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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.¹ 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.² Spirocyclic compounds can improve certain physicochemical properties such as lipophilicity, aqueous solubility and metabolic stability, in comparison to the respective monocyclic structure.³ 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.⁴ 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.⁵

This review focuses specifically on spirocyclic oxindoles (spirooxindoles or spiroindolones). These are a widespread

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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 phosphodiesterase inhibitor (Scheme 1A).²⁵ Since this low yielding and step-inefficient synthesis using strong base, Marini reported cyclopropanation using a vinyl selenone reagent in a domino Michael addition and cyclisation sequence (Scheme 1B).²⁶ When aryl-substituted vinyl selenone 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



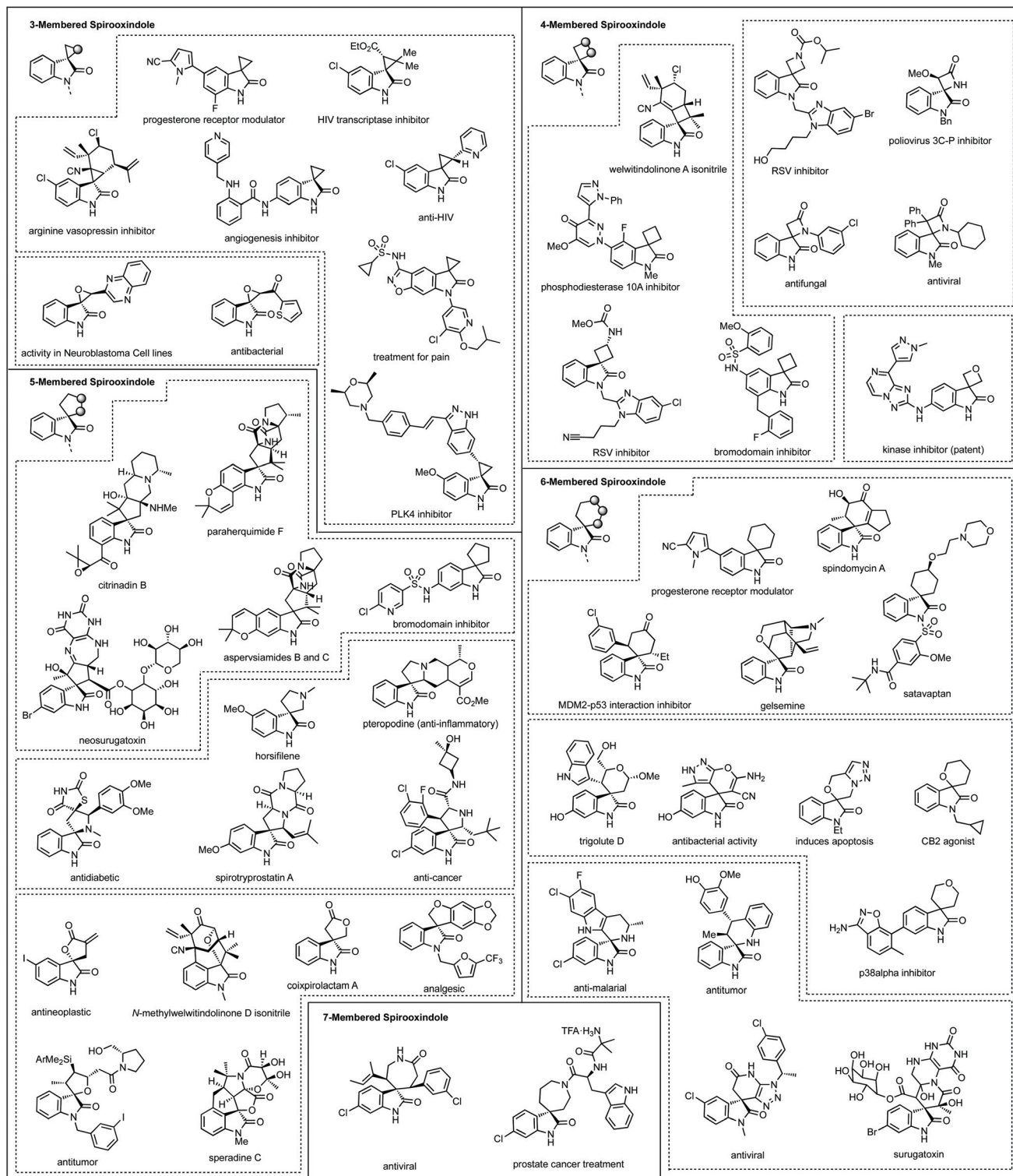


Fig. 1 Bioactive and naturally occurring spirooxindoles.

cyclopropanation (Scheme 1C).²⁷ 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).²⁸ Recently, Hajra reported a domino Corey–Chaykovsky reaction for obtaining the spirocyclic oxindole from the corresponding isatin, spiroepoxide or spiroaziridine (Scheme 1E).²⁹ Initially using standard Corey–Chaykovsky reaction conditions and generating the sulfur ylide



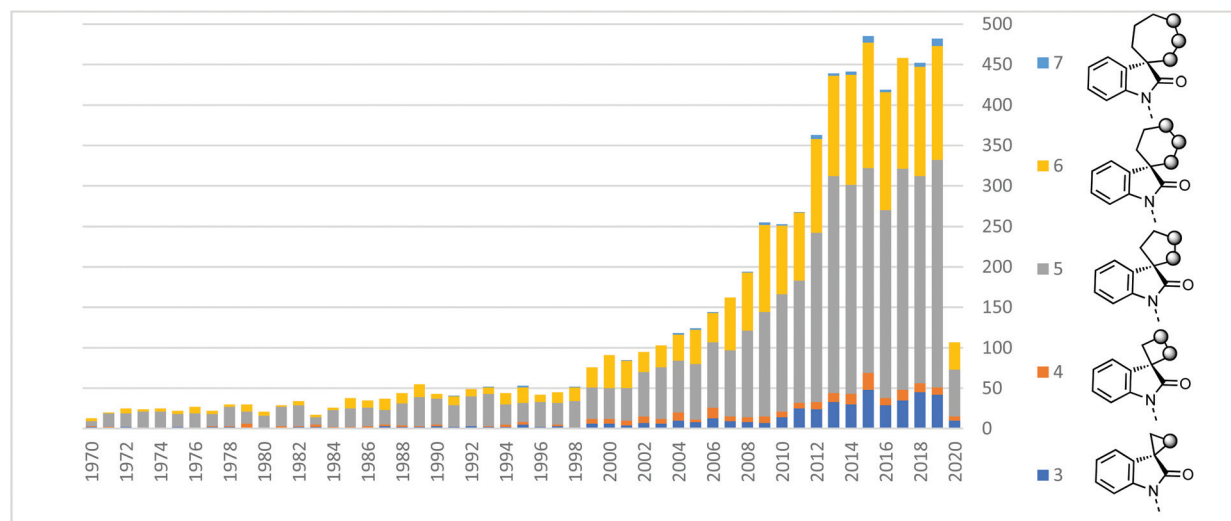
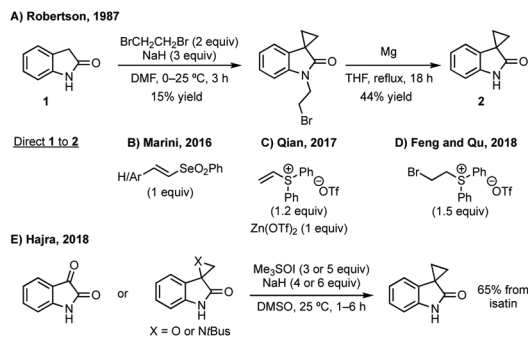


Fig. 2 Incidence of 3- to 7-membered spirooxindoles in the literature up to April 2020. No. of heteroatoms in ring ≤ 1 .¹⁵

X,X'-spiro	3-	3,2'-	3,3'-	3,4'-	3,2'-	3,3'-	3,4'-
	 17521	 147			 721		
	 7948	 462 ^a	 332		 155	 2	
	 7449	 11706	 8029		 2116	 2945	
	 7209	 933	 1937	 3234	 548	 369	 5816
	 46 (618) ^b	 22 (1) ^b	 4 (4) ^b	 217 (6) ^b	 2 (20) ^b	 0 (341) ^b	 68 (2) ^b

Fig. 3 The spirocyclic rings covered in this review and the number of hits for each heteroatom position.¹⁵ ^a Beta-lactams or derivatives thereof. ^b Numbers in brackets indicates bridged examples.



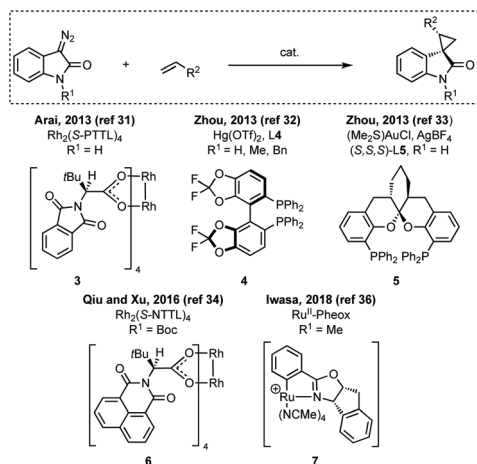
Scheme 1 Summary of recent advances in direct cyclopropanation of unprotected oxindoles.

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-diazo oxindoles. Diastereoselective cyclopropanations have been independently developed by Muthusamy, Subba Reddy and Padwa.³⁰ The first enantioselective versions were developed at similar times by Arai (up to 74% ee using chiral Rh cat. 3),³¹ Zhou (up to 99% ee using $\text{Hg}(\text{OTf})_2$ and a chiral phosphine ligand 4)³² and Zhou with Ding (up to 95% ee using a Au catalyst with chiral phosphine ligand 5) (Scheme 2).³³ 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.³⁴ Zhou and Ma have used the Au/5 system developed previously by Zhou for the cyclopropanation with alkenes bearing a difluoromethyl group.³⁵ Iwasa used chiral Ru(II) complex 7 to generate spirocyclopropyl oxindoles with high ee.³⁶ Ashfeld reported a cyclopropanation/ring expansion cascade reaction between 3-diazo oxindoles 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.³⁷

In 2014, Lu and Xiao showed a [3 + 2]-cycloaddition between 3-ylideneoxindoles and *in situ* generated 2,2,2-trifluorodiazethane could afford a pyrazoline which upon heating under reflux in toluene would ring contract to afford 3,3'-cyclo-



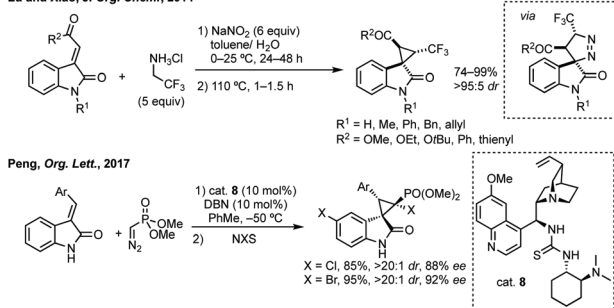


Scheme 2 Advances in enantioselective cyclopropanation of 3-diazo oxindoles.

propyl spirooxindoles.³⁸ Using chemistry first developed by Carreira,³⁹ sodium nitrite was used to oxidise 2,2,2-trifluoroethylamine-HCl to generate 2,2,2-trifluorodiazomethane 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.^{40,41} A significant advance in this methodology accesses enantioenriched spirocyclic cyclopropanes through a 1,3-dipolar cycloaddition between dimethyl (diazomethyl) phosphonate and 3-ylideneoxindoles followed by ring contraction mediated by NCS or NBS (this also caused chlorination/bromination by S_EAr).⁴² Peng used thiourea catalyst **8** derived from a *cinchona* alkaloid to induce enantioselectivity in the pyrazoline formation and this ee was retained in the 5- to 3-membered ring contraction (Scheme 3).

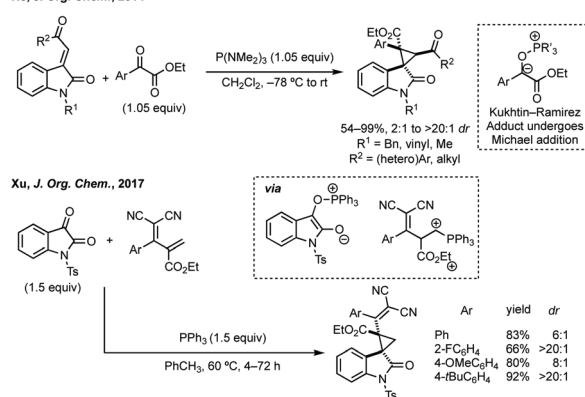
Cyclopropanation of 3-ylidene oxindoles. He developed a phosphorus mediated reductive cyclopropanation of 3-ylideneoxindoles (Scheme 4).⁴³ P(NMe₂)₃ in combination with

Lu and Xiao, *J. Org. Chem.*, 2014



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

He, *J. Org. Chem.*, 2014



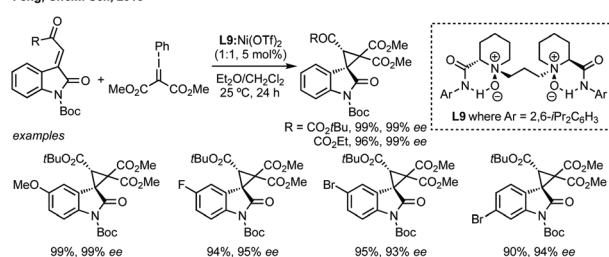
Scheme 4 P(NMe₂)₃-mediated reductive cyclopropanation via Kukhtin-Ramirez (K-R) adduct and K-R adduct reaction with diene activated by PPh₃.

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_N2 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.⁴⁴ In 2017, Xu reported the formation of Kukhtin-Ramirez adducts from isatins and their reactions with dienes to form spirocyclopropanes (Scheme 4).⁴⁵

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-dioxypyridines.⁴⁶ 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).⁴⁷ More recently, Feng used a related system for the Mg catalysed reaction of 3-ylidene oxindoles and sulfonium ylides.⁴⁸

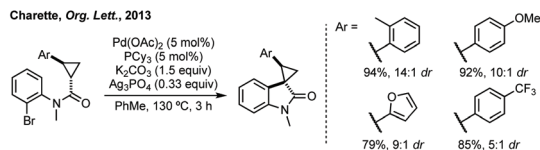
Other approaches. In 2013 Charette described an intramolecular C-H arylation of cyclopropanes to access 3,3'-spirocyclopropyl spirooxindoles (Scheme 6).⁴⁹ Using Pd(OAc)₂ with PCy₃ as a ligand in combination with K₂CO₃ and Ag₃PO₄ in

Feng, *Chem. Sci.*, 2016

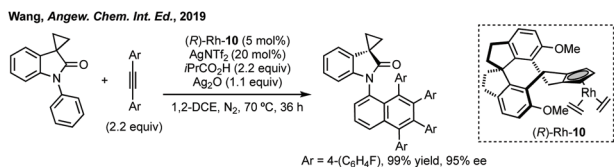


Scheme 5 Ni-Catalysed enantioselective cyclopropanation with phenyliodonium derived ylides.





Scheme 6 Pd-Catalysed C–H arylation to form 3,3'-spirooxindoles. Cy = cyclohexane.



Scheme 7 Enantioselective synthesis of axially chiral oxindoles by Rh catalysed dual C–H activation.

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 Rh^{III} catalyst **10** to perform a dual C–H activation forming an axially chiral spirocycle in high enantioselectivity (Scheme 7).⁵⁰

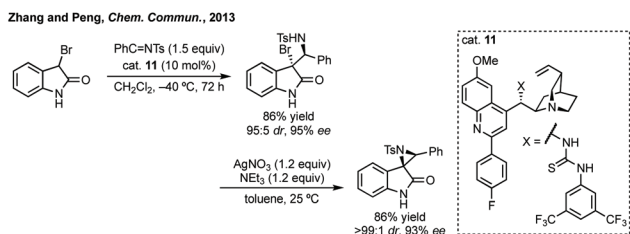
Spiroaziridinyl oxindoles

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.

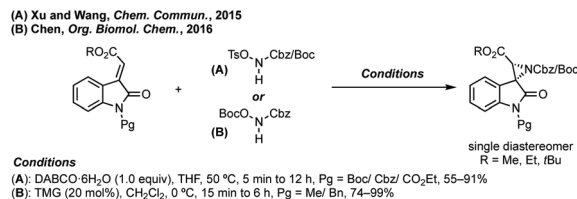
From 3-bromooxindoles. Zhang and Peng employed 3-bromooxindoles as nucleophiles in an enantioselective Mannich reaction catalysed by *cinchona* alkaloid derived cat. **11** (Scheme 8).⁵¹ Cyclisation mediated by silver nitrate afforded the aziridine in high yield and with retention of the ee induced in 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

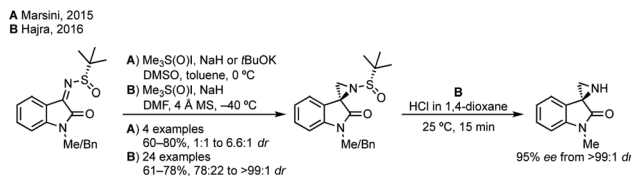
Aziridination of isatin ketimines. A team led by Marsini at Boehringer Ingelheim reported a diastereoselective aziridination of *N-tert*-butanesulfinyl ketimine esters at the end of 2015



Scheme 8 Enantioselective Mannich reaction followed by cyclisation.



Scheme 9 Aziridination of 3-ylideneoxindoles with carbamate protected amines. TMG = 1,1,3,3-tetramethylguanidine.



Scheme 10 Diastereoselective aziridination independently developed by Marsini and Hajra.

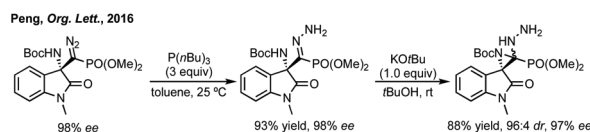
(Scheme 10).⁵⁴ At a similar time Hajra reported the same reaction with higher diastereoselectivity (up to >99:1 dr vs. 6.6:1 dr).⁵⁵ Both reports use trimethylsulfoxonium iodide with either NaH or *t*BuOK and Hajra found that using DMF as solvent at lower temperature gave much higher diastereoselectivity. 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 hydrazine which could be cyclised to afford 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)₂PHAL (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 er and dr of the resulting aziridine was not reported.

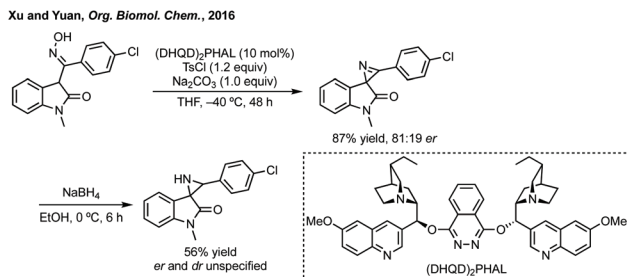
Spiroepoxy oxindoles

Applications. There are two recent examples of spiroepoxides in medicinal chemistry for antibacterial activity as well as



Scheme 11 Synthesis of enantioenriched spiroaziridine.



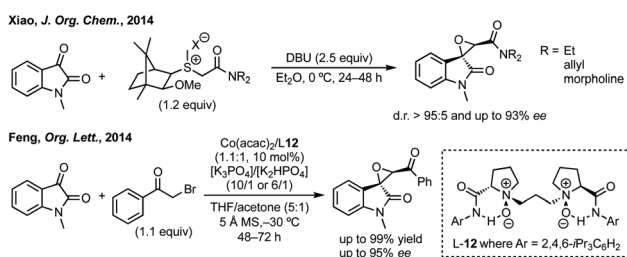


Scheme 12 Asymmetric Neber reaction followed by reduction to spiroaziridine.

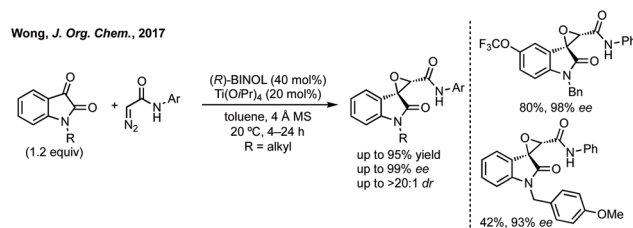
activity in Neuroblastoma cell lines (Fig. 1).⁵⁸ Spiro-epoxyoxindoles are also attractive synthetic building blocks.⁵⁹

Epoxidation of isatins and isatin derivatives. Though non-stereoselective, notable advances in the synthesis of spiro-epoxyoxindoles have been made recently by Wang and Zhang,⁶⁰ and Pace.⁶¹ Diastereoselective epoxidations have been developed,⁶² notably the use of a trifluoroethylsulfonium salt in a Corey–Chaykovsky reaction by Cheng and Zhai.⁶³ Lin and Jin recently developed a diastereoselective epoxidation mediated by visible light.⁶⁴ Bencivenni was able to form axially enantioenriched 3-methylene oxindoles through a Knoevenagel condensation and, upon epoxidation, the high axially chiral enantioenrichment was maintained with a 5 : 1 dr.⁶⁵

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



Scheme 13 Enantioselective epoxidations using Darzens reactions.



Scheme 14 Asymmetric Darzens reaction developed by Wong.

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 spiro-epoxides have been used to form enantioenriched products in a kinetic resolution. Sun, Hong and Wang used Bn-protected indole and naphthols 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

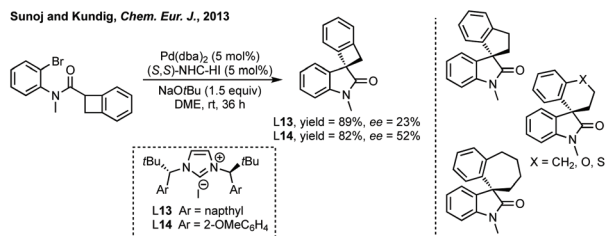
Natural product synthesis. Welwitindolinone A (Fig. 1) has inspired many approaches in total synthesis from the Baran⁷⁸ and Wood laboratories.⁷⁹

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-



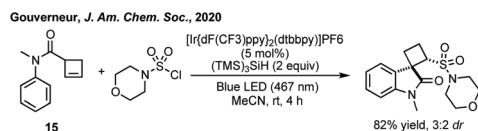


Scheme 15 Pd-Catalysed enantioselective C–H arylation.

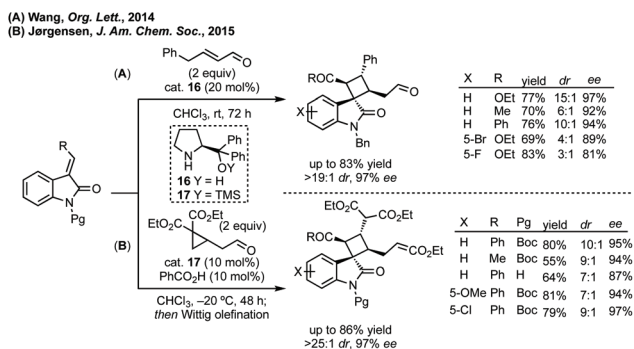
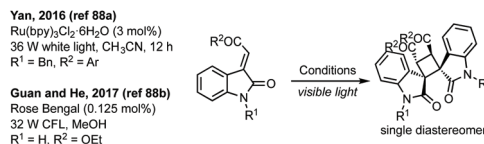
lic cascade reaction.^{82,83} Xu could form the same unsubstituted cyclobutane, as well as 5- and 6-membered analogues, in an intramolecular 1,5-HAT using aryl iodides by visible light photoredox catalysis.⁸⁴ Gouverneur recently developed a silyl radical-mediated hydrosulfamoylation using sulfonyl chlorides 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 α,α -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 bispirooxindole cyclobutane as a single



Scheme 16 Visible light mediated cascade spirocyclisation.

Scheme 17 Advances in organocatalytic [2 + 2]-cycloaddition of 3-ylideneoxindoles with α,β -unsaturated aldehydes, either directly or *in situ* generated.

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

diastereomer (Scheme 18).⁸⁸ Out of a possible 8 diastereomers, one diastereomer was formed in the cycloaddition reaction.

Spiroazetidinyloxindoles

There are very few examples of spirocyclic azetidinyloxindoles. Indeed, an analysis of all N-containing 4-membered 3,2'-spiro oxindole structures shows that all of them are beta-lactams or derivatives. Whereas for the corresponding 3,3'-spirocycles only one out of 332 is a β -lactam or derivative thereof (yet these are typically symmetrical and easily installed *via* traditional methods and do not feature heavily in this section). β -Lactams dominate the nitrogen containing bioactive compounds. This may reflect the lack of synthetic methods towards the unsubstituted spiroazetidinyloxindoles.

Applications. Spiroazetidine/spiro- β -lactam oxindoles have shown activity as antivirals,⁸⁹ antibacterials,⁹⁰ antifungals⁹¹ and insecticides (Fig. 1).⁹²

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

'Traditional' non-stereoselective methods. Notable examples of non-stereoselective β -lactam formation are [2 + 2] cycloadditions between diazo compounds and isatin derived ketimines or reaction of bromoacetyl bromide or chloroacetyl chloride with isatin derived ketimines.⁹⁴

Annulations using NHC catalysis. There have been significant advances in the stereoselective synthesis of β -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 β -lactam using either silica gel in toluene under reflux or trifluoroacetic acid in 1,2-dichloroethane, affording the unprotected β -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

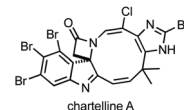


Fig. 4 Structure of chartelline A.



Spirooxetanyl oxindoles

Applications. Spirooxetanes have featured in only two recent reports for bioactivity in a Merck patent for kinase inhibitors,¹⁰⁶ as well as in an SAR study (see below, ref. 109).

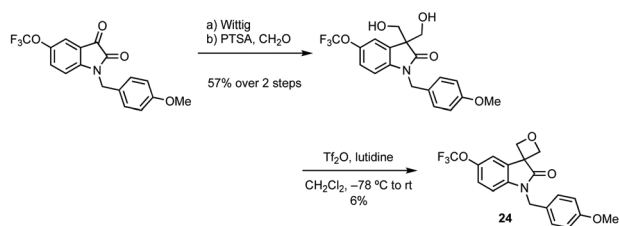
Non-stereoselective methods. As developments in stereoselective formation of spirooxetanes have been limited since 2012 (with the lowest number of hits out of any of the structures considered in this review), it is worthwhile mentioning papers that form spirooxetanes without stereoselectivity. Zhang formed spirocyclobutanes from a cascade spirooxetane/cyclopropane ring opening reaction using $\text{BF}_3 \cdot \text{Et}_2\text{O}$.⁸³ The oxetane starting materials were synthesised in a [2 + 2]-cycloaddition from the isatin and a tetrasubstituted alkene such as 1,1'-bi(cyclopropylidene).¹⁰⁷ In 2019, Marini reported a domino reaction of 3-hydroxyindoles and phenyl vinyl selenone.¹⁰⁸ 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.¹⁰⁹ 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.¹¹⁰ 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).

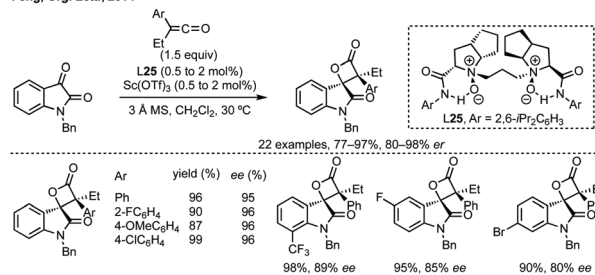
Five-membered rings

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.¹¹¹ 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.⁷⁵

Lindsley, *Bioorg. Med. Chem. Lett.*, 2013

Scheme 23 3-Step sequence to oxetane **24** in a SAR study towards a selective M_5 positive allosteric modulator.

Feng, *Org. Lett.*, 2014

Scheme 24 Enantioselective [2 + 2]-cycloaddition to form spirooxetanones.

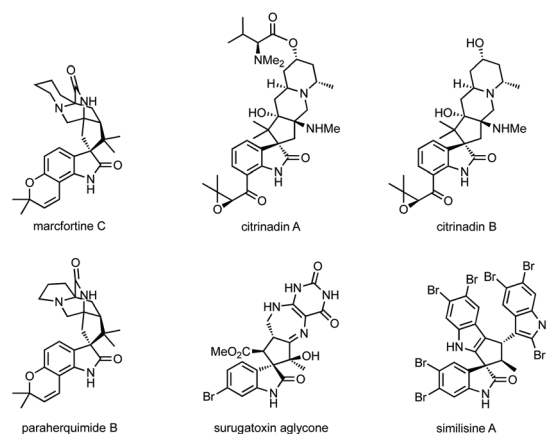
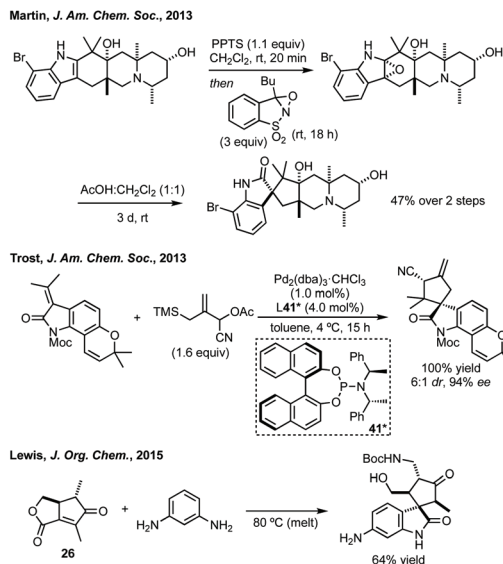


Fig. 5 Selected cyclopentane spiroindolones in nature.

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).¹¹² Selective epoxidation of the indole C2=C3 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.¹¹³ 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.¹¹⁴ Wood synthesised (+)-Citrinadin B forming the spirocyclopentane in a Pd-catalysed enyne cyclisation, initially developed by Trost.¹¹⁵ Trost has developed an asymmetric [3 + 2] Pd-trimethylenemethane (TMM) cycloaddition to form the spirocyclopentane core of Marcfortine B and C (Scheme 25).¹¹⁶ 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



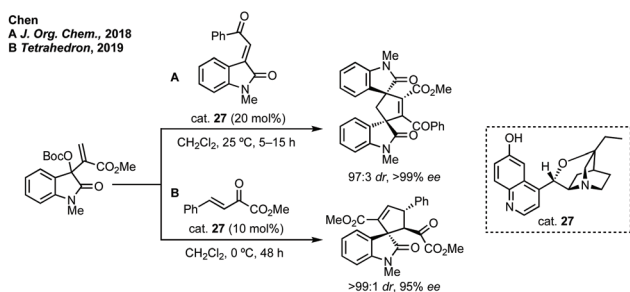


Scheme 25 Selected examples of spirocyclisation to cyclopentanes in total synthesis.

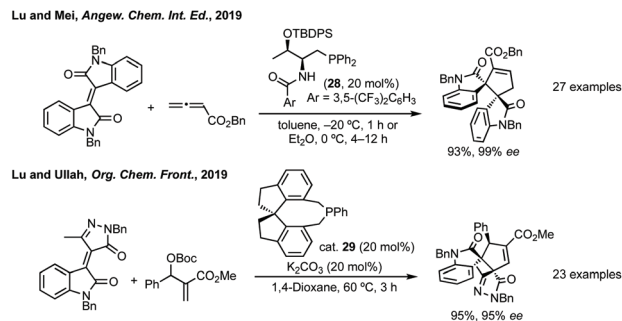
product see Fig. 5).¹¹⁷ Zhang and Jia recently described the total synthesis of similisines A and B (Fig. 5), enantiomeric tri-indole structures containing a spirocyclopentane oxindole core, through a key acid-mediated Friedel–Crafts cyclisation, though this was low yielding and non-stereoselective.¹¹⁸

[3 + 2]-Cycloaddition. 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.^{119,120} 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).¹²¹ In 2019, Chen described the [3 + 2] cycloaddition of isatin-derived MBH carbonates with β,γ -unsaturated α -keto esters using asymmetric nucleophilic catalyst **27** derived from quinidine (Scheme 26B).^{122,123}

Further advances in this field have been made using asymmetric phosphorus catalysis to activate allenes, MBH carbonates or alkynones to form spirooxindoles.^{124,125} In Lu and Mei’s 2019 report threonine derived cat. **28** was found to give



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

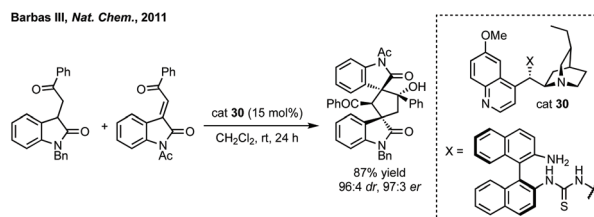


Scheme 27 Lu and coworkers’ achievements in asymmetric phosphine catalysed activation of electrophiles to form spirocyclopentene scaffolds.

the highest yield and enantioselectivity in Et₂O for the [3 + 2] annulation of isoindigos and allenes (Scheme 27).¹²⁶ 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 pyrazoloneyldiene oxindoles with MBH carbonates using asymmetric phosphorus catalyst, SITCP **29** (Scheme 27).¹²⁷ Both routes exploit the regioselective addition of the activated electrophile (MBH carbonate or allene) to the more electrophilic alkene carbon. Related reactions have been developed using isocyanides to activate similar electrophiles including allenes.¹²⁸

Domino Michael addition/aldol (or alternative cyclisation)

In 2011, Barbas III designed a bifunctional thiourea catalyst **30** for the domino Michael addition/aldol reaction to form bispirooxindoles from 3-substituted oxindoles and 3-methylene oxindoles (Scheme 28).¹²⁹ Since, this Michael addition/cyclisation strategy based upon hydrogen bonding catalysis has been employed to access spirocyclopentane oxindoles on a large number of occasions.¹³⁰ Notable examples include Kanger’s use of 3-ylidene oxindoles undergoing asymmetric thiourea catalysed Michael addition alpha to the nitro group of a γ -nitroketone 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).¹³¹ 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 28 Barbas III’s seminal work on an enantioselective domino Michael/aldol cyclisation.



to form an enantioenriched spirocyclopentane with moderate dr.¹³² Shi has utilised asymmetric phosphoric acid catalysts to employ various vinyl indoles to react with 3-ylidene oxindoles, formed *in situ* from 3-indolylmethanol, in a Michael/alkylation cascade.¹³³

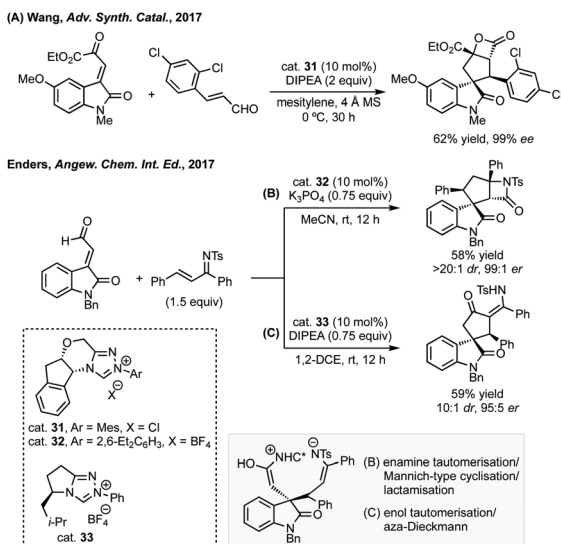
NHC catalysis. In 2017, Wang reported a Michael addition/intramolecular aldol/lactonization cascade of enals with 3-methylene oxindoles using an azolium NHC catalyst.^{134,135}

Up to 99% ee and >99:1 dr was achieved using cat. **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).¹³⁶

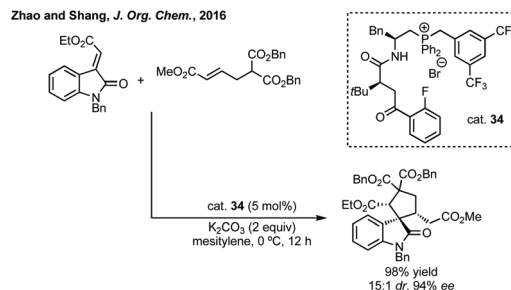
Enders also showed that using a different NHC catalyst (cat. **33**), base and solvent, a different spirocyclopentane scaffold could be formed in good yield and high dr and er (Scheme 29C). This switchable reactivity occurs from the same intermediate formed by Michael addition. This intermediate can 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.¹³⁷ Employing phosphonium phase transfer catalyst **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.¹³⁸

Spirocyclopentanyl oxindoles feature in a number of lead Calcitonin Gene-Related Peptide (CGRP) medicines developed



Scheme 29 Work by Zhang and ENDERS using NHC catalysis to synthesise diverse spirocyclopentanyl oxindoles.



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

by Merck, and more recently Sosei Heptares, for treatment of migraine (Fig. 6).¹³⁹

Towards an efficient asymmetric synthesis of the spirocyclopentane core of these compounds Merck developed an enantioselective phase transfer catalysed spirocyclisation.¹⁴⁰ Using a doubly quaternised *cinchona* alkaloid derived phase transfer catalyst **35** up to 96% ee was achieved for the transformation of substrates such as **36** to **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).¹⁴¹

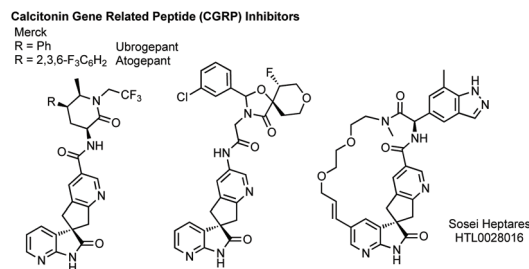
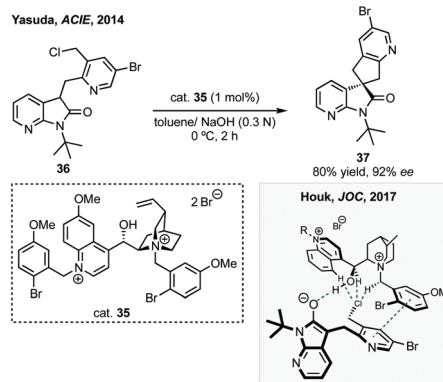


Fig. 6 Selected developments in structures of CGRP inhibitors.



Scheme 31 Merck's development of a phase transfer catalysed spirocyclisation and model for the enantioselectivity developed in collaboration with Houk.

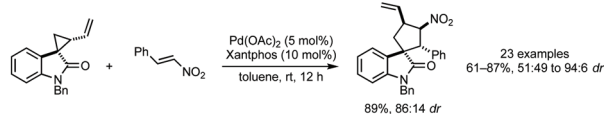


They proposed three key electrostatic interactions: (1) hydrogen bonding between the hydroxyl of the catalyst and the oxindole enolate; (2) a chloride-CH interaction activating the leaving group; (3) a π - π interaction between the pyridine of the formed cyclopentane and the quinuclidine benzyl group. Merck also recently published on the monitoring of the reaction kinetics of these inherently complex, dual-phased reaction mixtures in an automated fashion.¹⁴² These studies remain a significant advance in asymmetric phase transfer catalysis, as well as in the synthesis of enantioenriched spirooxindoles.

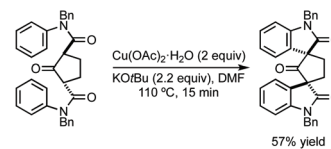
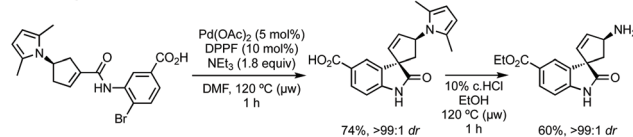
Metal/Lewis acid mediated approaches. Feng used a Mg/*N*, *N'*-dioxide catalyst system in a Michael/Friedel-Crafts/Mannich cascade of isocyanides to generate enantioenriched polycyclic spirocyclopentanes resembling strychnos alkaloids.¹⁴³ Franz recently used an Sc/pybox system for the [3 + 2]-cycloaddition 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 is 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(II)-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 cyclopentenes,¹⁵¹ to develop an intramolecular variant. Exploiting the selectivity of the Heck-Mizoroki reaction to afford spirocyclopentenes with high diastereocontrol (Scheme 33).¹⁵²

Su and Yang, *Org. Biomol. Chem.*, 2019

Scheme 32 Pd-Catalysed [3 + 2] annulation of spirovinylcyclopropyl oxindoles.

Taylor, *Org. Lett.*, 2014Larhed, *Org. Lett.*, 2017

Scheme 33 Selected C-H activation and cross-coupling procedures to access spirocyclopentane.

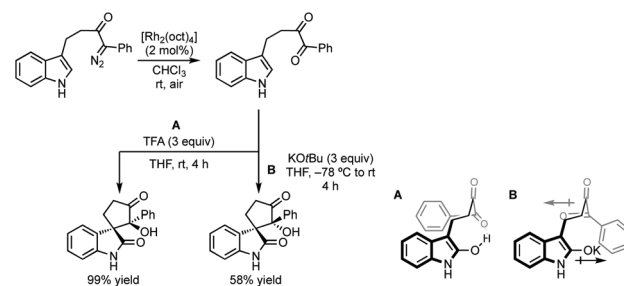
García-López and others have reported C-H activation and carbene insertion procedures to afford spirocyclopentanes.¹⁵³

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 enantiotopic 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 spirocyclopentanyl oxindole from the same intermediate.¹⁵⁵ Treatment of a ketodiaz 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).

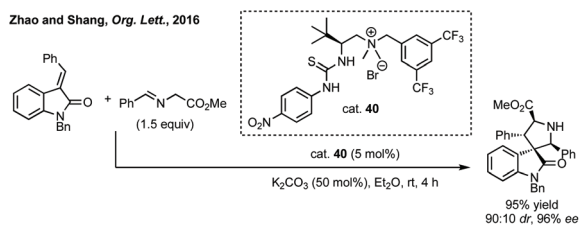
Spiropyrrolidinyl oxindoles

Applications. Spiropyrrolidine oxindoles are applied widely in medicinal chemistry. Indeed, many of the natural products featuring a 3,3'- or 3,2'-spiropyrrolidinyl motif display a wide variety of bioactivities.¹⁵⁶ One of the most significant pharmaceuticals is MI-888 (Fig. 7), a 3,3'-spiropyrrolidine 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 spiropyrrolidines include anti-

Taylor and Unsworth, *Angew. Chem. Int. Ed.*, 2016

Scheme 34 Taylor and Unsworth's approach using indole nucleophilicity.





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

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).¹⁹³ The natural stereochemistry of isatindigoindoline C was thus confirmed as *anti* by comparison of the ¹H NMR spectra.

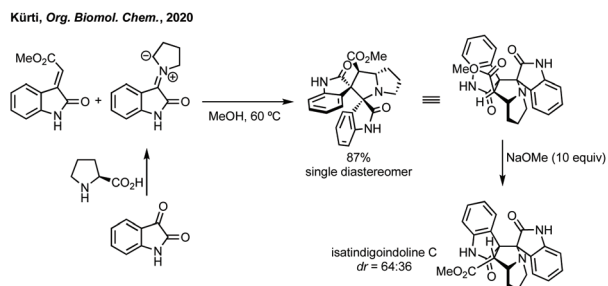
Ring expansion. A particularly important development in the synthesis of 3,3'-spirocyclopropyl oxindoles was reported by Carreira in 1999. Spirocyclopropyl oxindoles could be reacted with imines in a [3 + 2]-cycloaddition affording spirocyclopropyl oxindoles in good dr (up to 98 : 2) (Scheme 40).¹⁹⁴ Carreira and others have used this ring expansion/cyclo-

addition strategy on multiple occasions to affect racemic and stereoselective syntheses of natural products,¹⁹⁵ as well as being adapted.¹⁹⁶ Recently, Ip and Tong employed Carreira's method as the key step in the first enantioselective total synthesis of Rhynchophylline and Isoryhynchophylline using a cyclic imine (Scheme 40).¹⁹⁷

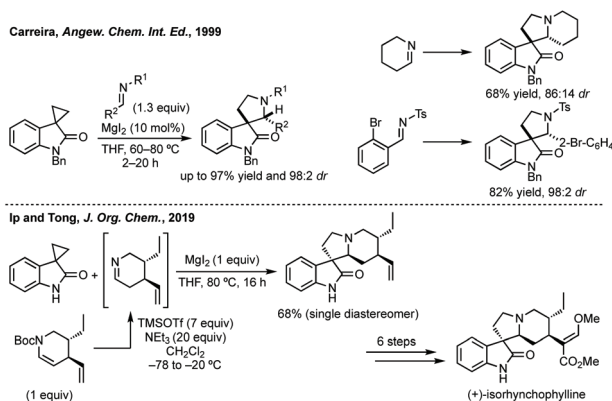
Budynina has performed a similar ring expansion in a sequential azide anion ring opening followed by a Staudinger/Wittig/Mannich reaction.¹⁹⁸ Whereas Hajra has ring expanded 3-spiroaziridinyl oxindoles using malonitrile (Scheme 41).¹⁹⁹ This type of ring expansion chemistry has also been carried out in an inverse fashion, *i.e.* Lu reacted a 3-ylidene oxindole with a vinyl aziridine (Scheme 41).²⁰⁰ 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'-spirocyclopropyl oxindole.²⁰¹

Budynina ring expanded a cyclopropane with an isatin derived ketimine (Scheme 42).²⁰² Chu, He and Liu have recently reported an enantioselective cycloaddition of vinyl cyclopropanes with isatin derived imines using ligand **42**, to form 3,2'-spiro-derivatives (Scheme 42).²⁰³

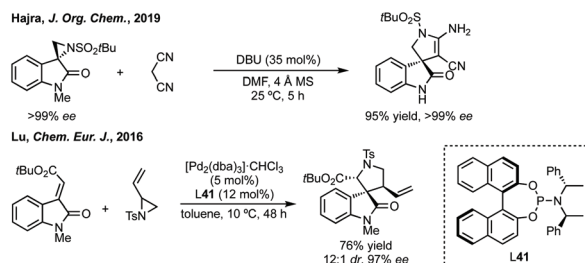
MBH carbonates. As seen throughout this review, the use of isatin derived MBH carbonates is significant to form a 1,3-dipole as a three carbon synthon.²⁰⁴ In 2017, Chen demonstrated the use of isatin derived MBH carbonates in a [3 + 2]-cycloaddition with isatin derived ketimines catalysed by bifunctional DMAP/prolinol catalyst **43** in high yield and enantioselectivity (Scheme 43).²⁰⁵ In 2018, Han and Cui



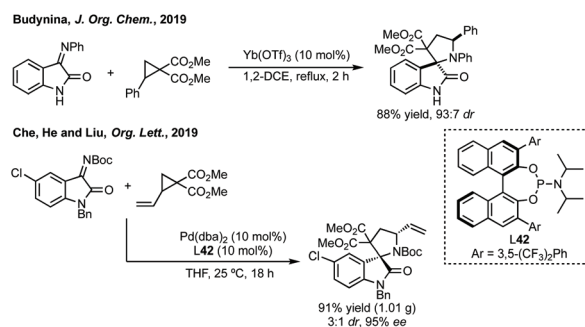
Scheme 39 Short synthesis of isatindigoindoline C using a key [3 + 2]-cycloaddition of an isatin-derived azomethine ylide and a 3-ylidene oxindole.



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

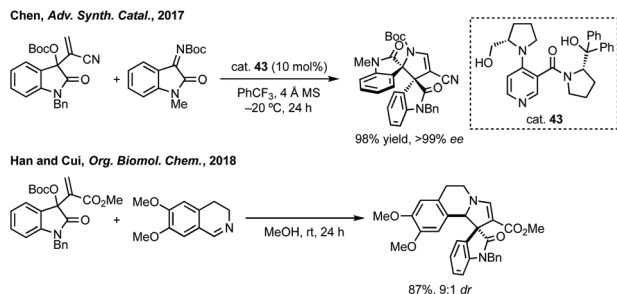


Scheme 41 3,3'-Spiropropylidene oxindoles synthesised by aziridine ring expansion.



Scheme 42 Selected examples of 3,2'-spirocyclopropylidene synthesis by cyclopropane ring expansion.





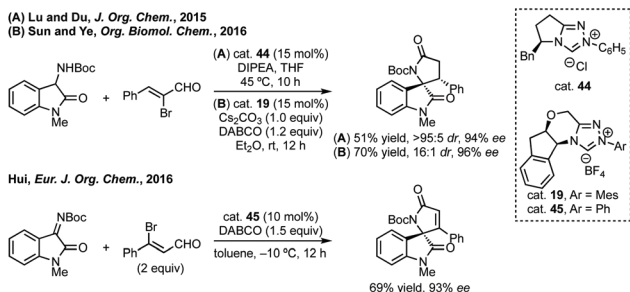
Scheme 43 Synthesis of 5-membered saturated nitrogen containing spirocycles from MBH carbonates.

reported the diastereoselective [3 + 2]-cycloaddition of isatin derived MBH carbonates and electron-rich aldimines (Scheme 43).²⁰⁶

NHC catalysis. In 2015, Lu and Du reported an NHC catalysed [3 + 2] annulation of 2-bromoaldehydes with 3-aminooxindoles (Scheme 44A).²⁰⁷ Using NHC cat. **44** Lu and Du achieved high enantioselectivity of the spirocyclic 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-bromoaldehydes and isatin *N*-Boc ketimines (Scheme 44).²⁰⁹ Using azolium cat. **45** with DABCO in toluene afforded the spirocycles in good yield, high enantioselectivity and good scope. More recently, Enders reported an NHC catalysed Mannich reaction between isatin derived ketimines and α,β -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 spirocyclic 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-iso-



Scheme 44 Selected examples of NHC catalysed [3 + 2]-cycloadditions.

thiocyanato oxindoles or (B) oxindoles with a nucleophilic C3 substituent reacting with olefins and (C) 3-ylidene oxindoles.

(A) 3-Isothiocyanato oxindoles. The use of 3-isothiocyanato oxindoles to synthesise 3,2'-spirocyclic 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**.²¹² Wang also showed cat. **45** could promote the reaction between the same oxindoles and with unsaturated pyrazolones.²¹³ At a similar time, Yuan showed that quinine derived thiocarbamate cat. **46** could promote the reaction of 3-isothiocyanato oxindole with alkylidene 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).²¹⁵ 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'-spirocyclic core of cyanogranamide.²¹⁷

(B) Nucleophilic C3 substituent. The second significant strategy to access 3,2'-spirocyclic structures 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 α,β -unsaturated acyl phosphonates as coupling partners, achieving high yield and enantioselectivity with cat. **57** (Scheme 45).^{219,220} With α,β -unsaturated aldehydes Wang used prolinol catalyst **17** to promote high enantioselectivity in the spirocyclic 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-bromoaldehydes 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'-spirocyclic products.

(C) 3-Ylidene oxindoles. A third significant method of accessing spirocyclic structures 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- δ -lactam oxindoles in high yield, ee and dr.²²⁵ Wang developed an iodine promoted Michael addition of 3-methylene oxindoles with enamino esters and concomitant DABCO mediated cyclisation to form 3,2'-spirocyclic



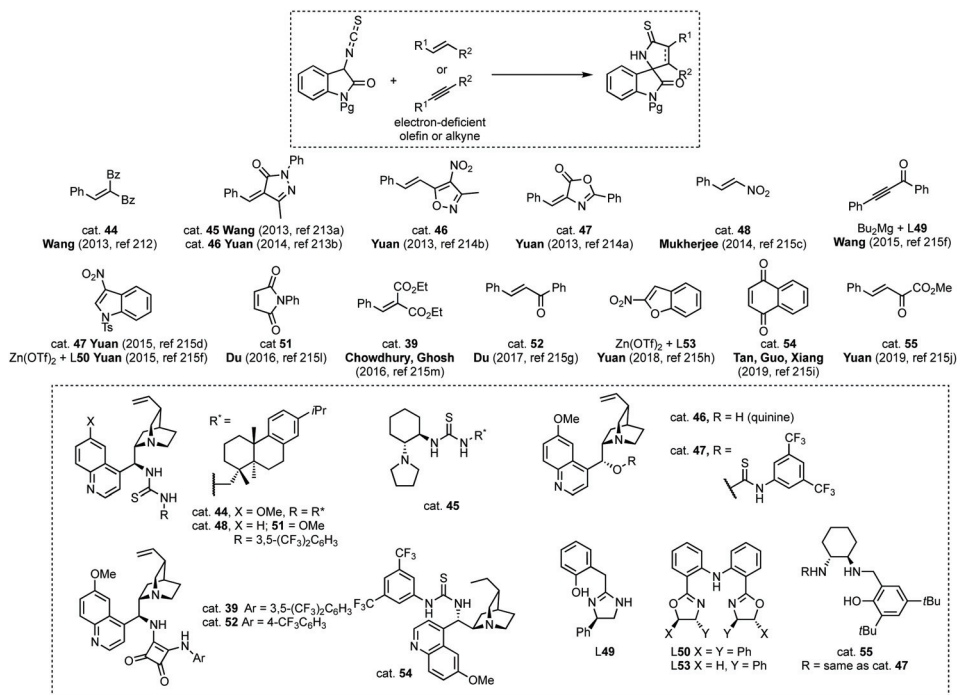
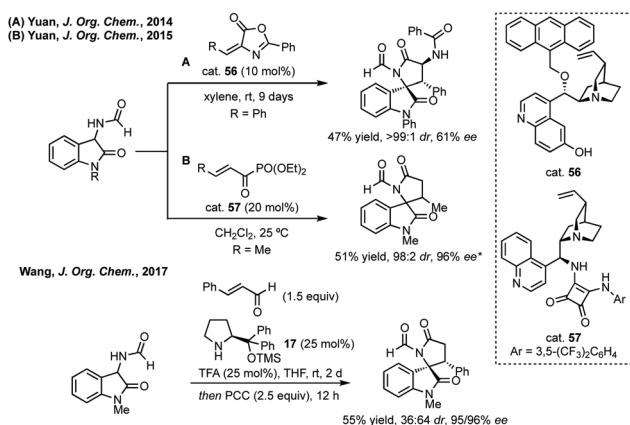
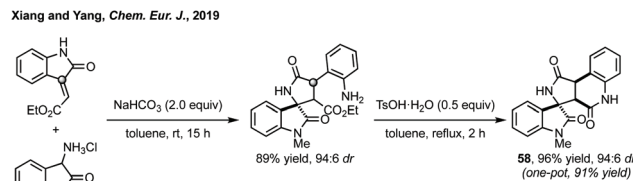


Fig. 8 Electrophiles and catalysts that have been developed for annulation of 3-isothiocyanato oxindoles.



Scheme 45 Selected examples of conjugate Michael addition/cyclisation of oxindoles with a nucleophilic C3 substituent. * Unspecified stereochemistry/unknown absolute stereochemistry.

oxindoles with good diastereoselectivity under ball-milling conditions.²²⁶ Combining strategies B and C, Xiang and Yang showed that the reaction of 3-aminooxindoles with 3-methylene oxindoles under basic conditions yielded a spiroactam which upon treatment with TsOH in one-pot cyclised to spiroactam **58** in high dr (Scheme 46).²²⁷ 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



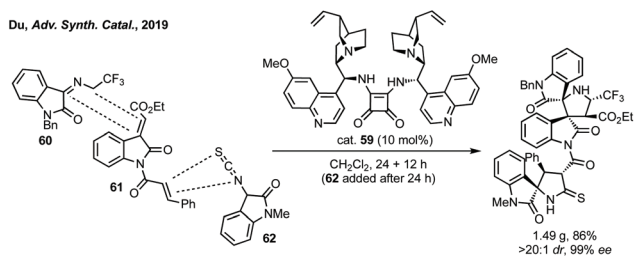
Scheme 46 Selected example of the combination of strategy B and C, using a nucleophilic C3 oxindole substituent and 3-ylidene oxindole.

isatin derived ketimines and 3-substituted oxindoles to bispirooxindoles.²²⁸

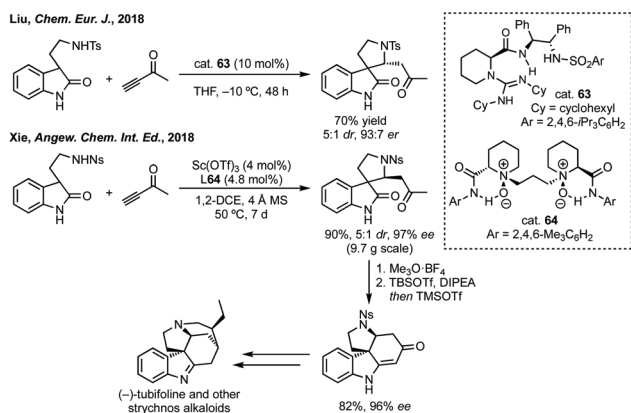
A remarkable extension of strategies A and C with dipolar cycloaddition has been developed by Du where compounds containing a spiro pyrrolidine oxindole and bispirooxindole were formed by a dual Michael/Mannich and Michael/cyclisation sequence (Scheme 47).²²⁹ Using dimeric squaramide cat. **59** the 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.

Domino Michael/Michael additions. An excellent advance in 3,3'-spiro pyrrolidine oxindole synthesis was made by Liu and at a similar time by Xie. Both teams independently developed a double Michael addition between oxindoles and alkynes with either a chiral guanidinium catalyst or a chiral *N,N'*-dioxide Sc(OTf)₃ complex (Scheme 48).²³⁰





Scheme 47 Example of the use of strategies A and C for the stereo-selective construction of seven stereocenters.

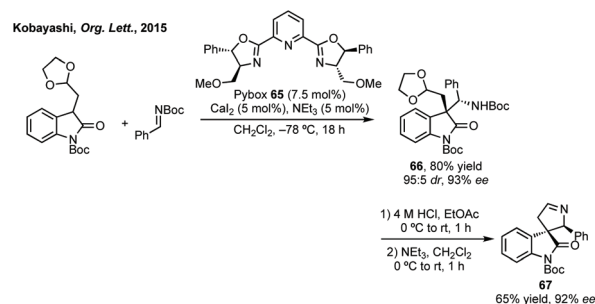


Scheme 48 Selected advances in Michael/Michael additions of alkynes.

Before this, Sasai had developed the same reaction using a chiral phosphine catalyst but with maximum 84% ee.²³¹ More recently, Wu and Zhang used a chiral bisphosphine catalyst for the same reaction.²³² 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.²³³ 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.²³⁴

Discrete coupling strategies

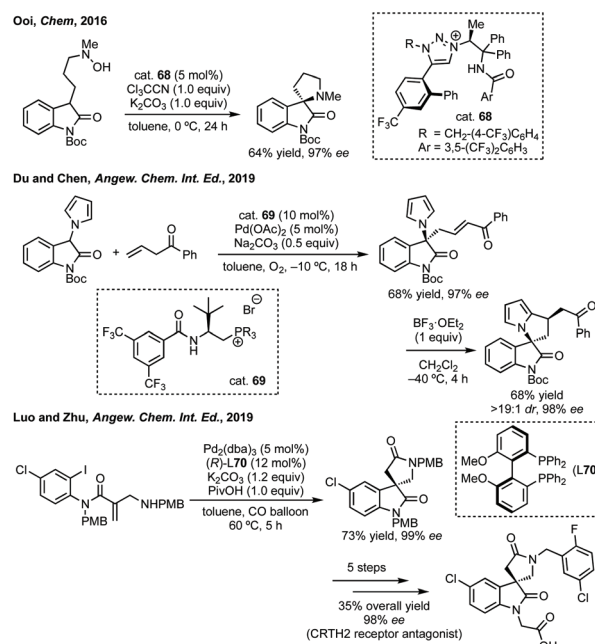
In this section strategies where a discrete coupling followed by cyclisation will be discussed. A common strategy towards spiropyrrolidine oxindoles is an asymmetric Mannich reaction using ketimines followed by cyclisation. In 2012, Lu and then Li and Wang reported significant advances in enantioselective Michael addition and allylic alkylation of nitroalkanes using *cinchona* alkaloid derived catalysts.²³⁵ Reductive cyclisation of the nitro group in the product then afforded spiro lactams in high ee. In 2015, Kobayashi developed a calcium/Pybox asymmetric Mannich reaction, which could be cyclised upon deprotection and basic cyclisation (Scheme 49).^{236,237} Using CaI₂ with Pybox ligand **65** in CH₂Cl₂ at -78 °C afforded the



Scheme 49 Enantioselective Mannich reaction followed by deprotection/cyclisation.

Mannich product in high dr (trans product favoured) and excellent enantioselectivity. From acetal product **66**, treatment with HCl followed by NEt₃ afforded 3,3'-spiropyrrolidinyl 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).²³⁸ 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).²³⁹ This remarkable reaction afforded good yields of the 3,2'-spiropyrrolidine 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'-spiropyrrolidone oxindoles from non-isatin



Scheme 50 Selected examples of phase transfer catalysed or metal-catalysed cross-coupling strategies to spiropyrrolidines. PMB = *para*-methoxybenzyl.

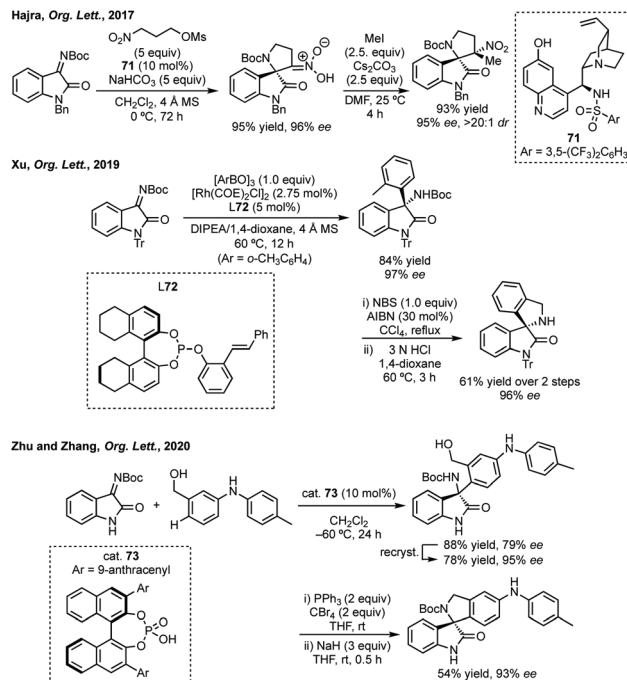


derived starting materials (Scheme 50).²⁴⁰ They employed chiral bidentate phosphine ligand L70 with Pd₂(dba)₃, K₂CO₃ and PivOH in toluene and a CO atmosphere to affect the Heck/carbonylation cascade. Notably, the methodology was limited to aryl protected lactams but high yields and enantioselectivities were observed when using the readily removable PMB group. The authors showed the application of this methodology to the synthesis of a CRTH2 receptor antagonist²⁴¹ in 6 steps in 35% overall yield and 98% ee (Scheme 50).

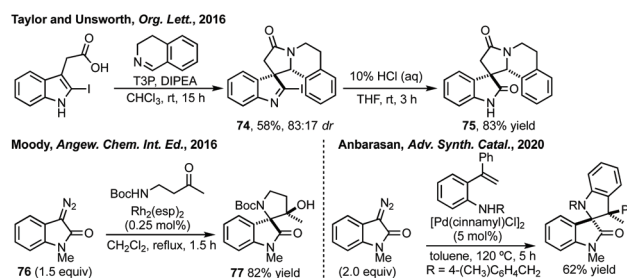
In a clearly distinct strategy Zhao and Xia developed a cross-dehydrogenative coupling of pyridines with 3-substituted oxindoles.²⁴² The pyridinium salts afforded could be reduced diastereoselectively with NaBH₄ in order to access racemic cornoxine in a rapid fashion (Scheme 51). Although the pyridine 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.²⁴³ Zhou used a triple catalysis cascade reaction to generate an isatin derived ketimine *in situ* which could then undergo Brønsted base catalysed 6π-electrocyclisation.²⁴⁴ Hajra developed an enantioselective tandem aza-Henry reaction-cyclisation of isatin-derived ketimines and nitroalkane mesylates to 3,2-spiropyrrolidine oxindoles (Scheme 52).²⁴⁵ 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 72 (Scheme 52). More recently, Zhu and Zhang reported an enantioselective *para*-C–H functionalisation of *N*-monosubstituted anilines with isatin derived ketimines using cat. 73.²⁴⁶ 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.²⁴⁷ Taylor and Unsworth at York used their previously disclosed direct imine acylation methodology²⁴⁸ to furnish indoleninyl halide 74 which upon hydrolysis with aqueous HCl formed 3,3'-spiropyrrolidone oxindole 75 in high yield and dr (Scheme 53).²⁴⁹ Further recent

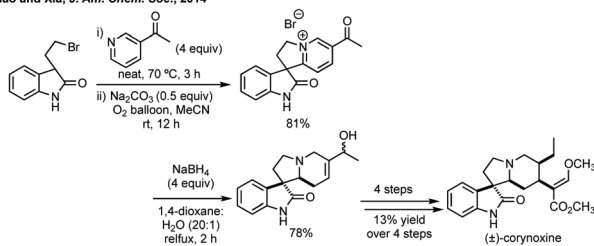


Scheme 52 Synthesis of 3,2'-spiropyrrolidine oxindoles following enantioselective additions to isatin derived ketimines.



Scheme 53 Selected examples of diastereoselective synthesis of spiropyrrolidines using spirindoleninyl halides and diazooxindoles.

Zhao and Xia, *J. Am. Chem. Soc.*, 2014

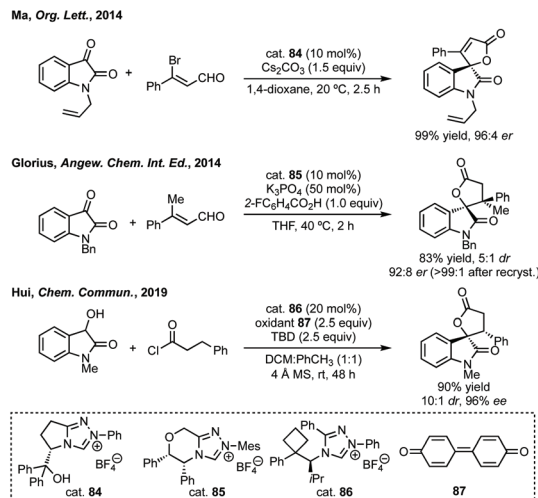


Scheme 51 Synthesis of spiropyrrolidine *via* pyridinium salts.

advances towards 3,2'-spiropyrrolidine oxindoles have been made using diazo compounds as starting materials. In 2016, Moody at Nottingham University developed a diastereoselective NH insertion of diazooxindole 76 with β-aminoketones to afford spiropyrrolidine 77 (Scheme 53).²⁵⁰ Very recently, Anbarasan reported Pd-catalysed amination of 3-diazooxindoles with *ortho*-vinyl anilines.²⁵¹

Photoredox. Zhao and Jiang have reported a photoredox asymmetric phosphoric acid catalysed combination of α-amino radicals and 3-aryloxindole radicals (Scheme 54).²⁵² The excited photoredox catalyst (dicyano-pyrazine (DPZ) derived) affects the decarboxylation of the aryl protected amino acid, generating an α-amino radical, which can combine with the 3-aryloxindole radical generated from 3-chlorooxindole with chirality induced by cat. 78. The intermediate then spontaneously cyclised in the case of the five-membered ring.

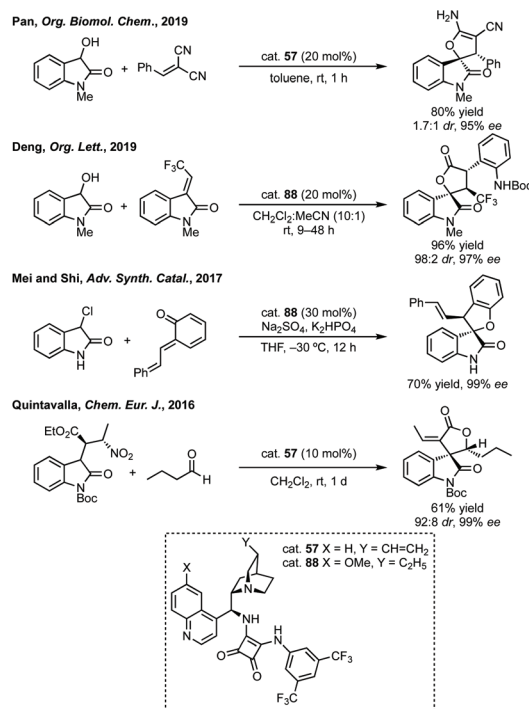




Scheme 57 Selected advances in NHC catalysed [3 + 2] annulations to spiroactones.

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 annulation 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 spiro pyrrolidines, 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 [4 + 1] annulation of 3-chlorooxindoles and *ortho*-quinone methides (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



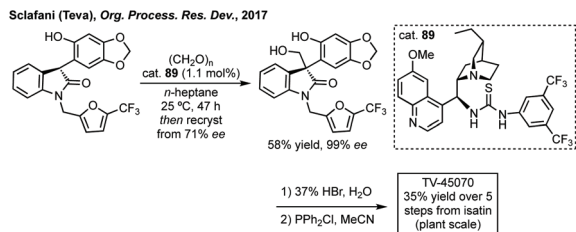
Scheme 58 Selected advances in annulations catalysed by bifunctional hydrogen bonding catalysts.

monoimines and multicomponent reactions of isonitriles, allenes and isatins.²⁸⁰

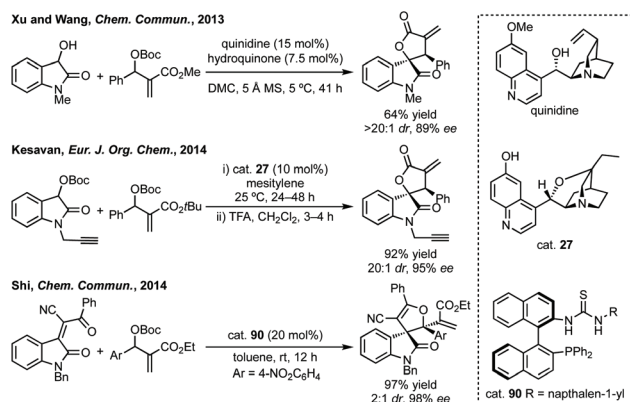
In 2016, Bisai reported an enantioselective aldol reaction of dimeric oxindoles which resulted in ring opening of one of the oxindoles, and in doing so developed a highly enantioselective thiourea catalysed aldol reaction with formaldehyde.²⁸¹ The first process scale synthesis of TV-45070 (Fig. 9) employed 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 spiroactone 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 alkylation of MBH carbonates which





Scheme 59 Plant scale synthesis of TV-45070.

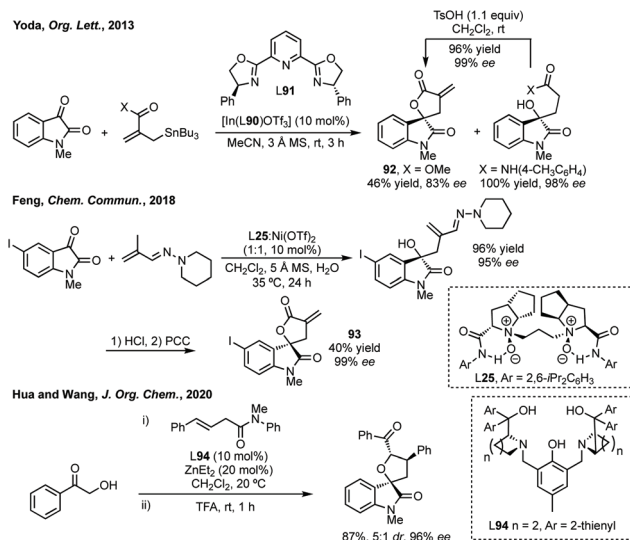


Scheme 60 Selected advances in the use of MBH carbonates to form spiro lactone and spiroTHF oxindoles.

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

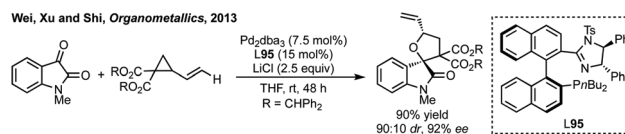
Yin has developed a Pd-catalysed cascade reaction involving dearomatisation of furans to form the THF core of the spirocycle.²⁹⁵ Other metal-mediated approaches include the use of Cu,²⁹⁶ Ti,²⁹⁷ Ru²⁹⁸ or Ni-catalysed²⁹⁹ spirocyclisations. Trost has also applied his development of Pd-allyl complexes previously discussed in the spiro pyrrolidine section to the synthesis of spiroTHFs.³⁰⁰ Similar to Moody's use of diazo compounds to synthesise spiro pyrrolidines, OH insertion/cyclisation could be used to synthesise spiroTHFs³⁰¹ and there have been many other approaches using Rh- or Cu-catalysed decomposition of diazo compounds.³⁰²



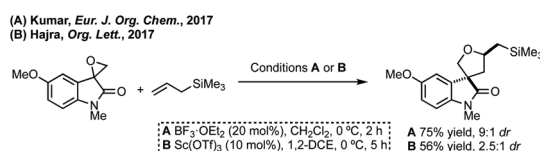
Scheme 61 Recent advances in metal-mediated spirocyclisation methods to spiroTHF oxindoles.

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 spiroTHF 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 2*H*-spirobenzofuran oxindoles.³⁰⁶

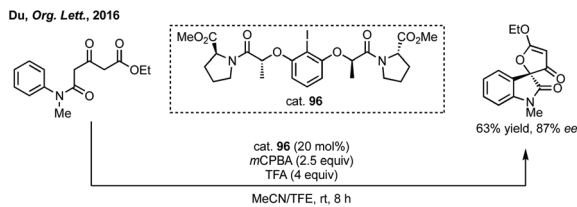


Scheme 62 Use of vinyl cyclopropanes to construct spiroTHFs.



Scheme 63 Use of spiroepoxy oxindoles in a ring opening/closure cascade.





Scheme 64 Chiral hypervalent iodine mediated asymmetric spirocyclisation.

Use of hypervalent iodine reagents. A clearly distinct strategy to access this type of spirocycle is the use of hypervalent iodine reagents.³⁰⁷ Building on the work of Gong for the synthesis of bispirooxindoles,³⁰⁸ Du developed an enantioselective spirocyclisation using catalytic chiral hypervalent iodine reagent **96** with *m*CPBA as oxidant (Scheme 64).³⁰⁹

Six-membered rings

Spirocyclohexanyl oxindoles

Applications. Satavaptan (Fig. 1) is a potent, selective Vasopressin V₂ receptor antagonist for treatment of hyponatremia.³¹⁰ Spirocyclohexane oxindoles also feature in a number of patents as anti-cancer,³¹¹ hepatitis C inhibitors³¹² and progesterone receptor modulators.³¹³

Natural product synthesis. Although not showing any notable bioactivity, gelsemine has proven to be an inspirational target within total synthesis (Fig. 10).³¹⁴ 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.³¹⁵ Mehta described an approach to spindomycin B (Fig. 10) through a Michael addition/S_NAr sequence.³¹⁶

[4 + 2]-Cycloaddition. 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.³¹⁷ Chen has developed a similar but enantioselective reaction.³¹⁸ Also in 2013, Ramachary reported the enantioselective [4 + 2] cycloaddition of alkynones and malonitrile oxindoles using cat. **97** (Scheme 65).³¹⁹ Notably, under these conditions an amino-nyne was formed between the primary amine of the *epi*-quinine derived cat. **97** due to protonation of the more Lewis basic quinuclidine nitrogen. There have been numerous related reports using malonitrile precursors³²⁰ and these reactions are also used to test new asymmetric ligands.³²¹ There

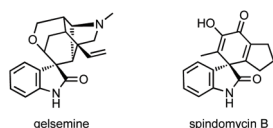
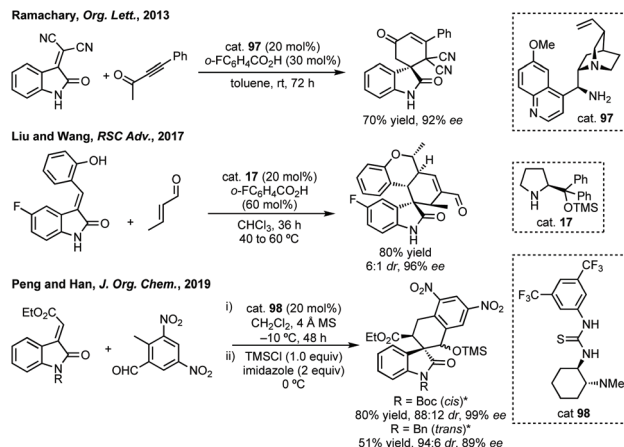


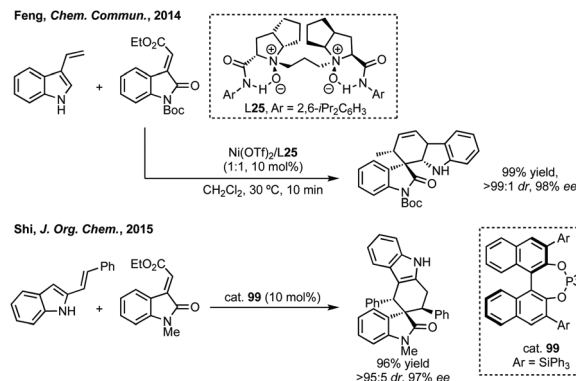
Fig. 10 Selected naturally occurring spirocyclohexane oxindole.



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

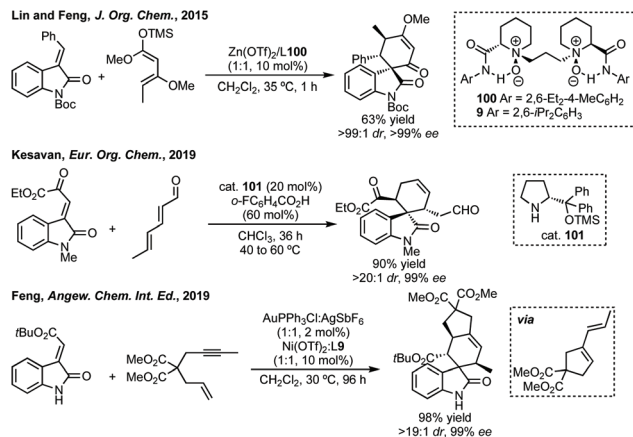
have been a number of reports of combining chromane scaffolds with spirocyclohexane oxindoles.³²² Of note is Liu and Wang's use of 3-methylene oxindoles with a phenol substituent undergoing a Michael/aldol/oxa-Michael cascade under iminium catalysis (Scheme 65).³²³ There have been many other developments of this type of annulation involving Michael/aldol³²⁴ or more elaborate³²⁵ cascade reactions employing various catalysis modes. An interesting Michael/aldol example was recently reported by Peng and Han with diastereodivergency observed depending on the oxindole *N*-protecting group (Scheme 65).³²⁶

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.³²⁷ These works laid the foundations for a body of work which provide tetrahydrocarbazoles fused with spirooxindoles.³²⁸ Notably, in 2014, Feng reported the asymmetric Diels–Alder reaction between 3-vinyl indoles and 3-methylene oxindoles using Ni catalysis (Scheme 66).³²⁹ Also, in 2015 Shi developed a similar reaction using 2-vinyl indoles using chiral phosphoric acid catalysis (Scheme 66).³³⁰ Oxygenated analogues of these tetrahydrocarbazoles, which



Scheme 66 Selected enantioselective [4 + 2] cycloadditions.



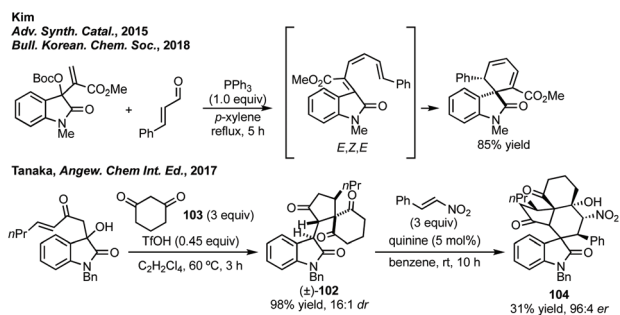


Scheme 67 Selected enantioselective Diels–Alder reactions to make spirooxindoles.

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).³³¹

Antilla described the use of chiral Mg-phosphate catalysis for an asymmetric Diels–Alder reaction.³³² For a related Diels–Alder reaction, Lin and Feng used $\text{Zn}(\text{OTf})_2$ complexed with **L100** in up to 99% ee (Scheme 67).^{333,334} In 2019, Kesavan described an asymmetric Diels–Alder reaction between 2,4-dienals and 3-methylene oxindoles catalysed by prolinol cat. **101** (Scheme 67).³³⁵ Feng has recently reported Au-catalysed cycloisomerisation followed by Ni-catalysed Diels–Alder cycloaddition to enantioenriched spirocyclohexanes (Scheme 67).³³⁶ Feng and Dong have also disclosed a $\text{Dy}(\text{OTf})_3$ -mediated ring-opening/[4 + 2]-cycloaddition of cyclobutenones and 3-methylene oxindoles.³³⁷

In terms of other cascade rearrangements, Kim has developed a diastereoselective 6π -electrocyclisation from MBH precursors.³³⁸ 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).³³⁹ In a distinct complexity-generating reaction, Tanaka could form racemic intermediate **102** in a [4 + 1] annulation of 3-methylene oxindole and di-



Scheme 68 Selected cycloadditions developed towards spirocyclohexane oxindoles.

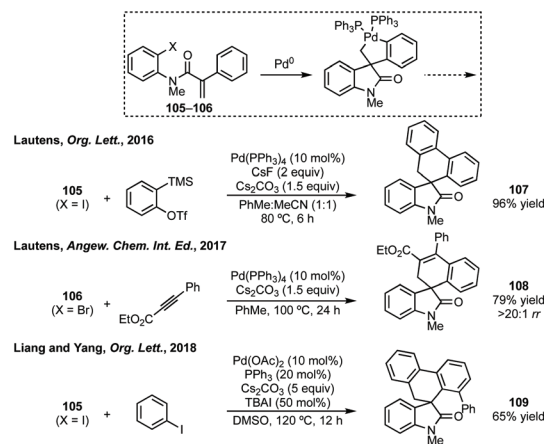
ketone **103** by treatment with TfOH (Scheme 68).³⁴⁰ In a Michael–Henry cascade reaction **102** could react with an electron-poor olefin (such as a nitroalkene) and form polycyclic spirocyclohexane oxindole containing product **104** with excellent enantioselectivity. The yields for these products 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.³⁴¹ More recently Lautens has developed a significant body of work using intercepted Pd-mediated spirocyclisations and in 2016 reported benzyne insertion to an alkylPd^{II} intermediate formed by C–H activation (Scheme 69).³⁴² This was followed by insertion of alkynes with high regioselectivity.³⁴³ These works were followed by Liang and Yang’s report on the synthesis of **109** in a triple C–H activation approach where the alkylPd^{II} intermediate is intercepted by 2 further equivalents of aryl iodide (Scheme 69).³⁴⁴ Another approach is Pd-catalysed migratory insertion of diazo compounds and Michael addition.³⁴⁵

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).³⁴⁶ Generally, electron-rich oxindoles were used *i.e.* phenylfused oxindoles, however, the enantioselectivity was highest for the synthesis of oxindole **110** using cat. **111**.

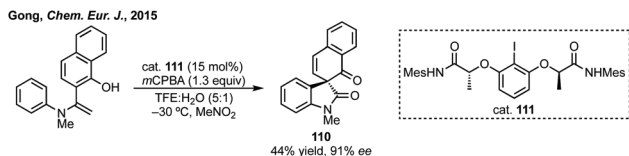
Spiropiperidinyl oxindoles

Applications. In the last decade spiro-piperidinyl oxindoles have been synthesised for medicinal chemistry applications against cancer,³⁴⁷ CNS disorders,³⁴⁸ renal failure,³⁴⁹ treatment of Dengue virus infection³⁵⁰ as well as other applications.³⁵¹ Surugatoxin related to neosurugatoxin is also a potent human toxin (Fig. 1).³⁵² Most prominently cipargamin (NITD609 or

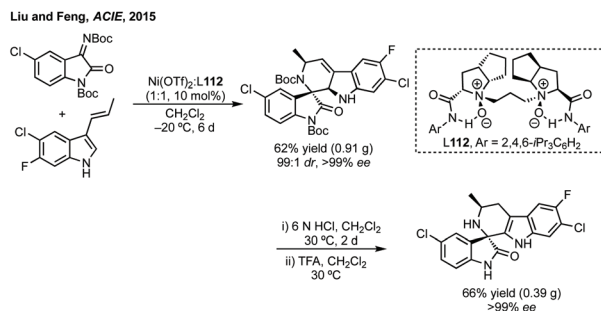


Scheme 69 Selected metal-mediated C–H activation approaches via alkyl-Pd^{II} intermediates.





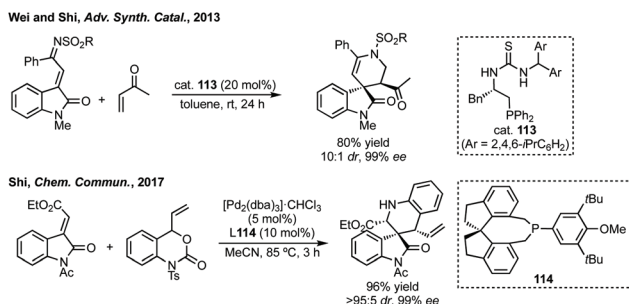
Scheme 70 Chiral iodine mediated spirocyclohexene oxindole formation.



Scheme 71 Concise synthesis of anti-malarial cipargamin.

KAE609) has been developed as an anti-malarial agent.³⁵³ Shibasaki used a key asymmetric alkylation of an isatin ketimine to synthesise cipargamin.³⁵⁴ Liu and Feng synthesised cipargamin in an aza-Diels–Alder process employing 3-vinyl indoles and Ni catalysis (Scheme 71).³⁵⁵

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.³⁵⁶ 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).³⁵⁷ In metal-mediated approaches, gold catalysed spirocyclisation of *in situ* generated indoles and isatins was reported by Subba Reddy.³⁵⁸ Related to Liu and Feng's reaction (ref. 355), Kumar developed an enantioselective aza-Diels Alder reaction catalysed by Dy(OTf)₃ and a ligand similar to **112** where Ar = 2,6-*i*Pr₂C₆H₄.³⁵⁹ Feng, Li and Xiao have independently developed 1,5-hydride transfer reactions to spiro-piperidines.³⁶⁰ More recently, Shi

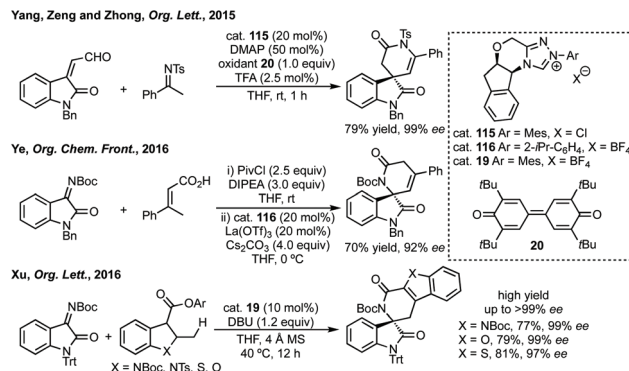


Scheme 72 Selected enantioselective [4 + 2]-cycloadditions.

developed a Pd-catalysed decarboxylative [4 + 2] cycloaddition strategy using vinyl benzoxazinones and 3-methylene oxindoles (Scheme 72).³⁶¹

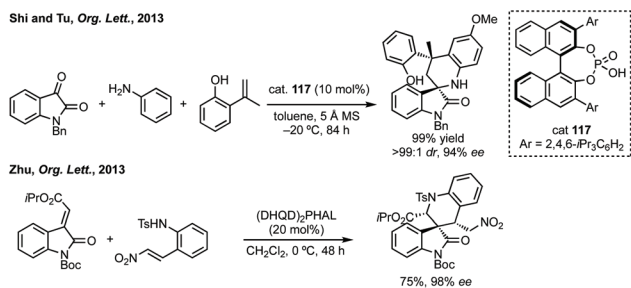
NHC catalysis. In 2013, Chi reported the NHC catalysed [3 + 3] annulation of α -aryl esters and isatin derived α,β -unsaturated ketimines to afford spirocyclic- δ -lactams in moderate diastereoselectivity in up to 62% ee with an asymmetric NHC.³⁶² Yang, Zeng and Zhong used asymmetric cat. **115** to make 3,4'-spiro-piperidine oxindoles from isatin derived α,β -unsaturated aldehydes and imines (Scheme 73).³⁶³ 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).³⁶⁴ Xu generated *ortho*-quinodimethanes to undergo [4 + 2] annulation with isatin ketimines using cat. **19** producing β -carboline spirooxindoles (Scheme 73).³⁶⁵ 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.³⁶⁶ Enders also recently reported related [3 + 3] annulations of isatin derived enals and cyclic *N*-sulfonyl ketimines.³⁶⁷

Cascade reactions. Shi and Tu reported an enantioselective Povarov reaction using asymmetric phosphoric acid cat. **117** affording 3,2'-spiro-piperidine scaffolds in up to 97% ee.^{368,369} 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.³⁷⁰ 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'-spiro-piperidine oxindoles (Scheme 74).³⁷¹ 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'-spiro-piperidine oxindoles.³⁷² Related reactions include aza-Michael/Michael addition, Michael/Mannich reaction, Michael addition/Pictet–Spengler, Michael/aldol,



Scheme 73 NHC catalysed cycloadditions to spiro- δ -lactams.

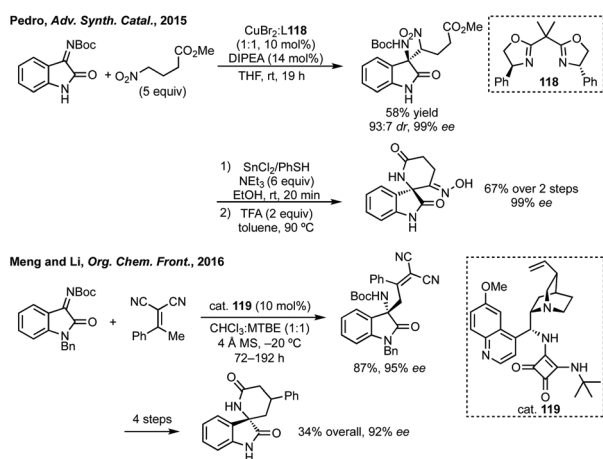




Scheme 74 Selected examples of phosphoric acid catalysed cascade reactions.

Mannich/hemi-aminalisation cascade reactions.³⁷³ 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.³⁷⁴ Due to the importance of cipargamin, synthesis of similar β -carboline spirooxindoles is very popular.³⁷⁵ 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,³⁷⁶ of note is Shi's enantioselective [3 + 3] annulation.³⁷⁷ Very recent advances include a copper catalysed aza-Henry reaction by Wang and Zhou³⁷⁸ and HFIP mediated C(sp³)-H functionalisation by hydride transfer.³⁷⁹

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-nitrobutyrate catalysed by a Cu(II)-Box system, which could be deprotected to undergo spontaneous cyclisation to the 3,2'-spiroperidine oxindole (Scheme 75).³⁸⁰ Hajra described an organocatalytic addition of a nitroalkyl group followed by intramolecular alkylation (Scheme 52).²⁴⁵ Meng and Li, and more recently Nakamura, reported enantioselective vinylogous Mannich reactions to generate intermediates which could be



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

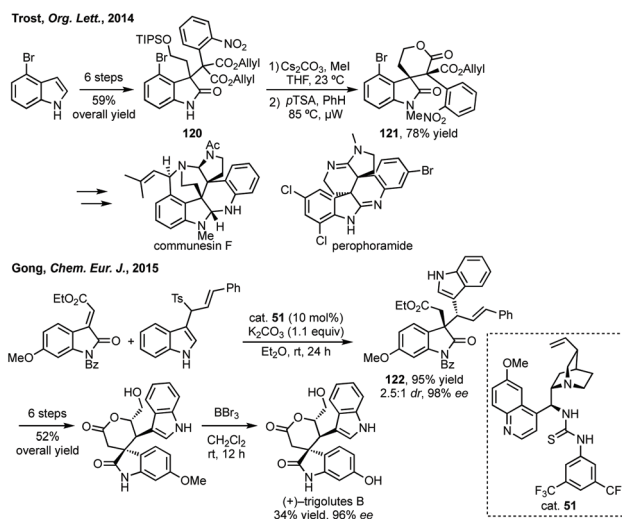
deprotected and cyclised to spiroactam products (Scheme 75).³⁸¹ Han has also developed an enantioselective Mannich reaction which upon deprotection of the generated Boc-protected amine undergoes lactamisation to the six-membered spirocycle.³⁸²

Spirotetrahydropyranyl oxindoles

Applications. SpiroTHP oxindoles have found application in induction of apoptosis,³⁸³ as anti-malarials,³⁸⁴ among others.³⁸⁵

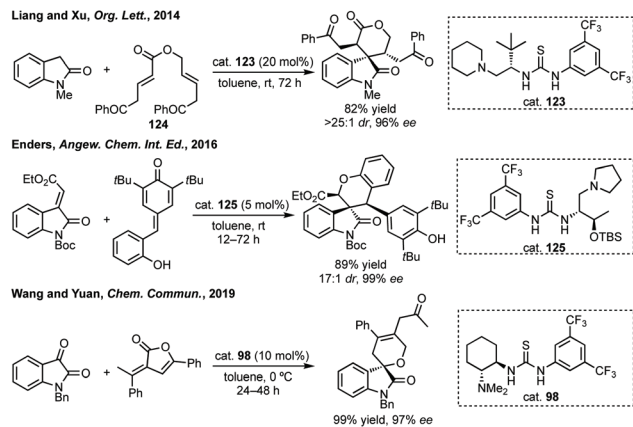
Natural product synthesis. Trost cyclised **120** to give cyclolactone **121** in 92% yield as one diastereomer as an intermediate for the total synthesis of communesin F and perophoramide (Scheme 76).³⁸⁶ Gong reported the first total synthesis of (+)-trigolutes B utilising an enantioselective substitution 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 cat. **123** in a double Michael addition cascade between *N*-methyl oxindole and **124** (Scheme 77).³⁸⁹ Using thiourea cat. **125** Enders developed an oxa-Michael/1,6-addition reaction to form 3,3'-spiroTHP oxindoles in high yield an enantioselectivity (Scheme 77).³⁹⁰ Zeng and Zhong reported an enantioselective Michael/aldol/hemiacetalisation process using iminium catalysis.³⁹¹ Han has developed an enantioselective vinylogous aldol/cyclisation/ring-opening cascade of 3-methylene oxindoles and isatins.³⁹² 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.^{393,394} 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).³⁹⁵ Some of these Michael/cyclisation procedures can be deemed formal hetero-Diels-Alder reactions.³⁹⁶



Scheme 76 Selected examples of spiroTHP oxindole synthesis in total synthesis.



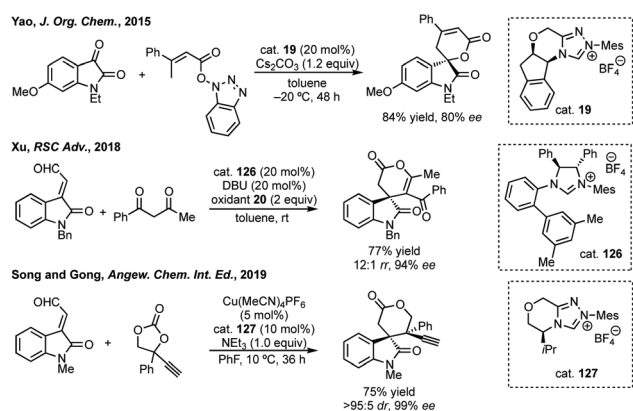


Scheme 77 Selected cascade reactions catalysed by thiourea catalysts.

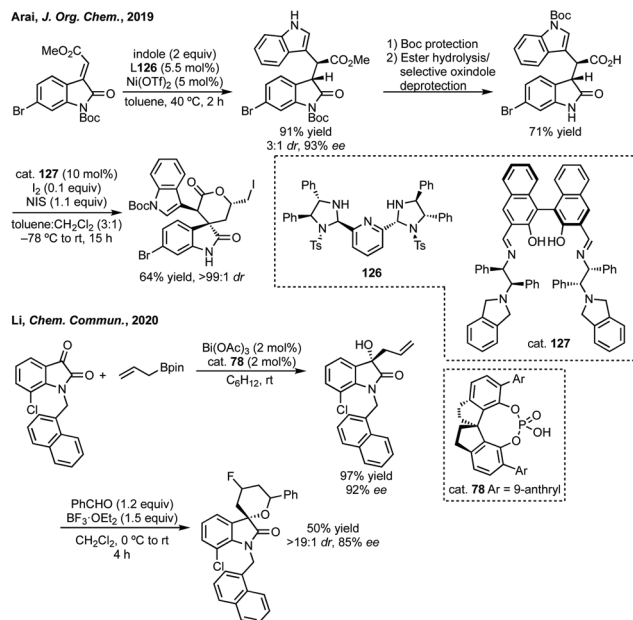
Recently, Xiao has used *ortho*-quinone methides derived *in situ* from oxindole *ortho*-hydroxybenzyl alcohols by acid in [4 + 2] annulations with 2,5-dialkylfurans or 1,3-diketones as dienophiles.³⁹⁷ These starting materials can also be used in a bis-electrophile coupling in a [4 + 2] annulation (as well as [4 + 1] annulation if a pyridinium salt is used instead of a bromide leaving group).³⁹⁸ THP fused indoles have been synthesised by enantioselective aldol/chloroetherification/aromatisation, as well as C–O coupling.³⁹⁹ MBH carbonates have also been used for [4 + 2]-annulations.⁴⁰⁰

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).⁴⁰¹ 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.⁴⁰² In a similar reaction, Xu reported the annulation of 3-ylidene oxindoles with 1,3-dicarbonyls (Scheme 78).⁴⁰³ In an excellent application of dual NHC and Cu-catalysis, Song and Gong used ethylethylene carbonates in a [3 + 3]-annulation of 3-ylidene oxindoles (Scheme 78).⁴⁰⁴

Stepwise approaches. Feng has employed a Mg/chiral N,N' -dioxide catalyst system for a hetero Diels–Alder reaction.⁴⁰⁵ Li has recently reported a Bi/chiral phosphoric acid 77 catalysed



Scheme 78 Selected NHC catalysed cycloadditions.



Scheme 79 Selected examples of stepwise synthesis of spiroTHP oxindoles by nucleophilic addition.

allylation of isatins which could be further elaborated to spiroTHP products (Scheme 79).⁴⁰⁶ Arai has employed a Ts-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).⁴⁰⁷

In other approaches, Subba Reddy has developed a $\text{BF}_3 \cdot \text{OEt}_2$ mediated Prins cascade cyclisation between aldehydes and butanamides to furnish spiroTHP oxindoles in high yield and good dr.⁴⁰⁸ Hu used Rh-carbenes generated from 3-diazo oxindoles to undergo C–H insertion/aldol condensation to afford spiroTHP oxindoles in high yield and diastereoselectivity.⁴⁰⁹ Another example of C–H activation has been shown by Messaoudi with glycosides.⁴¹⁰ The intramolecular Co-catalysed Pauson–Khand cyclisation of 1,7-enynes generated 3,2'-spiroTHPs with high diastereoselectivity.⁴¹¹

Seven-membered rings

Applications

Natural products containing seven-membered spirocyclic oxindoles are predominantly bridged carbocyclic examples of gelsemium alkaloids.⁴¹² There are not many examples of these rings in medicinal chemistry, though nitrogen containing examples do feature in some patents.⁴¹³ A spiroazepane oxindole was synthesised as a cipargamin analogue with antimalarial activity,¹⁶ and an example with activity against a prostate cancer target (Fig. 1).⁴¹⁴ 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



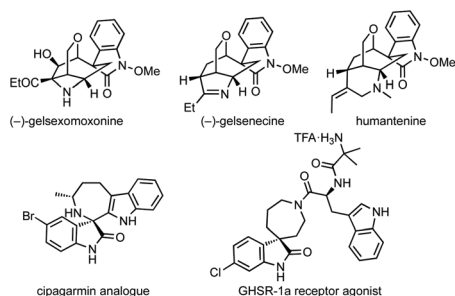


Fig. 11 Selected bioactive seven-membered rings.

examples.⁴¹⁵ 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

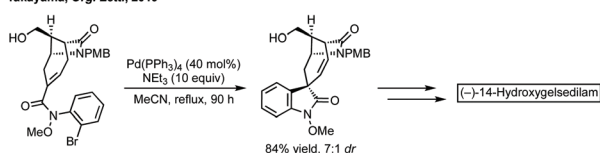
Total synthesis efforts centre around the synthesis of gelsemium alkaloids. Carreira has described elegant approaches to gelsemoxonine (see Fig. 11 for structure).⁴¹⁶ Ferreira constructed the oxindole of gelsencine with an oxidative cyclisation of a Weinreb amide with an aromatic ring.⁴¹⁷ Fukuyama and Ma have independently described divergent syntheses to many gelsedine type alkaloids.⁴¹⁸ Takayama recently described an asymmetric synthesis of (–)-14-hydroxygelsencine and six other gelsemium alkaloids.⁴¹⁹ 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 aza-*o*-quinone methides or azoalkenes to form spiro-benzazepinones or spiro-diazepinones (Scheme 81).⁴²⁰ Using cat. **128** with Cs₂CO₃ to form the aza-*o*-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**.

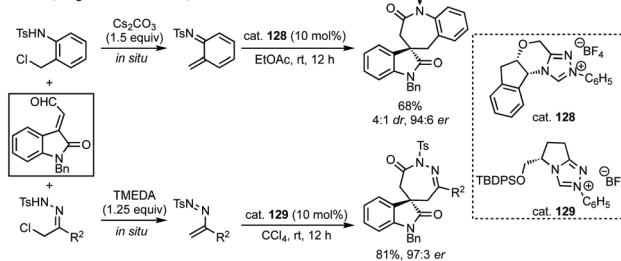
Li developed an NHC catalysed enantioselective synthesis of spirobenzoxepinones in a [4 + 3] cycloaddition of isatin derived enals and quinone methides (Scheme 82).⁴²¹ High enantioselectivity (up to >99% ee and >20 : 1 dr) was achieved using triazolium cat. **130** in combination with NaOAc in 1,2-dichloroethane. Enders published a similar reaction a month after Li's study, which employed cat. **131** to achieve up to 95 : 5

Takayama, *Org. Lett.*, 2019



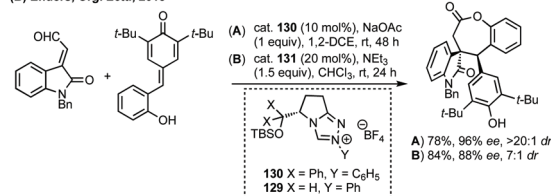
Scheme 80 Pd-Catalysed Heck reaction as key step in the total synthesis of (–)-14-hydroxygelsedilam.

Enders, *Angew. Chem. Int. Ed.*, 2016



Scheme 81 [4 + 3]-Cycloadditions with 3-ylidene oxindoles for 7-membered ring synthesis.

(A) Li, *Adv. Synth. Catal.*, 2018
(B) Enders, *Org. Lett.*, 2018



Scheme 82 Isatin-derived enals in [4 + 3] cycloaddition reactions.

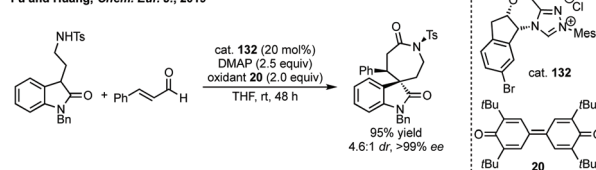
er and good dr.⁴²² This was followed by work by Yan Li and Ye on a related [4 + 3]-cycloaddition of isatin derived enals and aurone-derived azadienes.⁴²³ Using a similar NHC catalyst interesting spiroazepinones were formed with high enantioselectivity and diastereoselectivity. The compounds exhibited 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).⁴²⁴ Song and Gong's previously discussed excellent Cu/NHC dual catalysis could be used with ethynyl benzoxazinones to construct chiral azepines.⁴⁰⁴

MBH carbonates

Chen and coworkers reported a [4 + 3] cycloaddition of a bromo-substituted MBH derivative and an aza-*o*-quinone methide precursor (Scheme 84).⁴²⁵ Chen used tri-(4-fluoro) phenyl phosphine as a Lewis base to form an allylic ylide from the MBH precursor and Cs₂CO₃ as base to generate the aza-*o*-quinone methide. Xu published a related reaction at a similar time,⁴²⁶ using tributyl phosphine as Lewis base catalysis with a related MBH precursor and a Boc protected aza-*o*-quinone

Fu and Huang, *Chem. Eur. J.*, 2019



Scheme 83 Selected [4 + 3]-annulation reaction of oxotryptamines.



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 stereoselective 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 could 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.

Acknowledgements

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