 1). In 1987, a team at Lilly synthesised spirocycle 2 as a route to a phosphorodiesterase inhibitor (Scheme 1A).25 Since this low yielding and step-inefficient synthesis using strong base, Marini reported cyclopropanation using a vinyl selonene reagent in a domino Michael addition and cyclisation sequence (Scheme 1B).26 When aryl-substituted vinyl selonene reagents were used, high dr of the cyclopropane was observed with the aromatic rings in a cis-relationship. In 2017, Qian reported the use of a vinyl sulfonium salt in a zinc-mediated
cyclopropanation (Scheme 1C). This reaction was notable for its broad functional group tolerance and application to late-stage functionalisation of complex scaffolds. Following Qian’s report, Feng and Qu showed that a bromoethylsulfonium salt could be used in a similar process without the need for the Zn(OTf)₂ additive (Scheme 1D). Recently, Hajra reported a domino Corey–Chaykovsky reaction for obtaining the spirocyclic oxindole from the corresponding isatin, spiroepoxide or spiroaziridine (Scheme 1E). Initially using standard Corey–Chaykovsky reaction conditions and generating the sulfur ylide
from trimethyl sulfoxonium iodide, Hajra showed the ring opening of the epoxide followed by elimination to form the alkene and subsequent Corey–Chaykovsky reaction to the cyclopropane. In a similar manner, aziridines could be used as starting materials. Significantly the corresponding isatin could be used as starting material by increasing the equivalents of sulfoxonium iodide and sodium hydride. This works by generating the epoxide in situ followed by the optimised (ring opening/elimination) cyclopropanation reaction. All of these methods to access unprotected spirocyclic oxindoles also work with standard protecting groups in place.

**Cyclopropanation with diazo compounds.** A similarly active field is the direct cyclopropanation of 3-diazooxindoles. Diastereoselective cyclopropanations have been independently developed by Muthusamy, Subba Reddy and Padwa. The first enantioselective versions were developed at similar times by Arai (up to 74% ee using chiral Rh cat.31) Zhou (up to 99% ee using Hg(OTf)2 and a chiral phosphine ligand 4) and Zhou with Ding (up to 95% ee using a Au catalyst with chiral phosphine ligand 5) (Scheme 2). Since 2013, Qiu and Xu used chiral Rh cat. 6 to achieve up to 99% ee in the enantioselective cyclopropanation reaction with high ee for allyl alkene examples which performed poorly in previous reports. Zhou and Ma have used the Au/5 system developed previously by Zhou for the cyclopropanation with alkynes bearing a difluoromethyl group. Iwasa used chiral Ru(II) complex 7 to generate spirocyclopropyl oxindoles with high ee. Ashfeld reported a cyclopropanation/ring expansion cascade reaction between 3-diazooxindoles and vinyl isocyanate, in the case when the temperature was reduced from 50 °C to rt, the cyclopropane intermediate could be isolated as one diastereomer.

In 2014, Lu and Xiao showed a [3 + 2]-cycloaddition between 3-ylideneoxindoles and in situ generated 2,2,2-trifluorodiadiazene could afford a pyrazoline which upon heating under reflux in toluene would ring contract to afford 3,3′-cyclo-
propyl spirooxindoles. Using chemistry first developed by Carreira, sodium nitrite was used to oxidise 2,2,2-trifluoroethylamine·HCl to generate 2,2,2-trifluorodiazoethane which can undergo a [3 + 2]-cycloaddition with the electron deficient alkene followed by heating to liberate N2 and form the cyclopropane with high yield and dr (Scheme 3). Using a similar cycloaddition and ring contraction strategy, Babu demonstrated the synthesis of aryl substituted 3,3′-cyclopropyl spirooxindoles while Han and Chen have reported the synthesis of difluoromethyl substituted spirocyclic cyclopropanes. A significant advance in this methodology accesses enantioenriched spirocyclic cyclopropanes. A significant advance in this methodology accesses enantioenriched spirocyclic cyclopropanes (Scheme 3).

Cyclopropanation of 3-ylidene oxindoles. He developed a phosphorus mediated reductive cyclopropanation of 3-ylideneoxindoles (Scheme 4), in combination with α-ketoesters formed a Kukhtin–Ramirez adduct which behaves as a carbene surrogate and can undergo cyclopropanation via a reported Michael addition and intramolecular S_{2}1 reaction liberating triphenylphosphine oxide and the cyclopropyl spirooxindoles in high dr. Lu and Xu developed a related reaction mediated by dialkyl phosphite to couple isatins and α,β-unsaturated ketones. In 2017, Xu reported the formation of Kukhtin–Ramirez adducts from isatins and their reactions with dienes to form spirocyclopropanes (Scheme 4).

Du developed a Michael addition/alkylation cascade reaction between 3-chlorooxindoles and arylidenepyrazolones, alkenyl thiazolones (also developed by Sheng and Feng) or, more recently, 2,3-dioxopyrrolidines. In a quite distinct method, a Ni-catalysed enantioselective cyclopropanation developed by Feng utilised phenyliodonium ylides to generate a free carbene which can react with 3-ylideneoxindoles to generate 3,3′-cyclopropyl spirooxindoles in high yield, dr and ee (Scheme 5). More recently, Feng used a related system for the Mg catalysed reaction of 3-ylidene oxindoles and sulfonium ylides.

Other approaches. In 2013 Charette described an intramolecular C–H arylation of cyclopropanes to access 3,3′-spirocyclopropyl spirooxindoles (Scheme 6). Using Pd(OAc)_{2} with PCy_{3} as a ligand in combination with K_{2}CO_{3} and Ag_{3}PO_{4} in

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**Scheme 2** Advances in enantioselective cyclopropanation of 3-diazooxindoles.

**Scheme 3** 1,3-Dipolar cycloaddition followed by ring contraction to 3,3′-cyclopropyl spirooxindoles.

**Scheme 4** P(NMe_{2})_{3}-mediated reductive cyclopropanation via Kukhtin–Ramirez (K–R) adduct and K–R adduct reaction with diene activated by PPh_{3}.

**Scheme 5** Ni-Catalysed enantioselective cyclopropanation with phenyliodonium derived ylides.
toluene at 130 °C afforded high yields of the spirooxindole. When aryl substituted cyclopropanes were employed high dr was observed.

Wang reported an enantioselective Satoh–Miura type reaction using a RhIII catalyst to perform a dual C–H activation forming an axially chiral spirocycle in high enantioselectivity (Scheme 7).50

**Spiroaziridinyl oxindoles**

Spiroaziridines don’t commonly feature in natural products or medicines, but are utilised in synthesis, and protected versions could be envisaged to be of use in biology.

**From 3-bromo oxindoles.** Zhang and Peng employed 3-bromo oxindoles as nucleophiles in an enantioselective Mannich reaction catalysed by *cinchona* alkaloid derived cat. (Scheme 8).51 Cyclisation mediated by silver nitrate afforded the aziridine in high yield and with retention of the ee induced in the prior step.

**From 3-ylidene oxindoles.** Traditional, non-stereoselective approaches to aziridination employ ethyl nosyloxycarbamate and calcium oxide with 3-ylideneoxindoles.52 Xu and Wang, and Chen independently reported an aziridination of 3-ylideneoxindoles using hydroxycarbamate derivatives to afford a single diastereomer (Scheme 9).53

**Aziridination of isatin ketimines.** A team led by Marsini at Boehringer Ingelheim reported a diastereoselective aziridination of N-tert-butanesulfinyl ketimino esters at the end of 2015 (Scheme 10).54 At a similar time Hajra reported the same reaction with higher diastereoselectivity (up to >99 : 1 dr vs. 6.6 : 1 dr).55 Both reports use trimethylsulfoxonium iodide with either NaH or tBuOK and Hajra found that using DMF as solvent at lower temperature gave much higher diastereoselectivity. Hajra demonstrated one example of deprotection of the sulfinimide converting a protected aziridine with >99 : 1 dr to the free aziridine with 95% ee, which was subsequently shown to be unstable.55

Peng developed an asymmetric Mannich reaction of α-diazophosphonates as nucleophiles with isatin N-Boc ketimines catalysed by an asymmetric phosphoric acid (Scheme 11).56 The product diazo functionality could be reduced using tributylphosphine to afford the chiral hydrazone which could be cyclised to the enantiopure aziridine, with undefined stereochemistry at the hydrazine/phosphonate chiral centre.

**From azirines.** In 2016, Xu and Yuan reported an asymmetric Neber reaction catalysed by (DHQD)$_2$PHAL (Scheme 12).57 Good enantioselectivity was achieved in the Neber reaction to form the azirine. Sodium borohydride was used to reduce the azirine, although the ee and dr of the resulting aziridine was not reported.

**Spiroepoxy oxindoles**

**Applications.** There are two recent examples of spiroepoxides in medicinal chemistry for antibacterial activity as well as...
mediated by visible light.64 Bencivenni was able to form axially chiral enantioenrichment was maintained with a 5 : 1 dr.

The first report of an enantioselective epoxidation to form a spiro-epoxyoxindole was by Metzner and Briere in 2007, though only one example with 30% ee was given.66 In 2011, Gasperi developed a moderately stereoselective epoxidation of 3-ylideneoxindoles using tert-butyl hydroperoxide with a prolinol catalyst.67 More recently, Gasperi reported a full study of this work and disclosed a highly enantioselective epoxidation reaction of this type, when the oxindole protecting group was Boc, though the diastereoselectivity was poor.68 In 2014, Xiao reported the use of camphor-derived sulfonium salts in an asymmetric epoxidation of isatins (Scheme 13).69 Substitution on the oxindole did not significantly affect the high enantioselectivity, though changing the R group on the sulfonium salt did reduce the enantioselectivity slightly. Feng described an enantioselective Darzens reaction to synthesise spiro-epoxyoxindoles using L-12 as a hydrogen bonding ligand to induce enantioselectivity in an aldol reaction which is followed by cyclisation to afford the three-membered ring (Scheme 13).70 Lower enantioselectivities were observed when the aryl group of the acyl bromides or the fused oxindole ring were substituted (ee <85%).

Improved enantioselectivity was achieved by Wong in 2017 in an asymmetric Darzens reaction using diazoacetamides (Scheme 14).71 High yields and enantioselectivities (up to 99% ee) were observed using a titanium/BINOL complex and this reaction had a broad scope without reduction in enantioselectivity.

Other approaches. Recently, catalytic ring opening of spiroepoxides have been used to form enantioenriched products in a kinetic resolution. Sun, Hong and Wang used Bn-protected indole and napthols in an asymmetric phosphoric acid catalysed epoxide ring opening which resolved the racemic substrate to give one enantiomer in up to 99% ee.72 Zhou and Gao have developed a P(NMe2)3-mediated reductive epoxidation via a Kukhtin–Ramirez adduct similar to Scheme 4.73 High diastereoselectivity could be achieved in this coupling of isatins with aldehydes.

Four-membered rings

Spirocyclobutyl oxindoles

Applications. Spirocyclobutane oxindoles have shown biological activity against a wide variety of targets and disease areas, including phosphodiesterase inhibition74 (for treatment of Schizophrenia, Parkinson's or Huntington's), bromodomain inhibition,75 progesterone receptor antagonists76 and antivirals (see Fig. 1 for example structures).77

Natural product synthesis. Welwitindolinone A (Fig. 1) has inspired many approaches in total synthesis from the Baran78 and Wood laboratories.79

Advances in stereoselective spirocyclobutane oxindoles have been mainly limited to achievements in C-H activation chemistry and [2 + 2]-cycloadditions.

Metal-catalysed C-H activation/coupling. Inspired by Overman’s study of asymmetric Heck cyclisations to spirocyclic oxindoles,80 Sunoj and Kundig developed a Pd-catalysed enantioselective C-H arylation reaction to afford oxindole spirocycles of varying ring size (Scheme 15).81 The spirocyclic cyclobutane was formed in high yield, albeit with lower enantioselectivity than other ring sizes.

Baudoin formed 3-cyclobutyl N-methyl-oxindole through C-H activation when trying to develop an arylation/electrocyc-
lic cascade reaction.\(^{82,83}\) Xu could form the same unsubstituted cyclobutane, as well as 5- and 6-membered analogues, in an intramolecular 1,5-HAT using aryl iodides by visible light photoredox catalysis.\(^{84}\) Gouverneur recently developed a silyl radical-mediated hydrosulfamoylation using sulfonyl chlorides and could effect a cascade spirocyclisation (Giese-type addition followed by aryl C–H transfer) from cyclobutene 15, albeit with only poor diastereoselectivity (Scheme 16).\(^{85}\)

**[2 + 2]-Cycloaddition.** A significant advance in spirocyclobutyl oxindole synthesis was made by Wang and successively by Jørgensen in 2014/2015 in the field of organocatalytic [2 + 2]-cycloadditions of 3-ylideneoxindoles (Scheme 17). Wang reported a [2 + 2]-cycloaddition of 3-ylideneoxindoles and enals catalysed by \(\alpha,\beta\)-diphenyl prolinol cat. 16.\(^{86}\) Jørgensen further developed this type of reaction using a similar prolinol cat. 17 to mediate a cyclopropane ring opening to form a proposed dienamine which can undergo the [2 + 2]-cycloaddition.\(^{87}\)

Yan in 2016 and then Guan and He in 2017 have independently published a photocatalysed [2 + 2]-cycloaddition of 3-ylideneoxindoles to form a bispirexobutane cyclobutane as a single diastereomer (Scheme 18).\(^{88}\) Out of a possible 8 diastereomers, one diastereomer was formed in the cycloaddition reaction.

**Spiroazetidinyl oxindoles**

There are very few examples of spirocyclic azetidinyl oxindoles. Indeed, an analysis of all N-containing 4-membered 3,2\(^{\prime}\)-spirooxindole structures shows that all of them are beta-lactams or derivatives. Whereas for the corresponding 3,3\(^{\prime}\)-spirocycles only one out of 332 is a \(\beta\)-lactam or derivative thereof (yet these are typically symmetrical and easily installed via traditional methods and do not feature heavily in this section).

**Applications.** Spiroazetidinyl/spiro-\(\beta\)-lactam oxindoles have shown activity as antivirals,\(^{89}\) antibacterials,\(^{90}\) antifungals\(^{91}\) and insecticides (Fig. 1).\(^{92}\)

**Natural product synthesis.** In terms of total synthesis, Weinreb explored the synthesis of chartelline A via the spiro-\(\beta\)-lactam oxindole as a key intermediate (Fig. 4).\(^{93}\)

**‘Traditional’ non-stereoselective methods.** Notable examples of non-stereoselective \(\beta\)-lactam formation are [2 + 2] cycloadditions between diazo compounds and isatin derived ketimines or reaction of bromoacetyl bromide or chloracetyl chloride with isatin derived ketimines.\(^{94}\)

**Annulations using NHC catalysis.** There have been significant advances in the stereoselective synthesis of \(\beta\)-lactam containing spirooxindoles by organocatalysed annulation of ketimine derived isatins. In 2014, Ye reported an asymmetric Staudinger reaction of ketenes with isatin derived ketimines catalysed by NHC 18 (Scheme 19A).\(^{95}\) In 2017, Xu and Ren developed an NHC catalysed asymmetric Mannich reaction between aldehydes and isatin derived ketimines using cat. 19 in combination with oxidant 20 (Scheme 19B).\(^{96}\) Both of these reports demonstrated Boc deprotection of the \(\beta\)-lactam using either silica gel in toluene under reflux or trifluoroacetic acid in 1,2-dichloroethane, affording the unprotected \(\beta\)-lactam in 95% and 98% ee respectively. In 2019, Deng reported an isothiourea (HBTM, 21) catalysed asymmetric Mannich reaction between ketimines and carboxylic acids (Scheme 19C).\(^{97}\)

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**Scheme 15** Pd-Catalysed enantioselective C–H arylation.

**Scheme 16** Visible light mediated cascade spirocyclisation.

**Scheme 17** Advances in organocatalytic [2 + 2]-cycloaddition of 3-ylideneoxindoles with \(\alpha,\beta\)-unsaturated aldehydes, either directly or in situ generated.

**Scheme 18** [2 + 2]-Photocycloaddition of 3-ylideneoxindoles.

**Fig. 4** Structure of chartelline A.
Deng’s work does not use an NHC catalyst and uses a relatively more stable starting material while yielding the products in very high enantioselectivity.

**Annulations using Cu/guanidinium catalysis.** In 2014, Shamugam reported a copper-catalysed one-pot, three-component diastereoselective synthesis of 3-spiroazetidinimine-2-oxindoles as masked β-lactams (Scheme 20A). The spirocycle was built with high anti-diastereoselectivity. In 2018, Liu advanced this type of reaction in a highly diastereoselective and enantioselective variant using a chiral guanidinium ligand (Scheme 20B).

**Azetidines from allene activation.** The two main advances in the synthesis of spiroazetidine oxindoles (non-2-azetidinone structures) are from the Silvani lab in 2016 and 2017 involving allene activation. In 2016, Silvani reported a DABCO catalysed annulation of tert-butyl sulfinyl ketimines with allenes to form spiroazetidinyl oxindoles in high dr (Scheme 21). This could be followed by HCl mediated deprotection of the Ellman auxiliary and generating the spiroazetidine in 64% yield. In 2017, Silvani published a follow up study using cinchona derived organocatalyst 23 for the same reaction with a tBus protecting group instead of the Ellman auxiliary and generating the spiroazetidine in up to 83 : 17 er (Scheme 21).

**By nucleophilic addition.** Other recent advances involve nucleophilic addition to isatin or isatin derived ketimines. In 2016, Xu developed an asymmetric Reformatsky reaction of tert-butyl sulfinyl isatin ketimines and ethyl bromoacetate to afford a disubstituted isatin in high yield with high diastereoselectivity (Scheme 22). Zhang developed an asymmetric allylboration of isatin mediated by a chiral amino alcohol (Scheme 22). Both Xu and Zhang showed how this diastereoselectivity could be converted to highly enantioenriched products in 4/5 steps. Noda and Shibasaki developed an asymmetric Mannich reaction mediated by a cinchona alkaloid dimer (Scheme 22). The enantioenriched product could be converted to a spirocyclic β-lactam in 2 steps involving Zn mediated N–O bond cleavage followed by lactamisation mediated by HCTU.
Spirooxetanyl oxindoles

**Applications.** Spirooxetanes have featured in only two recent reports for bioactivity in a Merck patent for kinase inhibitors, as well as in an SAR study (see below, ref. 109).

**Non-stereoselective methods.** As developments in stereoselective formation of spirooxetanes have been limited since 2012 (with the lowest number of hits out of any of the structures considered in this review), it is worthwhile mentioning papers that form spirooxetanes without stereoselectivity. Zhang formed spirocyclobutanes from a cascade spirooxetane/cyclopropane ring opening reaction using BF$_3$·Et$_2$O. The oxetane starting materials were synthesised in a [2 + 2]-cycloaddition from the isatin and a tetrasubstituted alkene such as 1,1′-[bi(cyclopropylidene)]. In 2019, Marini reported a domino reaction of 3-hydroxyindoles and phenyl vinyl sele none. Using KOH in aqueous conditions Marini showed that protected or unprotected isatins could be used to produce a variety of 3,2′-spirooxetanes in 34–73% yield. Lindsley synthesised 3,3′-spirooxetane 24 from the corresponding isatin in 3 steps in an SAR study to find a sub micromolar and selective M$_5$ (muscarinic acetylcholine receptor 5) positive allosteric modulator for the treatment of a variety of neurological diseases. Final treatment of the diol with triflic anhydride afforded the oxetane in only 6% yield (Scheme 23).

**Lewis acid catalysed cycloaddition.** In 2014, Feng reported the reaction of isatins with ketenes catalysed by an N,N′-dioxide ligand and Sc Lewis acid to form spirooxetanones. In terms of optimisation, Feng reported that a N-Bn protecting group gave a significant improvement in ee compared to Me and molecular sieves increased the yield. The reaction was tolerant of a range of electronics on both aromatic rings giving high yield, dr and ee (Scheme 24).

Five-membered rings

**Spirocyclopentyl oxindoles**

**Applications.** Spirocyclopentyl oxindoles feature in many natural products and active pharmaceuticals (see Fig. 1 and 5). For example, neosurugatoxin is a specific antagonist of nicotinic acetylcholine receptors. This core scaffold has also been developed for treatment of migraine, which is discussed in the relevant section (ref. 139), as well as bromodomain inhibitors.

**Natural product synthesis.** Spirocyclopentane oxindoles have been the focus of many total synthesis studies, with several of these appearing since 2013. Martin reported the total synthesis of (−)-citrinadin A, forming the spirocyclopentane oxindole in an epoxidation/semi-pinacol rearrangement cascade using Davis’ oxaziridine reagent (Scheme 25). Selective epoxidation of the indole C$_2$–C$_3$ followed by stereoselective collapse of the epoxide results in spirocyclopentane formation. Sarpong, Simpkins, Sun and Li have reported total syntheses of numerous natural products using a similar spirocyclisation strategy employing various epoxidising reagents. A recent study of the biosynthetic spirocyclisation of the paraherquimides (related natural products) by Sherman and coworkers showed that this semi-pinacol rearrangement was the biosynthetic pathway to these spirooxindoles. Wood synthesised (+)-Citrinadin B forming the spirocyclopentane in a Pd-catalysed enyne cyclisation, initially developed by Trost. Trost has developed an asymmetric [3 + 2] Pd-trimethylenemethane (TMM) cycloaddition to form the spirocyclopentane core of Marefortine B and C (Scheme 23). Lewis developed an efficient complexity generating spirocyclisation heating phenylenediamine and 26 to form the spirocyclopentane, by ring opening of the ester and ortho-alkylation by a Friedel–Crafts reaction, in 64% yield and 3.7:1 dr as a precursor to surugatoxin aglycone (Scheme 25, for structure of natural

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Review

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**Fig. 5** Selected cyclopentene spiroindolones in nature.

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Scheme 23 3-Step sequence to oxetane 24 in a SAR study towards a selective M$_5$ positive allosteric modulator.

Scheme 24 Enantioselective [2 + 2]-cycloaddition to form spirooxetanones.
Zhang and Jia recently described the total synthesis of similisines A and B (Fig. 5), enantiomeric trisindole structures containing a spirocyclopentane oxindole core, through a key acid-mediated Friedel–Crafts cyclisation, though this was low yielding and non-stereoselective. A significant route for construction of cyclopentane spirooxindoles has been through [3 + 2] cycloaddition utilising Morita–Baylis–Hillman (MBH) carbonates, either to react with or situated on the isatin core. Recent highlights include Chen’s demonstration of a [3 + 2] cycloaddition between isatin derived MBH carbonates and 3-ylidene oxindoles to form bispirooxindole products in high diastereo- and enantiocontrol (Scheme 26A). In 2019, Chen described the [3 + 2] cycloaddition of isatin-derived MBH carbonates with β,γ-unsaturated α-keto esters using asymmetric nucleophilic catalyst derived from quinidine (Scheme 26B).

Further advances in this field have been made using asymmetric phosphorus catalysis to activate allenes, MBH carbonates or alkynones to form spirooxindoles. In Lu and Mei’s 2019 report threonine derived cat. 28 was found to give the highest yield and enantioselectivity in Et₂O for the [3 + 2] annulation of isoindigos and allenes (Scheme 27). Lu and Mei additionally showed unsymmetrical isoindigos in this process with high regiocontrol, as well as the formal syntheses of a number of complex natural products. Lu, with Ullah, then reported the annulation of pyrazolonyldiene oxindoles with MBH carbonates using asymmetric phosphorus catalyst, SITCP (Scheme 27).

Domino Michael addition/aldol (or alternative cyclisation)

In 2011, Barbas III designed a bifunctional thiourea catalyst for the domino Michael addition/aldol reaction to form bispirooxindoles from 3-substituted oxindoles and 3-methylene oxindoles (Scheme 28). Since, this Michael addition/cyclisation strategy based upon hydrogen bonding catalysis has been employed to access spirocyclopentane oxindoles on a large number of occasions. Notable examples include Kanger’s use of 3-ylidene oxindoles undergoing asymmetric thiourea catalysed Michael addition alpha to the nitro group of a γ-nitroketo and spontaneous stereoselective aldol formation (determined by stereochemistry of the first step) to give the five-membered ring (for a related reaction see Scheme 75). Johnston and Cordova used a prolinol aminocatalyst to promote a Michael addition between an alkyne substituted oxindole and an α,β-unsaturated aldehyde followed by cyclisation.

Scheme 25 Selected examples of spirocyclisation to cyclopentanes in total synthesis.

Scheme 26 Selected isatin derived MBH carbonates in a cycloaddition with 3-methylenoxindoles and β,γ-unsaturated α-keto esters.

Scheme 27 Lu and coworkers’ achievements in asymmetric phosphine catalysed activation of electrophiles to form spirocyclopentene scaffolds.

Scheme 28 Barbas III’s seminal work on an enantioselective domino Michael/aldol cyclisation.
to form an enantioenriched spirocyclopentane with moderate dr.\textsuperscript{132} Shi has utilised asymmetric phosphoric acid catalysts to employ various vinyl indoles to react with 3-ylidene oxindoles, formed \textit{in situ} from 3-indolylmethanol, in a Michael/alkylation cascade.\textsuperscript{133}

**NHC catalysis.** In 2017, Wang reported a Michael addition/intramolecular aldol/lactonization cascade of enals with 3-methylene oxindoles using an azolium NHC catalyst.\textsuperscript{134,135} Up to 99% ee and >99 : 1 dr was achieved using cat. \textsuperscript{31} and DIPEA for the spirooxindole products (Scheme 29A). Subsequently, Enders published a related study where fused β-lactam spirooxindoles could be formed (Scheme 29B).\textsuperscript{136} Enders also showed that using a different NHC catalyst (cat. \textsuperscript{33}), base and solvent, a different spirocyclopentane scaffold could be formed in good yield and high dr and er (Scheme 29C). This switchable reactivity occurs from the same intermediate formed by Michael addition. This intermediate can then undergo either (B) intramolecular Mannich reaction then lactamisation or (C) aza-Dieckmann type cyclisation and tautomerisation.

**Phase transfer catalysis.** Zhao and Shang reported a tandem Michael/Michael addition sequence catalysed by an asymmetric phase transfer catalyst.\textsuperscript{137} Employing phosphonium phase transfer catalyst \textsuperscript{34}, deprotonation of the malonate initiates Michael addition to the 3-ylidene oxindole followed by subsequent Michael addition to the α,β-unsaturated ester (Scheme 30). Significant reduction in enantioselectivity was observed when attempting to form the six-membered analogue. Zhao and Zou also reported an ammonium phase transfer catalysed asymmetric vinylation of 3-phenyloxindoles which were shown to undergo Pd-catalysed Heck cyclisation and oxidative cleavage to give a spirocyclopentane oxindole with retention of ee.\textsuperscript{138}

Spirocyclopentanyloxindoles feature in a number of lead Calcitonin Gene-Related Peptide (CGRP) medicines developed by Merck, and more recently Sosei Heptares, for treatment of migraine (Fig. 6).\textsuperscript{139}

Towards an efficient asymmetric synthesis of the spirocyclopentane core of these compounds Merck developed an enantioselective phase transfer catalysed spirocyclisation.\textsuperscript{140} Using a doubly quaternised \textit{cinchona} alkaloid derived phase transfer catalyst \textsuperscript{35} up to 96% ee was achieved for the transformation of substrates such as \textsuperscript{36} to \textsuperscript{37} in quantitative yield which could conceivably be elaborated via the halogenated pyridine (Scheme 31). Merck subsequently collaborated with Houk to model how the novel phase transfer catalysts promote the reaction and induce enantioselectivity (Scheme 31).\textsuperscript{141}

**Fig. 6** Selected developments in structures of CGRP inhibitors.

**Scheme 29** Work by Zhang and Enders using NHC catalysis to synthesise diverse spirocyclopentanyloxindoles.

**Scheme 30** Phase transfer catalysed enantioselective double Michael addition chemistry to spirocyclopentanes.

**Scheme 31** Merck’s development of a phase transfer catalysed spirocyclisation and model for the enantiocselectivity developed in collaboration with Houk.
They proposed three key electrostatic interactions: (1) hydrogen bonding between the hydroxyl of the catalyst and the oxindole enolate; (2) a chloride–CH interaction activating the leaving group; (3) a π–π interaction between the pyridine of the formed cyclopentane and the quinclidine benzyl group. Merck also recently published on the monitoring of the reaction kinetics of these inherently complex, dual-phased reaction mixtures in an automated fashion. These studies remain a significant advance in asymmetric phase transfer catalysis, as well as in the synthesis of enantioenriched spirooxindoles.

Metal/Lewis acid mediated approaches. Feng used a Mg/N, N'-dioxide catalyst system in a Michael/Friedel–Crafts/Mannich cascade of isocyanides to generate enantioenriched polycyclic spirocyclopentanes resembling strychnos alkaloids.143 Franz recently used an Sc/pybox system for the [3 + 2]-cycloaddition of allenes with 3-ylidene oxindoles.144 In a distinct strategy, Su and Yang developed a Pd-catalysed [3 + 2] annulation of spirovinylcyclopropyl oxindoles with α,β-unsaturated nitroalkenes (Scheme 32).145 Using Pd(OAc)2 and Xantphos in toluene the spirovinylcyclopropyl ring opened to form an amphoteric π-allyl species which undergoes the [3 + 2] annulation in a diastereoselective manner, invoking a π-stacking between the aromatic ring of the oxindole and the aromatic substituent of the nitroalkene. Rios had previously developed a similar strategy showing one example with 76% ee using a prolinol catalyst with α,β-unsaturated aldehydes.146

C–H activation/cross-coupling. Cross-coupling methodologies have been extensively utilised to access spirocyclopentane oxindoles.147 Related to Trost’s development of Pd-catalysed cyclisations towards the Marcfortines (see Scheme 25), Córdova has developed an iminium catalysed asymmetric Michael addition/Pd-catalysed intramolecular allylic alkylation.148 Trost has continued to innovate in this field, developing new Pd-catalysed [3 + 2]-cycloadditions from allene and CF3-containing trimethylenemethane precursors with application to enantioenriched spirocyclopentane oxindoles.149

Taylor et al. reported a Cu(n)-mediated double C–H/Ar–H coupling of bis-anilides to form bispirooxindoles (Scheme 33).150 This strategy was notable for the trans-diastereoselectivity observed and the flexibility in increasing the size of the central ring. Larhed and co-workers, in collaboration with AstraZeneca, have built on their previous work on the Heck–Mizoroki reaction to generate functionalised cyclopentanes,151 to develop an intramolecular variant. Exploiting the selectivity of the Heck–Mizoroki reaction to afford spirocyclopentanes with high diastereocntrol (Scheme 33).152

García-López and others have reported C–H activation and carbene insertion procedures to afford spirocyclopentanes.153 Related to these C–H activation approaches is the stereoselective oxidation of spirocyclopentane oxindole C–H bonds using Ru or Mn catalysis.154 Initially developed by Bach in 2014, selective oxidation of one of the enantiopure carbons of the cyclopentane gave cyclopentanones in high er.

Other approaches. Taylor and Unsworth have a program of work on the synthesis of diverse spirocycles. In 2016, they described the controlled synthesis of two diastereomers of a spirocyclopentany1 oxindole from the same intermediate.155 Treatment of a ketodiazo with Rh2(oct)4 in the presence of air afforded the diketone which under either acidic or basic conditions provided the opposite diastereomers of the spirocyclopentanol (Scheme 34). Spiropyrrolidine oxindoles

Applications. Spiropyrrrolidine oxindoles are applied widely in medicinal chemistry. Indeed, many of the natural products featuring a 3,3'- or 3,2'-spiropyrrrolidinyl motif display a wide variety of bioactivities.156 One of the most significant pharmaceuticals is MI-888 (Fig. 7), a 3,3'-spiropyrrrolidine containing MDM2 inhibitor against tumour growth.157 The success of this ligand has inspired many other derivatives,158 including proteolysis targeting chimeras (PROTACs)159 and a molecular glue.160 Other applications of spiropyrrrolidines include anti-
cancer,\textsuperscript{161} treatment for Alzheimer’s,\textsuperscript{162} diabetes,\textsuperscript{163} HIV\textsuperscript{164} and tuberculosis.\textsuperscript{165}

**Natural product synthesis.** Spiropyrrrolidinyl oxindoles, particularly spiro-3,3\textsuperscript{3'-pyrrolidinyl oxindoles, have been the target and inspiration for many total syntheses.\textsuperscript{166} Horsifilene and coerulescine (Fig. 7) are undoubtedly the simplest spiropyrrrolidinyl oxindoles in nature and have been the focus of short, elegant total syntheses.\textsuperscript{167} For more complex products, a general approach is to synthesise the corresponding annulated \(\beta\)-carboline, typically synthesised via a Pictet–Spengler reaction and perform an oxidative rearrangement with \(\text{BuOCl}\). This reduces the problem down to the construction of the \(\beta\)-carboline (typically from tryptophan) and these products have received significant synthetic attention.\textsuperscript{168} This was the strategy used by Cook in his total syntheses of (iso)\textsuperscript{169} alstonisine oxindole and (iso)\textsuperscript{169} gardmultimine A (for structures see Fig. 7 and Scheme 35).\textsuperscript{172} Rhynchophylline and isorhynchophylline have been synthesised formally by Amat and more recently totally by Ip and Tong (Scheme 40).\textsuperscript{173}

\[ [3 + 2]-\text{Cycloaddition} \]

**Dipolar cycloaddition.** For the synthesis of spiropyrrrolidinyl oxindoles, particularly towards 3,3\textsuperscript{3'-pyrrolidinyl oxindoles, there is a plethora of reports of the use of \([3 + 2]\)-cycloaddition chemistry. To orientate the advances made in the recent decade it is important to include here Gong’s seminal study from 2009. Gong reported the first one-pot catalytic enantioselective \([3 + 2]\)-cycloaddition of 3-ylidene oxindoles with \textit{in situ} generated azomethine ylides (Scheme 36).\textsuperscript{174,175} Gong used asymmetric phosphoric acid cat. \textsuperscript{38} to afford spiropyrrrolidinyl oxindoles in high yield, dr and ee.

\[ \text{Scheme 36} \quad \text{Seminal report of catalytic enantioselective [3 + 2]-cycloaddition via azomethine ylides.} \]

The utility of this approach by Gong has been demonstrated by the multitude of reports in this area since. These advances include the combination of an isatin derived dipole reacting with an external alkene dipolarophile,\textsuperscript{176} or other dipolarophiles\textsuperscript{177} such as alkyynes\textsuperscript{178} or allenes.\textsuperscript{179} Often these dipoles are derived from aminoxindoles\textsuperscript{180} or they could be malonitrile dipolarophiles,\textsuperscript{181} azomethine imines\textsuperscript{182} or pyridinium ylides.\textsuperscript{183} There are also many applications of this methodology for the synthesis of bispirooxindoles.\textsuperscript{184} Advances have also been made with related systems using copper catalysis.\textsuperscript{185} This azomethine ylide cycloaddition has been used by Hoffman-La Roche to synthesise MDM2 antagonist MI-888 (Fig. 7, ref. 157), including >100 g scale synthesis of the final enantiopure product by chiral resolution.\textsuperscript{186}

For the construction of 3,2\textsuperscript{3'-pyrrolidinyl oxindoles, isatin derived ketimines can be used.\textsuperscript{187} N-2,2,2-Trifluoroethylisatin ketimines are very popular as a starting material because of the resultant inclusion of a CF\textsubscript{3} group in the final product. In 2015, Yan, K. Wang and R. Wang demonstrated the first enantioselective \([3 + 2]\)-cycloaddition of N-2,2,2-trifluoroethylisatin ketimines using prolinol cat. \textsuperscript{17} (Scheme 37A).\textsuperscript{188} The same authors subsequently reported a similar cycloaddition catalysed by a \textit{cinchona} alkaloid derived squaramide catalyst (Scheme 37B).\textsuperscript{189} These reports were followed by many diastereoselective\textsuperscript{190} and enantioselective\textsuperscript{191} cycloadditions using N-2,2,2-trifluoroethylisatin ketimines as 1,3-dipole starting materials.

Zhao and Shang developed an asymmetric phase transfer catalysed \([3 + 2]\)-cycloaddition using a thiourea containing ammonium salt \textsuperscript{40} with K\textsubscript{2}CO\textsubscript{3} as base to form polysubstituted 3,3\textsuperscript{3'-pyrrolidinyl oxindoles in up to 99% ee (Scheme 38).\textsuperscript{192}
Finally, Kürti demonstrated the utility of [3 + 2]-cycloaddition chemistry. Kürti demonstrated the total synthesis of natural isatindigoindoline C in short sequence from isatin through a diastereoselective [3 + 2]-cycloaddition followed by base mediated epimerisation (Scheme 39). The natural stereochemistry of isatindigoindoline C was thus confirmed as anti by comparison of the $^1$H NMR spectra.

**Ring expansion.** A particularly important development in the synthesis of 3,3′-spiropyrrolidinyl oxindoles was reported by Carreira in 1999. Spirocyclopropyl oxindoles could be reacted with imines in a [3 + 2]-cycloaddition affording spiro-pyrrolidinyl oxindoles in good dr (up to 98 : 2) (Scheme 40). Carreira and others have used this ring expansion/cycloaddition strategy on multiple occasions to affect racemic and stereoselective syntheses of natural products, as well as being adapted. Recently, Ip and Tong employed Carreira’s method as the key step in the first enantioselective total synthesis of Rhynchophylline and Isoyrynhchophylline using a cyclic imine (Scheme 40).

Budynina has performed a similar ring expansion in a sequential azide anion ring opening followed by a Staudinger/Wittig/Mannich reaction. Whereas Hajra has ring expanded 3-spiroaziridinyl oxindoles using malonitrile (Scheme 41). This type of ring expansion chemistry has also been carried out in an inverse fashion, i.e. Lu reacted a 3-ylidine oxindole with a vinyl aziridine (Scheme 41). In a related aziridine ring expansion, Hajra used Cu(OTf)$_2$ as catalyst to ring expand an aziridine reacting with a 3-substituted isatin to form a 3,2′-spiropyrrolidine.

Budynina ring expanded a cyclopropane with an isatin derived ketimine (Scheme 42). Chu, He and Liu have recently reported an enantioselective cycloaddition of vinyl cyclopropanes with isatin derived imines using ligand, to form 3,2′-spiropyrrolidinyl oxindoles (Scheme 42).

**MBH carbonates.** As seen throughout this review, the use of isatin derived MBH carbonates is significant to form a 1,3-dipole as a three carbon synthon. In 2017, Chen demonstrated the use of isatin derived MBH carbonates in a [3 + 2]-cycloaddition with isatin derived ketimines catalysed by bifunctional DMAP/prolinol catalyst in high yield and enantiorectivity (Scheme 43). In 2018, Han and Cui

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**Scheme 38** Asymmetric phase-transfer catalysed [3 + 2]-cycloaddition.

**Scheme 39** Short synthesis of isatindigoindoline C using a key [3 + 2]-cycloaddition of an isatin-derived azomethine ylide and a 3-ylidine oxindole.

**Scheme 40** Carreira’s seminal ring expansion strategy and Ip and Tong’s application of this methodology in total synthesis.

**Scheme 41** 3,3′-Spiropyrrrolidine oxindoles synthesised by aziridine ring expansion.

**Scheme 42** Selected examples of 3,2′-spiropyrrrolidine synthesis by cyclopropane ring expansion.
reported the diastereoselective [3 + 2]-cycloaddition of isatin derived MBH carbonates and electron-rich alkylamines (Scheme 43).206

**NHC catalysis.** In 2015, Lu and Du reported an NHC catalysed [3 + 2] annulation of 2-bromoenals with 3-aminooxindoles (Scheme 44A).207 Using NHC cat. 44 Lu and Du achieved high enantioselectivity of the spiropyrrolidinone product. This report was followed by a similar reaction using NHC cat. 19 by Sun and Ye (Scheme 44B).208 Also, Hui and co-workers reported the [3 + 2] annulation of 3-bromoenals and isatin N-Boc ketimines (Scheme 44).209 Using azolium cat. 45 with DABCO in toluene afforded the spiropyrrolidines in good yield, high enantioselectivity and good scope. More recently, Enders reported an NHC catalysed Mannich reaction between isatin derived ketimines and \(\alpha,\beta\)-unsaturated aldehydes.210 When the ketimine was protected with an ortho-phenol, which can bind the acyl-azolium intermediate allowing cyclisation, overall an enantioselective [3 + 2] cycloaddition was achieved.

**Domino conjugate addition/cyclisation**

Conjugate addition/cyclisation is a common tactic employed to access spiropyrrolidinyl oxindole scaffolds stereoselectively, and highlights the continuum between concerted [3 + 2]-annulation chemistry and stepwise sequences. Stepwise but simultaneous addition/cyclisation sequences will be dealt with first followed by discrete additions and sequential asynchronous cyclisations. Domino Michael addition/cyclisation reactions have been separated according to the isatin reactants: (A) 3-isothiocyanato oxindoles or (B) oxindoles with a nucleophilic C3 substituent reacting with olefins and (C) 3-yldene oxindoles.

**A 3-Isothiocyanato oxindoles.** The use of 3-isothiocyanato oxindoles to synthesise 3,2′-spiropyrrolidine structures in cascade Michael/cyclisation reactions has been extensively studied by the groups of Wang and Yuan, among others (Fig. 8).211 In 2013, Wang demonstrated the reaction of 3-isothiocyanato oxindoles with electron deficient olefins catalysed by cat. 44.211 Wang also showed cat. 45 could promote the reaction between the same oxindoles and with unsaturated pyrazolones.211 At a similar time, Yuan showed that quinine derived thiocarbamate cat. 46 could promote the reaction of 3-isothiocyanato oxindole with alkylidine azlactones, and quinine could promote the same reaction with 3-methyl-4-nitro-5-alkenyl isoxazoles.214 This spate of reports in 2013 was followed by the application of a similar strategy with other electron deficient olefins including notable further work by Yuan (Fig. 8).213 There has also been significant advances in using this chemistry for the synthesis of bispirooxindoles.216 Lindel has recently used this approach to construct the 3,2′-spiropyrrolidone core of cyanogramide.217

**B Nucleophilic C3 substituent.** The second significant strategy to access 3,2′-spiropyrrolidines is through domino Michael addition/cyclisation by a nucleophilic C3 substituent on the oxindole reacting with an olefin. In 2014, Yuan reported the reaction of acyl-protected 3-aminooxindoles with olefinic azlactones in good yield and diastereoselectivity using DBU as catalyst (Scheme 45).218 Yuan also showed a preliminary asymmetric variant of this reaction using cat. 56 to obtain the product in 61% ee. Xu and Yuan then further developed this chemistry with \(\alpha,\beta\)-unsaturated acyl phosphonates as coupling partners, achieving high yield and enantioselectivity with cat. 57 (Scheme 45).219,220 With \(\alpha,\beta\)-unsaturated aldehydes Wang used prolinol catalyst 17 to promote high enantioselectivity in the spirolactam product, albeit with moderate yields and diastereoselectivity (Scheme 45).221 Recently, Hua and Wang employed 3-aminooxindoles in a Michael/keto-imine/Friedel-Crafts cascade to form bispirooxindoles in high dr and ee.222 Related to these methods is the use of an electrophilic substituent instead of nucleophilic substituent at C3 of the oxindole *i.e.* Cl or Br. An example of this was Liu and Chen’s use of 3-bromooxindoles in an enantioselective [4 + 1] annulation with azadienes using a *cinchona* alkaloid derived catalyst.223 As this strategy relies on the nucleophilic displacement by or with a component on the oxindole starting material it ultimately results in 3,2′-spiropyrrrolidinyl products.

**C 3-Yldene oxindoles.** A third significant method of accessing spiropyrrolidinyls in a cascade Michael addition/cyclisation process is using 3-methylene oxindoles as starting materials.224 In 2016, Zhang described an enantioselective Michael addition catalysed by a thiourea-*cinchona* alkaloid derived catalyst followed by one-pot Mannich/lactamisation to afford 3,3′-spiro(β)-lactam oxindoles in high yield, ee and dr.225 Wang developed an iodine promoted Michael addition of 3-methylene oxindoles with enamo esters and concomitant DABCO mediated cyclisation to form 3,2′-spiropyrrrolinyl...
oxindoles with good diastereoselectivity under ball-milling conditions. Combining strategies B and C, Xiang and Yang showed that the reaction of 3-aminooxindoles with 3-methylene oxindoles under basic conditions yielded a spiro lactam which upon treatment with TsOH in one-pot cyclised to spiro lactam 58 in high dr (Scheme 46). The C3 position of the aminooxindole was sufficiently nucleophilic under these conditions to undergo conjugate addition alpha to the ester, whereupon the free amine ring opens the oxindole. Du combined the use of acyl protected 3-aminooxindoles and 3-methylene oxindoles to form bispirooxindoles and Enders showed a Mannich/deprotection/aza-Michael cascade between isatin derived ketimines and 3-substituted oxindoles to bispirooxindoles.

A remarkable extension of strategies A and C with dipolar cycloaddition has been developed by Du where compounds containing a spiropyrrolidine oxindole and bispirooxindole were formed by a dual Michael/Mannich and Michael/cyclisation sequence (Scheme 47). Using dimeric squaramide cat. 59 the reaction between N-2,2,2-trifluoroethylisatin ketimine 60 and 3-methyleneoxindole 61 could be promoted, followed by the reaction between 3-isothiocyanato oxindole 62 and the pendant α,β-unsaturated amide on 61. The bispirooxindole-spirooxindole compounds with seven stereocentres were afforded in high yield, dr and ee, including on gram scale.

**Scheme 46** Selected example of the combination of strategy B and C, using a nucleophilic C3 oxindole substituent and 3-ylidene oxindole.

**Scheme 45** Selected examples of conjugate Michael addition/cyclisation of oxindoles with a nucleophilic C3 substituent. * Unspecified stereochemistry/unknown absolute stereochemistry.
Before this, Sasai had developed the same reaction using a chiral phosphine catalyst but with maximum 84% ee. More recently, Wu and Zhang used a chiral bisphosphine catalyst for the same reaction. A clear demonstration of the utility of these methods was given by Xie who showed the total synthesis of some strychnos alkaloids (Scheme 48). A related reaction has been developed by Miesch involving a copper catalysed hydroamination process. In a related strategy, Peng and Shao reported an asymmetric propargylation followed by iodocyclisation to construct polycyclic spirooxindoles in one-pot or as a discrete asymmetric coupling step followed by cyclisation.

Discrete coupling strategies

In this section strategies where a discrete coupling followed by cyclisation will be discussed. A common strategy towards spiropyrolidine oxindoles is an asymmetric Mannich reaction using ketimines followed by cyclisation. In 2012, Lu and then Li and Wang reported significant advances in enantioselective Michael addition and allylic alkylation of nitroalkanes using *cinchona* alkaloid derived catalysts. Reductive cyclisation of the nitro group in the product then afforded spirocycles in high ee. In 2015, Kobayashi developed a calcium/Pybox asymmetric Mannich reaction, which could be cyclised upon deprotection and basic cyclisation (Scheme 49). Using CaI₂ with Pybox ligand 65 in CH₂Cl₂ at −78 °C afforded the Mannich product in high dr (trans product favoured) and excellent enantioselectivity. From acetal product 66, treatment with HCl followed by NET₃ afforded 3,3′-spiropyrolinyl oxindole 67 in 65% yield and 92% ee.

In 2016, Ooi used triazolium phase transfer catalyst 68 to effect the C–H amination of a hydroxylamine derivative in high ee for 5- and 6-membered saturated nitrogen heterocycles (Scheme 50). More recently, Du and Chen developed an asymmetric allylic alkylation from 3-phenyloxindoles using phase transfer catalyst 69 and Pd(OAc)₂ with Na₂CO₃ as base (Scheme 50). This remarkable reaction afforded good yields of the 3,2′-spiropyrolidine oxindole products in high ee. The products could be readily derivatised to numerous spirocycles including spirocyclohexanes, piperidines and pyrrolidines. Luo and Zhu developed a Heck/carbonylative cyclisation sequence to 3,3′-spiropyrolidone oxindoles from non-isatin...
derived starting materials (Scheme 50). They employed chiral bidentate phosphate ligand L70 with Pd3(dba)3, K2CO3 and PivOH in toluene and a CO atmosphere to affect the Heck/carbonylation cascade. Notably, the methodology was limited to aryl protected lactams but high yields and enantioselectivities were observed when using the readily removable PMB group. The authors showed the application of this methodology to the synthesis of a CRTH2 receptor antagonist (Scheme 50) in 6 steps in 35% overall yield and 98% ee (Scheme 50).

In a clearly distinct strategy Zhao and Xia developed a cross-dehydrogenative coupling of pyridines with 3-substituted oxindoles. The pyridinium salts afforded could be reduced diastereoselectively with NaBH4 in order to access racemic cornoxine in a rapid fashion (Scheme 51). Although the pyridine scope was limited to electron withdrawing groups at C3, the reaction notably worked on unprotected oxindoles.

Addition to isatin derived ketimines is a common route to spiropyrrolidines. Liu reported a one-pot Mannich/hydroamination approach using isatin ketimines. Zhou used a triple catalysis cascade reaction to generate an isatin derived ketimine in situ which could then undergo Brønsted base catalysed 6π-electrocyclisation. 

Hajra developed an enantioselective tandem aza-Henry reaction-cyclisation of nitroalkane mesylates to 3,2-spiropyrrolidinyl oxindoles (Scheme 52). These conditions were also applicable to piperidine derivatives with a chain extended nitro mesylate substrate. Xu reported a Rh-catalysed arylation of these ketimines, when using o-tolylboroxine, treatment of the product with NBS and Boc deprotection allowed cyclisation to product (Scheme 52). More recently, Zhu and Zhang reported an enantioselective para-C–H functionalisation of N-monosubstituted anilines with isatin derived ketimines using cat. 73. The enantioenriched 3-aminooxindoles were readily cyclised to spiropyrrolidines in good yield and high ee (Scheme 52).

Other approaches. Van der Eycken has described a post-Ugi reaction Pd-catalysed Buchwald–Hartwig/Michael reaction sequence to very quickly couple four components into 3,2′-spiropyrrolidinyl oxindoles. Taylor and Unsworth at York used their previously disclosed direct imine acylation methodology to furnish indoleninyl halide which upon hydrolysis with aqueous HCl formed 3,3′-spiropyrrolidone oxindole in high yield and dr (Scheme 53). Further recent advances towards 3,2′-spiropyrrolidinyl oxindoles have been made using diazo compounds as starting materials. In 2016, Moody at Nottingham University developed a diastereoselective NH insertion of diazooxindole with o-aminoketones to afford spiropyrrolidine 77 (Scheme 53). Very recently, Anbarasan reported Pd-catalysed amination of 3-diazoindoles with ortho-vinyl anilines.

Photoredox. Zhao and Jiang have reported a photoredox asymmetric phosphoric acid catalysed combination of α-amino radicals and 3-aryl oxindole radicals (Scheme 54). The excited photoredox catalyst (dicyano-pyrazine (DPZ) derived) effects the decarboxylation of the aryl protected amino acid, generating an α-amino radical, which can combine with the 3-aryl oxindole radical generated from 3-chlorooxindole with chirality induced by cat. The intermediate then spontaneously cyclised in the case of the five-membered ring.
Spirotetrahydrofuranyl oxindoles

Applications. There are numerous bioactive spiroTHF oxindoles (Fig. 9). Of note is XEN402 (Funapide), developed by xenon and licensed by Teva (TV-45070) for treatment of pain (synthesis discussed below). Other applications of spiroTHFs include anti-tumour as well as antibacterial activity. Spring reported an example in a diversity-oriented synthesis of a library of drug-like macrocycles.

Natural product synthesis. Garg demonstrated the importance of spirotetrahydrofuran oxindoles in the stereocontrolled total synthesis of N-methylwelwitindolinone D isonitrile. Late-stage installation of the key spiroTHF ring proved troublesome and an attempt to cyclise 79 (X = Br) under aerobic conditions afforded a spirocyclobutyl oxindole in high yield (Scheme 55). However, Garg and co-workers were able to develop two oxidative functionalisations of the oxindole C3 to afford the spirobutyrolactone 80 which was 5 steps from the natural product. The total synthesis of (±)-aspergilline A in 16 steps was developed by Wood and co-workers. More recently Jia reported a ten-step total synthesis of the related natural product Speradine C with a key oxidative spirocyclisation to form the spiroTHF ring at a late stage. Treatment of 81 with NCS formed a chloronium ion which was spontaneously attacked by the methyl ester to form 82 in 35% yield, which was one oxidative cyclisation step away from speradine C (Scheme 55). This use of the nucleophilicity of an indole is reminiscent of the strategy observed extensively for spiropyrrolidine synthesis (Scheme 35), indeed, Scheidt has synthesised (−)-coixspirolactam C (Fig. 9) from indole fused THPs (formed in an Oxa-Pictet–Spengler) by bromonium ion formation and rearrangement. Dixon synthesised the spiroTHF oxindole core of the tryptoquivalines using a stereoselective aldol cyclisation/acidic hydrolysis (for the THF ring) and a Cu-catalysed Buchwald type C=N bond formation (for the oxindole).

Cycloaddition

Iminium ion catalysis. In 2012, Melchiorre reported the reaction of 3-hydroxyoxindoles with enals under iminium ion catalysis for the synthesis of chiral butyrolactones and the preparation of mareaemycin A. In 2013, Melchiorre was able to further develop this chemistry with dienals to favour 1,6-addition in favour of 1,4-addition by using prolinol catalyst 83 where the β-substituent constrains the dienal in the S-cis conformation (Scheme 56). In seminal work, Ma reported an NHC catalysed [3 + 2] annulation of 3-bromoenals and isatins for the synthesis of spirotetrahydrofuran oxindoles (Scheme 57). Using NHC cat. 84 Ma achieved high enantioselectivity of the spirobutenolide oxindole products. This reaction occurred through NHC activation of the aldehyde to form a Breslow intermediate. This intermediate can then react through the carbon alpha to the bromo substituent to afford the oxindole alcohol which undergoes spirocyclisation. At a similar time, Glorius reported a similar annulation between isatins and enals, providing spirocycles with two contiguous quaternary stereocentres, which was highly diastereoselective and enantioselective when cat. 85 was...
used, importantly in conjunction with ortho-fluorobenzoic acid (Scheme 57).266 In 2017, Du reported a diastereoselective [3 + 2] annulation of oxindole derived aliphatic acids and isatins or α,α,α-trifluoroacetophenone with good diastereoselectivity using an NHC catalyst.267 Ye then developed a highly diastereoselective and moderately enantioselective [3 + 2]-annulation of 3-hydroxyoxindoles and enals, yielding similar products to the work of Glorius, reportedly by a radical pathway.268 Very recently, Hui showed the enantioselective oxidative annihilation of acyl chlorides with 3-hydroxyoxindoles (Scheme 57).269 There have also been other significant advances in NHC catalysis expanding the starting materials used in conjunction with isatins.270

**Cascade reactions.** As seen for the synthesis of spiropyrrolidines, the use of cascade Michael/cyclisation procedures is also common for spiroTHF oxindoles.271 Related to Yuan’s use of phosphonates as leaving groups for the Michael addition/cyclisation (ref. 219), Du used N-acylated succinimides as leaving groups.272 There are a number of reports of coupling of 3-hydroxyoxindoles and malonitriles,273 of note is Pan’s highly enantioselective Michael/Pinner cascade reaction using cat. 57 (Scheme 58).274 Deng reported an asymmetric Michael/lactonization procedure between 3-hydroxyoxindoles and 3-methylene oxindoles which resulted in ring opening of the oxindole coupling partner (Scheme 58).275,276 Similar to ref. 227 (Scheme 46), Chen and Yang reported a Michael addition/ring opening/ring closing cascade, however, the resultant aniline formed cyclised with the ester of the 3-methylene oxindole in the final step.277 In a distinct reaction but using a similar catalyst, Mei and Shi reported an enantioselective Michael/Pinner cascade reaction using cat. 57 (Scheme 58).278 Again in a somewhat distinct cascade sequence, Quintavalla has developed an aldol/lactonization/elimination sequence catalysed by cat. 57 (Scheme 58).279 Other approaches include the use of quinone monoimines and multicomponent reactions of isonitriles, allenes and isatins.280

In 2016, Bisai reported an enantioselective aldol reaction of dimeric oxindoles which resulted in ring opening of one of the oxindoles, and in doing so developed a highly enantioselective thiourea catalysed aldol reaction with formaldehyde.281 The first process scale synthesis of TV-45070 (Fig. 9) employed a phase-transfer catalysed asymmetric alkylation using a Lygo phase transfer catalyst.282 Due to the requirement for multiple protecting groups in the first process scale synthesis of TV-45070, a new route was developed using a thiourea catalysed aldol reaction similar to the one developed by Bisai (Scheme 59). Only moderate enantioselectivity was observed using cat. 89 (up to 73% ee), but this could be improved by recrystallisation, followed by further two steps to afford the final API.

**MBH carbonates.** A common precursor to these types of spirocycles is an MBH carbonate. In 2013, Xu and Wang reported a [3 + 2] annulation of 3-hydroxyoxindoles with MBH carbonates catalysed by quinidine affording spirolactone oxindoles in high yields and dr and ee (Scheme 60).283 In a one-pot reaction Zhou performed a MBH reaction/bromination/[3 + 2]-annulation sequence to access bispirooxindoles in exceptional ee.284 In 2014, Kesavan reported a one-pot alkylation/cyclisation of 3-OBoc-oxindoles with MBH carbonates with high enantiocontrol using cat. 27 (Scheme 60).285 Related to this, Shi reported an asymmetric phosphine catalysed [4 + 1] annulation of MBH carbonates (Scheme 60).286,287 Chen used EBX reagents to promote an alkynylation of MBH carbonates which...
could be cyclised to 5- or 6-membered oxygenated spirocycles.288

**Metal/Lewis acid catalysis.** Yoda described an indium catalysed asymmetric allylation which depending on the substrate could spontaneously form spirocycle 92 or the alcohol product could be treated with acid to afford the cyclised product with retention of ee (Scheme 61).289,290 Feng has reported a Ni catalysed addition of vinyl hydrazones to isatins which upon acidic removal of the hydrazone and oxidative cleavage forms the antineoplastic agent 93 in high ee (Scheme 61).291 Trost first used Zinc catalysis to synthesise spiroTHF oxindoles in 2012.292 In 2019, Chang and Wang used a related Zn based system to promote a Michael/hemiketalisation/Friedel–Crafts cascade reaction to form bispiroTHF oxindoles. 293 More recently, Hua and Wang reported a related reaction using α-hydroxyacetophenone (Scheme 61).294

Yin has developed a Pd-catalysed cascade reaction involving dearomatisation of furans to form the THF core of the spirocycle.295 Other metal-mediated approaches include the use of Cu,296 Ti,297 Ru,298 or Ni-catalysed spirocyclisations. Trost has also applied his development of Pd-allyl complexes previously discussed in the spiropyrrolidine section to the synthesis of spirotHFs.299 Similar to Moody’s use of diazo compounds to synthesise spiropyrrolidines, OH insertion/cyclisation could be used to synthesise spirotHFs300 and there have been many other approaches using Rh- or Cu-catalysed decomposition of diazo compounds.301

**Ring expansion of small-rings.** Using the ring strain of cyclopropanes or epoxides for [3 + 2] cycloadditions is a common strategy for the synthesis of five-membered oxygen heterocycles. In an interesting strategy, Shi and co-workers used vinylcyclopropanes with Pd2(dba)3 to form a Pd-allyl complex which reacted with isatin to form a spirotHF oxindole with excellent dr and ee when using ligand 95 (Scheme 62).303 In 2019, Su incorporated the vinyl cyclopropane into the oxindole unit and reacted this with an isatin using Pd(OAc)2/XantPhos to afford bispirooxindole THFs diastereoselectively.304

Hajra and Kumar have independently developed Lewis acid-mediated ring expansion of spiroepoxides with allylsilanes to afford spirotHFs oxindoles with moderate to good dr (Scheme 63).305 In 2016, Hajra had used spiroepoxy oxindoles in a regioselective Friedel–Crafts alkylation, the alcohol product could then undergo an Appel reaction and spontaneous cyclisation through the phenol to afford 2H-spirobenzofuran oxindoles.306

**Scheme 59** Plant scale synthesis of TV-45070.  
**Scheme 60** Selected advances in the use of MBH carbonates to form spiro lactone and spirotHFs oxindoles.  
**Scheme 61** Recent advances in metal-mediated spirocyclisation methods to spirotHFs oxindoles.  
**Scheme 62** Use of vinyl cyclopropanes to construct spirotHFs.  
**Scheme 63** Use of spiroepoxy oxindoles in a ring opening/closure cascade.
Use of hypervalent iodine reagents. A clearly distinct strategy to access this type of spirocycle is the use of hypervalent iodine reagents. Building on the work of Gong for the synthesis of bispirooxindoles, Du developed an enantioselective spirocyclisation using catalytic chiral hypervalent iodine reagent with mCPBA as oxidant (Scheme 64).

Six-membered rings
Spirocylohexanyl oxindoles
Applications. Satavaptan (Fig. 1) is a potent, selective Vasopressin V₂ receptor antagonist for treatment of hyponatremia. Spirocylohexane oxindoles also feature in a number of patents as anti-cancer, hepatitis C inhibitors and progesterone receptor modulators.

Natural product synthesis. Although not showing any notable bioactivity, gelsemine has proven to be an inspirational target within total synthesis (Fig. 10). Since 2013, there have been a couple of approaches to gelsemine, including an attempt by Vanderwal from a Zincke aldehyde and a Diels–Alder approach taken by Zhai and Qiu. Mehta described an approach to spindomycin B (Fig. 10) through a Michael addition/SNAr sequence. By far the most significant route to spirocyclohexane oxindoles is [4 + 2]-cycloaddition. In 2013, Marinetti reported a PPh₃ catalysed diastereoselective [4 + 2] cycloaddition of 3-methylene oxindoles and allenes. Chen has developed a similar but enantioselective reaction. Also in 2013, Ramachary reported the enantioselective [4 + 2] cycloaddition of alkynones and malonitrile oxindoles using cat. Due to protonation of the more Lewis basic quinclidine nitrogen. There have been numerous related reports using malonitrile precursors and these reactions are also used to test new asymmetric ligands. There have been a number of reports of combining chromane scaffolds with spiropyrrolidine oxindoles. Of note is Liu and Wang’s use of 3-methylene oxindoles with a phenol substituent undergoing an Michael/aldol/oxa-Michael cascade under iminium catalysis (Scheme 65). There have been many other developments of this type of annulation involving Michael/aldol or more elaborate cascade reactions employing various catalysis modes. An interesting Michael/aldol example was recently reported by Peng and Han with diastereodivergence observed depending on the oxindole N-protecting group (Scheme 65).

In 2011, Melchiorre and Barbas III reported asymmetric Diels–Alder reactions between 3-vinyl indoles and electron poor olefins using iminium ion catalysis and hydrogen bonding catalysis. These works laid the foundations for a body of work which provide tetrahydrocarbazoles fused with spirooxindoles. Notably, in 2014, Feng reported the asymmetric Diels–Alder reaction between 3-vinyl indoles and 3-methylene oxindoles using Ni catalysis (Scheme 66). Also, in 2015 Shi developed a similar reaction using 2-vinyl indoles using chiral phosphoric acid catalysis (Scheme 66). Oxygenated analogues of these tetrahydrocarbazoles, which

![Scheme 64](image1)

**Fig. 10** Selected naturally occurring spirocyclohexane oxindole.

![Scheme 65](image2)

**Scheme 65** Selected [4 + 2] annulations. * Indicates stereochemical relationship between OTMS and ester group on cyclohexane ring.

![Scheme 66](image3)

**Scheme 66** Selected enantioselective [4 + 2] cycloadditions.
could be produced by an Oxa-Pictet–Spengler reaction can undergo a Claisen rearrangement to spirocyclohexanes (which as we have seen can also form spiroTHF products). Antilla described the use of chiral Mg-phosphate catalysis for an asymmetric Diels–Alder reaction. For a related Diels–Alder reaction, Lin and Feng used Zn(OTf)$_2$ complexed with L in up to 99% ee (Scheme 67). In 2019, Kesavan described an asymmetric Diels–Alder reaction between 2,4-dienals and 3-methylene oxindoles catalysed by prolinol cat. (Scheme 67). Feng and Dong have also disclosed a Dy(OTf)$_3$-mediated ring-opening/[4 + 2]-cycloaddition of cyclobutenones and 3-methylene oxindoles.

In terms of other cascade rearrangements, Kim has developed a diastereoselective 6π-electrocyclisation from MBH precursors. Kim further developed this to a one-pot PPh$_3$ mediated coupling of MBH carbonates and enals where favourable disrotatory ring closure from the E,Z,E-isomer proceeds to the major diastereomer (Scheme 68). In a distinct complexity-generating reaction, Tanaka could form racemic intermediate 102 in a [4 + 1] annulation of 3-methylene oxindole and di-ketone 103 by treatment with TFOH (Scheme 68). In a Michael–Henry cascade reaction 102 could react with an electron-poor olefin (such as a nitroalkene) and form polycyclic spirocyclohexane oxindole containing product 104 with excellent enantioselectivity. The yields for these products were low due to only one enantiomer of 102 reacting, therefore, the reaction could also serve to furnish highly enantioenriched 102 in a kinetic resolution.

**Metal-mediated C–H activation approaches.** In 2015, Kim reported a Pd-catalysed Heck/C–H activation approach to spirocyclohexene oxindoles with moderate diastereoselectivity. More recently Lautens has developed a significant body of work using intercepted Pd-mediated spirocyclisations and in 2016 reported benzylene insertion to an allylPd$^{ll}$ intermediate formed by C–H activation (Scheme 69). This was followed by insertion of alkynes with high regioselectivity. These works were followed by Liang and Yang’s report on the synthesis of 109 in a triple C–H activation approach where the allylPd$^{ll}$ intermediate is intercepted by 2 further equivalents of aryl iodide (Scheme 69). Another approach is Pd-catalysed migratory insertion of diazo compounds and Michael addition.

**Chiral hypervalent iodine mediated.** In the sole example of the application of asymmetric hypervalent iodine mediated dearomative spirocyclisation, Gong synthesised spirooxycyclohexene oxindoles in moderate yields but high enantioselectivity (Scheme 70). Generally, electron-rich oxindoles were used i.e. phenylfused oxindoles, however, the enantioselectivity was highest for the synthesis of oxindole 110 using cat. 111.

**Spiropiperidinyl oxindoles**

**Applications.** In the last decade spiropiperidinyl oxindoles have been synthesised for medicinal chemistry applications against cancer, CNS disorders, renal failure, treatment of Dengue virus infection as well as other applications. Surugatoxin related to neosurugatoxin is also a potent human toxin (Fig. 1). Most prominently cipargamin (NITD609 or...
KAE609) has been developed as an anti-malarial agent. Shibasaki used a key asymmetric alkylation of an isatin ketimine to synthesise cipargamin. Liu and Feng synthesised cipargamin in an aza-Diels–Alder process employing 3-vinyl indoles and Ni catalysis (Scheme 71). Similar to other ring sizes we have considered, there have been a number of efforts made towards the synthesis of rings with more than one heteroatom, here we only consider the synthesis of piperidines or δ-lactam scaffolds. Wei and Shi developed a [4 + 2]-cycloaddition of vinyl ketones and α,β-unsaturated imines derived from isatins catalysed by a bifunctional asymmetric phosphorus-thiourea catalyst (Scheme 72, R = 2,4,6-triisopropyl phenyl). In metal-mediated approaches, gold catalysed spirocyclisation of in situ generated indoles and isatins was reported by Subba Reddy. Related to Liu and Feng’s reaction (ref. 355), Kumar developed an enantioselectiveaza-Diels–Alder reaction catalysed by Dy (OTf)₃ and a ligand similar to where Ar = 2,6-iPr₂C₆H₄. Feng, Li and Xiao have independently developed 1,5-hydride transfer reactions to spiropiperidines. More recently, Shi developed a Pd-catalysed decarboxylative [4 + 2] cycloaddition strategy using vinyl benzoazinanones and 3-methylene oxindoles (Scheme 72). NHC catalysis. In 2013, Chi reported the NHC catalysed [3 + 3] annulation of α-aryl esters and isatin derived α,β-unsaturated ketimines to afford spirocyclic-δ-lactams in moderate diastereoselectivity in up to 62% ee with an asymmetric NHC. Yang, Zeng and Zhong used asymmetric cat. 115 to make 3,4′-spiropiperidine oxindoles from isatin derived α,β-unsaturated aldehydes and imines (Scheme 73). This reaction proceeds through imine conversion to the corresponding enamine to avoid unwanted [3 + 2] cycloaddition with the enal. Ye reported a [4 + 2] cycloaddition of α,β-unsaturated carboxylic acids (via the dienolate) and isatin ketimines to form 3,2′-spiro-δ-lactam oxindoles using NHC cat. 116 (Scheme 73). Xu generated ortho-quinodimethanes to undergo [4 + 2] annulation with isatin ketimines using cat. 19 producing β-carboline spirooxindoles (Scheme 73). More recently, Xu and Ren reported a [4 + 2] annulation of aliphatic aldehydes and oxindole derived α,β-unsaturated ketimines catalysed by an NHC catalyst. Enders also recently reported related [3 + 3] annulations of isatin derived enals and cyclic N-sulfonyl ketimines. Cascade reactions. Shi and Tu reported an enantioselective Povarov reaction using asymmetric phosphoric acid cat. 117 affording 3,2′-spiropiperidine scaffolds in up to 97% ee. Initial formation of a ketimine between the aniline and isatin is followed by an acid catalysed vinylogous Mannich reaction and Friedel–Crafts alkylation closes the ring (Scheme 74). This report was followed by a related reaction by Zhou and Shi using 3-vinyl indoles in place of the ortho-vinyl phenol. Zhu employed ortho-vinyl phenols and 3-methylene oxindoles to react in a Michael addition/Friedel–Crafts cascade catalysed by (DHQD)²PHAL to form 3,3′-spiropiperidine oxindoles (Scheme 74). In a related Michael addition/Friedel–Crafts sequence, Yuan utilised electron rich pyrroles to react with an iminium formed from an α,β-unsaturated aldehyde to form pyrrole-fused 3,2′-spiropiperidine oxindoles. Related reactions include aza-Michael/Michael addition, Michael/Mannich reaction, Michael addition/Pictet–Spengler, Michael/aldol, Scheme 70 Chiral iodine mediated spirocyclohexene oxindole formation.

Scheme 71 Concise synthesis of anti-malarial cipargamin.

Scheme 72 Selected enantioselective [4 + 2]-cycloadditions.

Scheme 73 NHC catalysed cycloadditions to spiro-δ-lactams.
Mannich/hemi-aminalisation cascade reactions. He and Han developed a \( [2 + 2 + 2] \) annulation via a Michael/aza-Henry cascade reaction and evaluated the products ability to inhibit proliferation of cancer cell lines. Due to the importance of cipargamin, synthesis of similar β-carboline spirooxindoles is very popular. Also, due to the number of bioactive compounds containing the spirodihydropyridine oxindole scaffold, there has been a significant amount of work aimed at racemic synthesis of Shi’s enantioselective \([3 + 3]\) annulation. Very recent advances include a copper catalysed aza-Henry reaction by Wang and Zhou and HFIP mediated C\((sp^3)\)–H functionalisation by hydride transfer.

**Stepwise strategies.** There are also a number of related works where an asymmetric reaction is followed by consequent deprotection/cyclisation steps. For example, Pedro developed an aza-Henry reaction between isatin ketimines and 4-nitrobutyric acid catalysed by a Cu(II)-Box system, which could be deprotected to undergo spontaneous cyclisation to the 3,2′-spiropiperidine oxindole (Scheme 75). Hajra described an organocatalytic addition of a nitroalkyl group followed by intramolecular alkylation (Scheme 52). Meng and Li, and more recently Nakamura, reported enantioselective vinylogous Mannich reactions to generate intermediates which could be deprotected and cyclised to spiro lactam products (Scheme 75). Han has also developed an enantioselective Mannich reaction which upon deprotection of the generated Boc-protected amine undergoes lactamisation to the six-membered spirocycle.

**Spirotetrahydropyranyl oxindoles**

**Applications.** SpiroTHP oxindoles have found application in induction of apoptosis, as anti-malarial agents, among others.

**Natural product synthesis.** Trost cyclised 120 to give cyclolactone 121 in 92% yield as one diastereomer as an intermediate for the total synthesis of communesin F and perophoramide (Scheme 76). Gong reported the first total synthesis of (+)-trigolutes B utilising an enantioselective substitution reaction to form 122 which in 7 steps could be transformed to the natural product (Scheme 76).387,388

**Cycloaddition/cascade.** Liang and Xu employed thiourea catalysed double Michael addition cascade between N-methyl oxindole and 124 (Scheme 77). Using thiourea catalysed 125 Enders developed an oxo-Michael/1,6-addition reaction to form 3,3′-spiroTHP oxindoles in high yield an enantioselectivity (Scheme 77). Zeng and Zhong reported an enantioselective Michael/aldol/hemiacetalisation process using iminium catalysis. Han has developed an enantioselective vinylogous aldol/cyclisation/ring-opening cascade of 3-methylene oxindoles and isatins. Wu reported an enantioselective Michael/cyclisation reaction between dimedone and isatylidene malonitriles with high yields and enantioselectivities, the trityl protecting group on the isatin was important. More recent examples include a Michael/aldol/cyclisation cascade to form 5- or 6-membered oxygenated spirocycles by Zhang and a vinylogous aldol reaction/transesterification by Yuan, both using thiourea catalysts (Scheme 77). Some of these Michael/cyclisation procedures can be deemed formal hetero-Diels–Alder reactions.

**Scheme 74** Selected examples of phosphoric acid catalysed cascade reactions.

**Scheme 75** Selected advances in asymmetric Mannich reactions followed by elaboration to six-membered spirocycles.

**Scheme 76** Selected examples of spiroTHP oxindole synthesis in total synthesis.
Recently, Xiao has used ortho-quinone methides derived in situ from oxindole ortho-hydroxybenzyl alcohols by acid in [4 + 2] annulations with 2,5-dialkylfurans or 1,3-diketones as dienophiles. These starting materials can also be used in a bis-electrophile coupling in a [4 + 2] annulation (as well as [4 + 1] annulation if a pyridinium salt is used instead of a bromide leaving group). THP fused indoles have been synthesised by enantioselective aldol/chloroetherification/aromatisation, as well as C–O coupling. MBH carbonates have also been used for [4 + 2]-annulations.

**NHC catalysis.** Yao developed the [4 + 2] annulation of isatins with the HOBt ester of α,β-unsaturated carboxylic acids, achieving good enantioselectivity with cat. 19 (Scheme 78). Lu and Du reported the NHC catalysed [3 + 3] annulation of isatin derived α,β-unsaturated acids and α-ketoesters with up to 74% ee. In a similar reaction, Xu reported the annulation of 3-ylidene oxindoles with 1,3-dicarbonyls (Scheme 78). In an excellent application of dual NHC and Cu-catalysis, Song and Gong used ethylene carbonates in a [3 + 3]-annulation of 3-ylidene oxindoles (Scheme 78).

**Stepwise approaches.** Feng has employed a Mg/chiral N,N'-dioxide catalyst system for a hetero Diels–Alder reaction. Li has recently reported a Bi/chiral phosphoric acid 77 catalysed alkylation of isatins which could be further elaborated to spiroTHP products (Scheme 79). Arai has employed a Tso-PyBidine-Ni complex to catalyse the asymmetric addition of indole to 3-ylidene oxindoles and a highly diastereoselective iodocyclisation to 6-membered products was developed using cat. 77 (Scheme 79).

In other approaches, Subba Reddy has developed a BF₃·OEt₂ mediated Prins cascade cyclisation between aldehydes and butanamides to furnish spiroTHP oxindoles in high yield and good dr. Hu used Rh-carbenes generated from 3-diazooxindoles to undergo C–H insertion/aldol condensation to afford spiroTHP oxindoles in high yield and diastereoselectivity. Another example of C–H activation has been shown by Messaoudi with glycosides. The intramolecular Co-catalysed Pauson–Khand cyclisation of 1,7-enynes generated 3,2'-spiroTHPs with high diastereoselectivity.

**Seven-membered rings Applications**

Natural products containing seven-membered spirocyclic oxindoles are predominantly bridged carbocyclic examples of gelsenium alkaloids. There are not many examples of these rings in medicinal chemistry, though nitrogen containing examples do feature in some patents. A spiroazepline oxindole was synthesised as a cipargamin analogue with antimalarial activity, and an example with activity against a prostate cancer target (Fig. 1). While natural products tend to favour bridged carbocyclic seven-membered rings (Fig. 11) and there are some methodologies to synthesise bridged seven-membered rings, this section will focus on non-bridged...
examples. Additionally, we have grouped the methodologies in terms of similarity rather than into C/N/O-containing rings due to the small number of publications, the vast majority of which are aimed at spiroazepane synthesis.

Natural product synthesis

Total synthesis efforts centre around the synthesis of gelsemium alkaloids. Carreira has described elegant approaches to gelsemoxonine (see Fig. 11 for structure). Ferreira constructed the oxindole of gelsenicine with an oxidative cyclisation of a Weinreb amide with an aromatic ring. Fukuyama and Ma have independently described divergent syntheses to many gelsedine type alkaloids. Takayama recently described an asymmetric synthesis of (−)-14-hydroxygelsemicine and six other gelsemium alkaloids. The spirooxindole was constructed in a diastereoselective Heck cyclisation (Scheme 80).

NHC catalysis

In 2016, Enders pioneered the use of NHCs for the [3 + 4]-cycloaddition of isatin derived enals with azo-quinone methides or azoalkenes to form spiro-benzazepinones or spiro-diazepinones (Scheme 81). Using cat. 128 with Cs$_2$CO$_3$ to form the azo-quinone methide in situ from the N-(o-chloromethyl)aryl amide in EtOAc gave high enantioselectivity and atroposelectivity. Switching starting material in order to make diazepinones was highly stereoselective using cat. 129.

Li developed an NHC catalysed enantioselective synthesis of spirobenzoxepinones in a [4 + 3] cycloaddition of isatin derived enals and quinone methides (Scheme 82). High enantioselectivity (up to >99% ee and >20:1 dr) was achieved using triazolium cat. 130 in combination with NaOAc in 1,2-dichloroethane. Enders published a similar reaction a month after Li’s study, which employed cat. 131 to achieve up to 95:5 er and good dr. This was followed by work by Yan Li and Ye on a related [4 + 3]-cycloaddition of isatin derived enals and aurone-derived azadienes. Using a similar NHC catalyst interesting spiroazepinones were formed with high enantioselectivity and diastereoselectivity. The compounds exhibited moderate cytotoxicity against cancer cell lines.

More recent advances include Fu and Huang’s NHC catalysed [4 + 3]-annulation of α,β-unsaturated aldehydes and amine substituted oxindoles (oxotryptamines, Scheme 83). Song and Gong’s previously discussed excellent Cu/NHC dual catalysis could be used with ethynyl benzoxazinanones to construct chiral azepines.

MBH carbonates

Chen and coworkers reported a [4 + 3] cycloaddition of a bromo-substituted MBH derivative and an azo-quinone methide precursor (Scheme 84). Chen used tri-(4-fluoro) phenyl phosphine as a Lewis base to form an allylic ylide from the MBH precursor and Cs$_2$CO$_3$ as base to generate the azo-quinone methide. Xu published a related reaction at a similar time, using tributyl phosphine as Lewis base catalysis with a related MBH precursor and a Boc protected azo-quinone.
methide precursor to generate seven-membered spirocycles in good yields, including on gram-scale. In a similar fashion, Du recently employed ortho-quinone methides in combination with an isatin derived MBH precursor to affect a \( [4 + 3] \)-cycloaddition. Using DABCO as Lewis base catalyst in MeCN, high diastereoselectivity with electron-rich ortho-quinone methides was observed (Scheme 84).

Du and Chen have collaboratively reported an asymmetric Ir catalysed \( [4 + 3] \)-cycloaddition between an MBH carbonate and \( \pi \)-allyl precursor (Scheme 85). The \( \pi \)-allyl precursor includes a vinylogous leaving group i.e. vinyl-OBoc, ethylene oxazinanones or vinyl aziridines (for six-membered rings) which forms an asymmetric Ir-allyl complex to react with the DABCO activated MBH carbonate.

Other approaches to spiroazepanes include a desymmetrising Cu-catalysed C–N bond formation in high ee (Scheme 86). Budynina has used azide anion ring opening of spirocyclopropyl oxindoles (ref. 198) in a Staudinger, domino Michael/aza-Wittig and reduction sequence. Yang developed a Pd-NHC catalysed allylic alkylation, the products of which could readily elaborated to a spiroazepinone.

Eight-membered rings

As with seven-membered spiro-oxindoles there are very few examples of syntheses capable of accessing the eight-membered analogues. Shi and Zhao independently published the Pd-catalysed \( [5 + 3] \)-cycloaddition of N-2,2,2-trifluoromethylisatin ketimines and vinylene carbonates (Scheme 87). Shi employed \( \text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 \) and Xantphos as a ligand for the decarboxylative allylic substitution and a racemic phosphoric acid catalyst to effect the cyclisation. Meanwhile, Zhao used \( \text{Pd}(\text{PPh}_3)_4 \) in combination with \( \text{PPh}_3 \) as ligand and pyridine as base for the cyclisation. Both procedures afford the anti-product as the major product in high yields and dr. Shi demonstrated a preliminary result for the enantioselective allylation using \( \text{tBu-RuPhos} \) as ligand affording the eight-membered spirocycle in 63% ee. Furthermore, Shi showed that epoxidation of the endogenous double bond with mCPBA would lead to spontaneous epoxide ring opening to form spiropyrrolidine 134 (Scheme 87A).

Summary and conclusions

We have reviewed the developments in state-of-the-art stereoselective spiroindolone synthesis between 2013 and 2020. The progress of synthetic methodology for each ring size (3- to 8-) has been discussed. The importance of these advances should not be understated, with reference to the significant potential of many of these structures in medicinal chemistry, which we have highlighted with numerous examples. The trends we have observed within this review can be summarised as follows:

1. Spirooxindoles represent a very important class of structures within medicinal chemistry, featuring in approved medicines with a large variety of biological activity, as well as acting as the structural core in a significant number of natural products (eg Fig. 1). Where possible we have highlighted how the synthetic methodologies discussed in this review have influenced the process scale synthesis of these pharmaceuticals, for example in Scheme 59.

2. Spirooxindoles serve as a benchmark in asymmetric synthesis. Many of the methods reviewed here have made substantial advances in asymmetric catalysis. This may be due to the fused backbone of the indolone providing a flat and rigid plat-
form for construction of 3D spirocycles. These advances are doubly valuable because they fulfill the object of advancing asymmetric methodology while making biologically relevant scaffolds for screening against biologically relevant targets.

3. The advances that have been observed in spirooxindole synthesis generally reflect the advance of organic synthesis since 2013. While there has been a significant rise in the number of publications on this topic, there are a growing number of excellent and innovative reports targeting these scaffolds (Fig. 2). This review has covered advances in stereo- selective NHC catalysis, chiral acid catalysis, aminocatalysis, metal catalysis including cross-coupling, hydrogen bonding catalysis and phase transfer catalysis. We have also highlighted total syntheses of natural products containing these core structures.

There will likely be sustained interest in these scaffolds because of the trends observed in recent years coupled with the success of many of the pharmaceutical agents. We envisage that future developments may be targeted to the following objectives:

1. More general methods to access multiple ring sizes. Currently, there are few methodologies that can access multiple ring sizes with simple changes i.e. to starting material structure. For example, ring expansion strategies making use of small rings are useful to access more than one ring size. Ideal methods could also access more than one heteroatom pattern on the spirocyclic ring and be able to control ring substitution.

2. A wider variety of synthetic targets through asymmetric synthesis. Unsubstituted rings can often be synthesised as racemates using traditional methods. Yet, asymmetric synthesis of unsubstituted rings is a challenge and though there are examples within this review there is still a requirement to access the unsubstituted scaffold.

3. Small and larger ring spirocycles. As can be seen from the analysis of the publication numbers (Fig. 2) and reflected in the number of strategies discussed in this review, there is a plethora of methods for 5- and 6-membered rings. Future endeavours in this area should seek to synthesise small or larger rings, eg azetidines and oxetanes are increasingly useful for medicinal chemistry and have not received the same level of attention. Furthermore, 7- and 8-membered rings have not received significant attention due to the difficulty in accessing these structures and we envisage that synthetic advances seen in this review will likely be applied to larger ring synthesis. 8-Membered ring spirocycles, as the first member of the medium rings, may require significant new method development. Higher medium ring homologues were not within the scope of this review, but could pose interesting targets for medicinal chemistry. New syntheses of these smaller and larger ring spirocycles will lead to improved access to this valuable and underexplored chemical space.

We hope that this review will serve as a reference for medicinal and synthetic chemists aiming to synthesise this type of ring structure and inspire future advances in the synthesis of spirooxindoles.

Conflicts of interest
There are no conflicts to declare.

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