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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



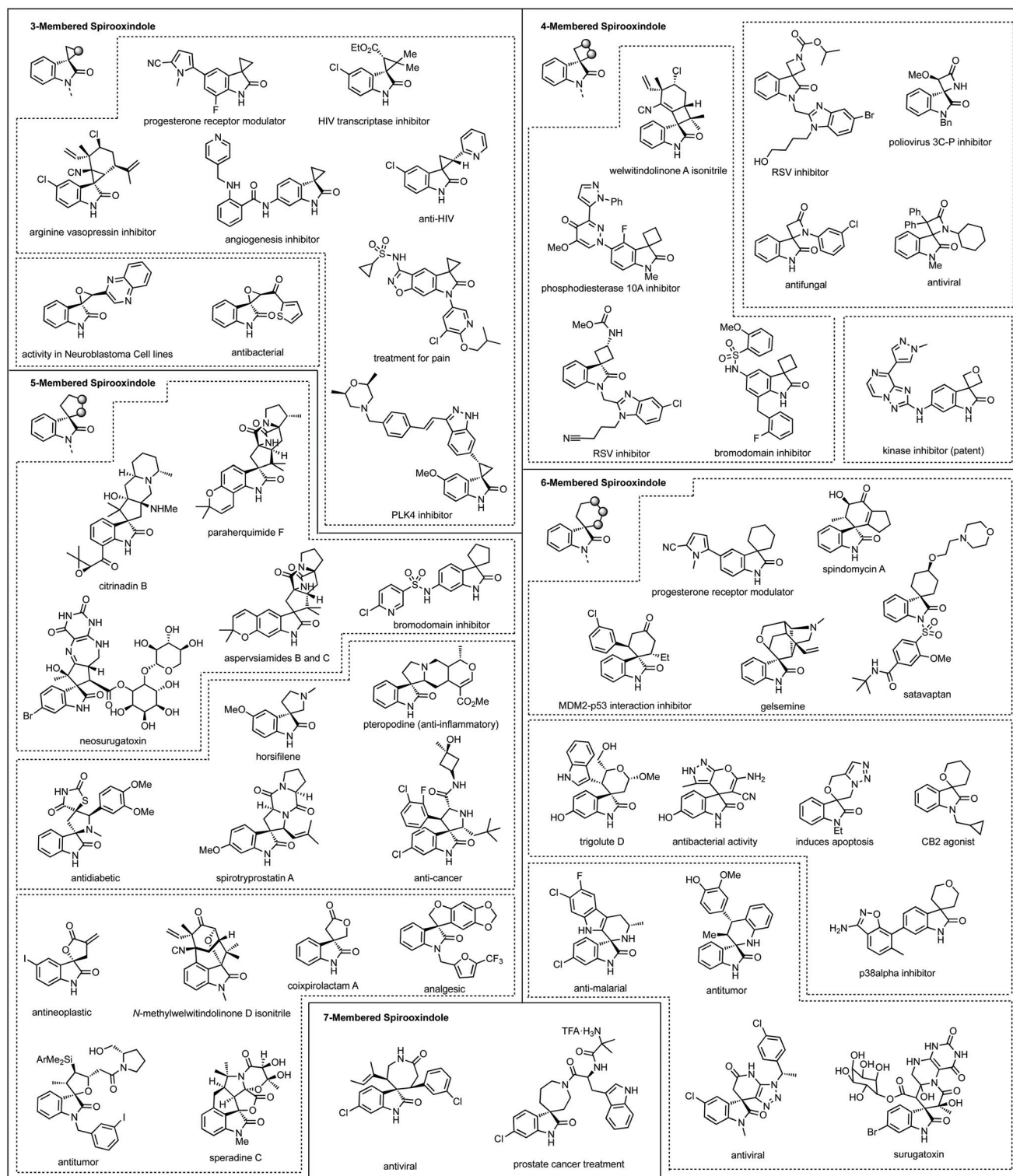


Fig. 1 Bioactive and naturally occurring spirooxindoles.

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



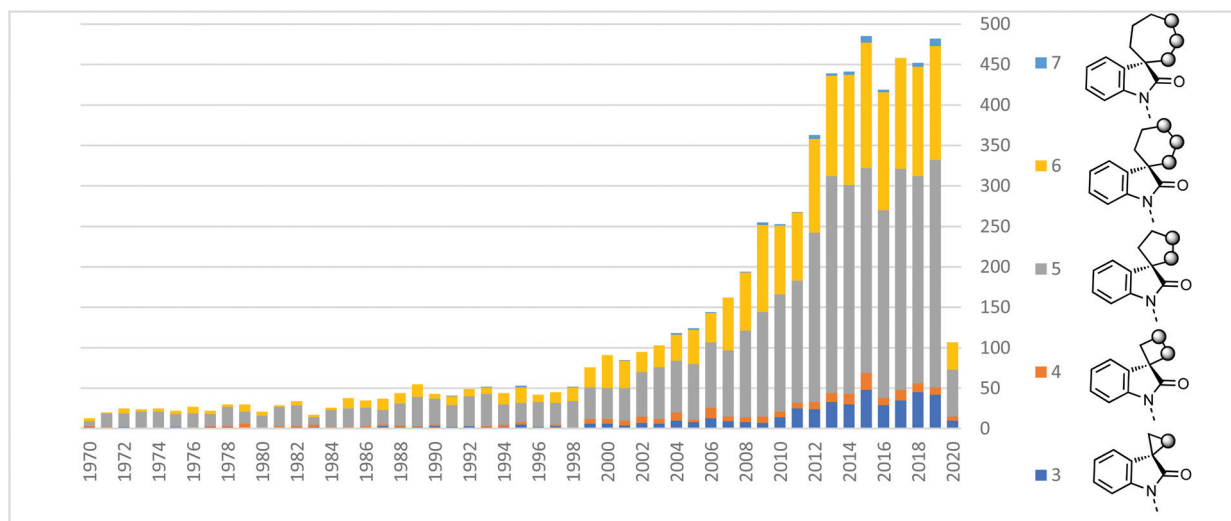
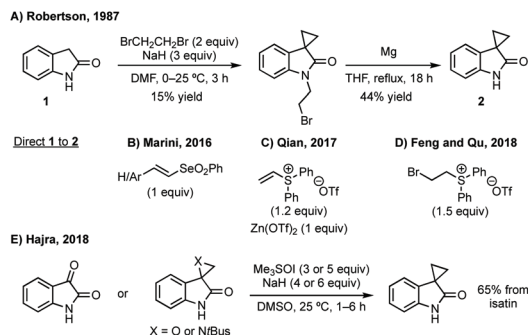


Fig. 2 Incidence of 3- to 7-membered spirooxindoles in the literature up to April 2020. No. of heteroatoms in ring ≤ 1 .¹⁵

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.



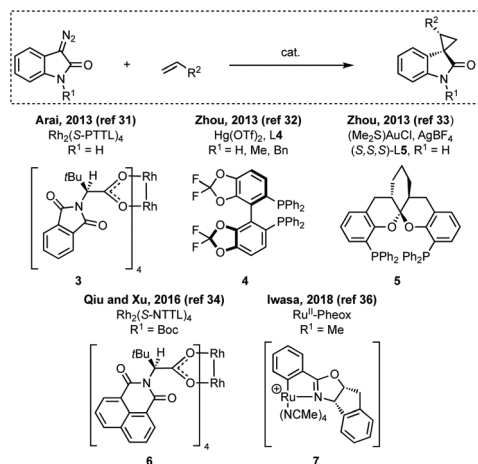
Scheme 1 Summary of recent advances in direct cyclopropanation of unprotected oxindoles.

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-ylidene oxindoles 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-

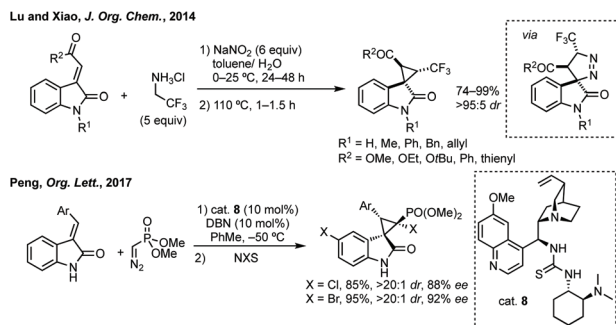




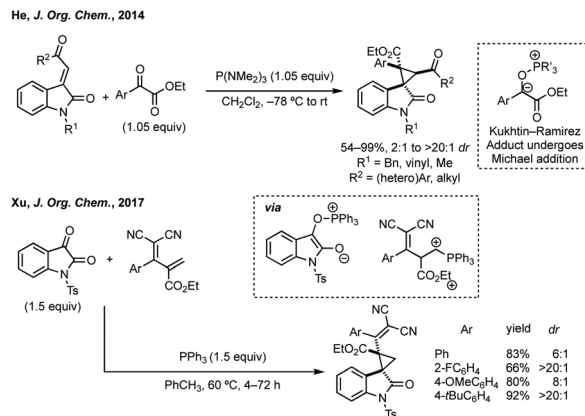
Scheme 2 Advances in enantioselective cyclopropanation of 3-diazoindoles.

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-trifluorodiazooethane 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



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

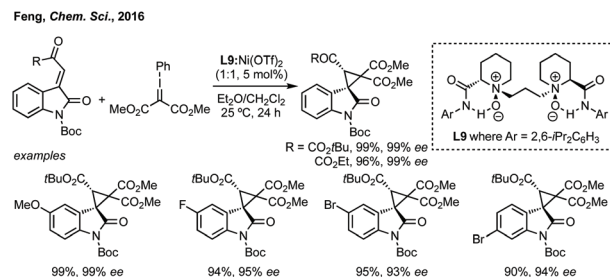


Scheme 4 P(NMe₂)₃-mediated reductive cyclopropanation via Kukhtin-Ramirez (K-R) adduct and K-R adduct reaction with diene activated by PPh₃.

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

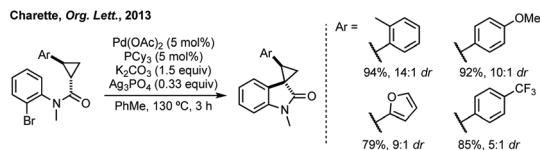
Du developed a Michael addition/alkylation cascade reaction between 3-chlorooxindoles and arylidenepyrazolones, alkenyl thiazolones (also developed by Sheng and Feng) or, more recently, 2,3-dioxypyrolidines.⁴⁶ In a quite distinct method, a Ni-catalysed enantioselective cyclopropanation developed by Feng 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

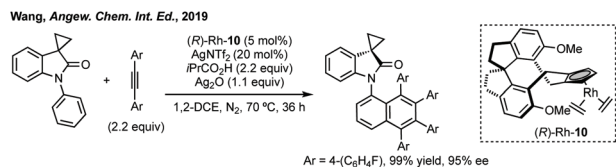


Scheme 5 Ni-Catalysed enantioselective cyclopropanation with phenyliodonium derived ylides.





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

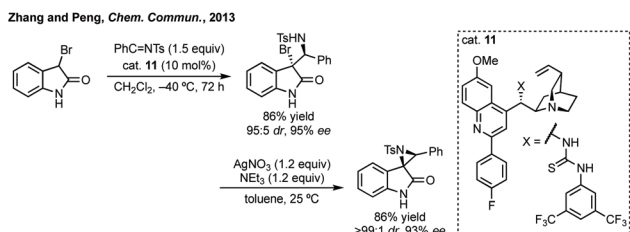
Spiroaziridinyloxindoles

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.

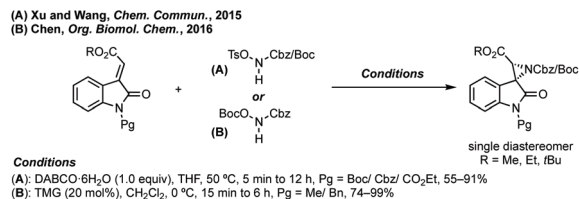
From 3-bromooxindoles. Zhang and Peng employed 3-bromooxindoles as nucleophiles in an enantioselective Mannich reaction catalysed by *cinchona* alkaloid derived cat. **11** (Scheme 8).⁵¹ Cyclisation mediated by silver nitrate afforded the aziridine in high yield and with retention of the ee induced in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

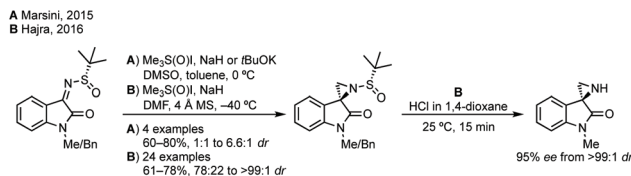
Aziridination of isatin ketimines. A team led by Marsini at Boehringer Ingelheim reported a diastereoselective aziridination of *N-tert*-butanesulfinyl ketimino esters at the end of 2015



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.

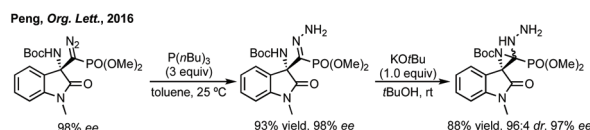
(Scheme 10).⁵⁴ At a similar time Hajra reported the same reaction with higher diastereoselectivity (up to >99:1 dr vs. 6.6:1 dr).⁵⁵ Both reports use trimethylsulfoxonium iodide with either NaH or *t*BuOK and Hajra found that using DMF as solvent at lower temperature gave much higher diastereoselectivity. Hajra demonstrated one example of deprotection of the sulfinamide 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.

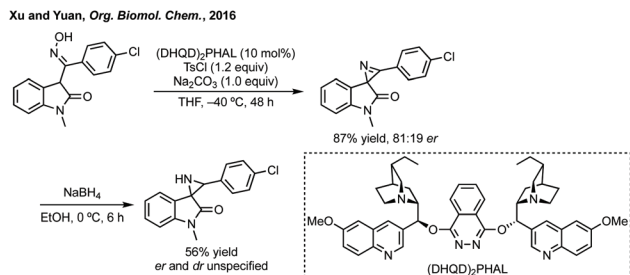
Spiroepoxy oxindoles

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



Scheme 11 Synthesis of enantioenriched spiroaziridine.



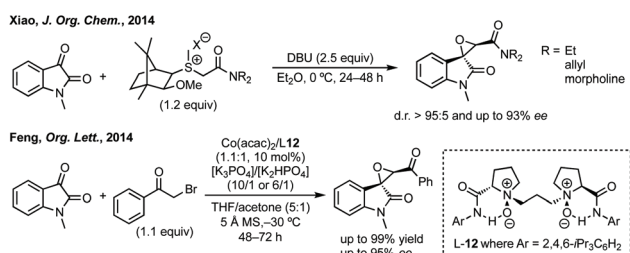


Scheme 12 Asymmetric Neber reaction followed by reduction to spiroaziridine.

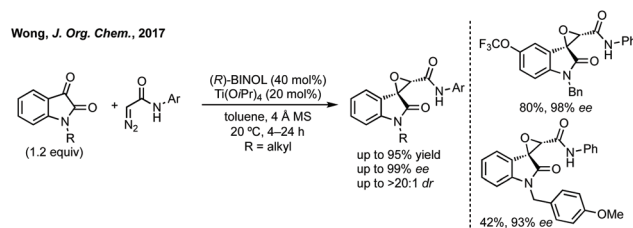
activity in Neuroblastoma cell lines (Fig. 1).⁵⁸ Spiro-epoxyoxindoles are also attractive synthetic building blocks.⁵⁹

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

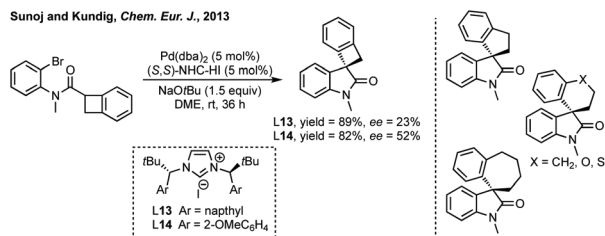
Natural product synthesis. Welwitindolinone A (Fig. 1) has inspired many approaches in total synthesis from the Baran⁷⁸ and Wood laboratories.⁷⁹

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-



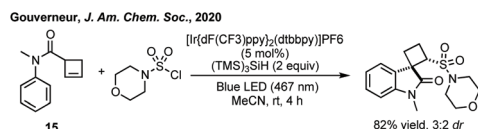


Scheme 15 Pd-Catalysed enantioselective C–H arylation.

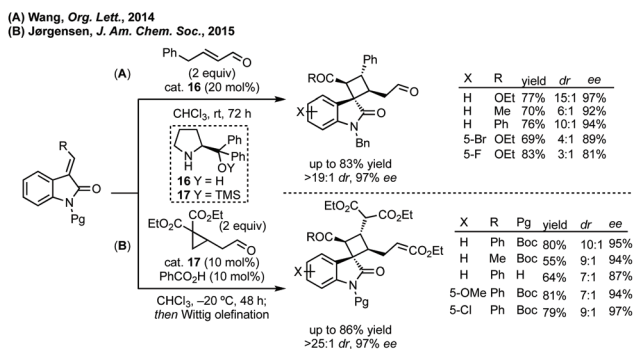
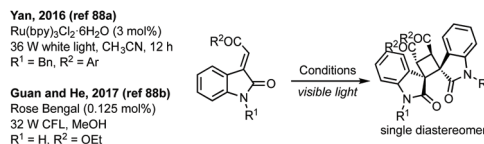
lic cascade reaction.^{82,83} Xu could form the same unsubstituted cyclobutane, as well as 5- and 6-membered analogues, in an intramolecular 1,5-HAT using aryl iodides by visible light photoredox catalysis.⁸⁴ Gouverneur recently developed a silyl radical-mediated hydrosulfamoylation using sulfonyl chlorides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

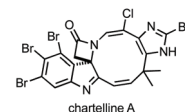
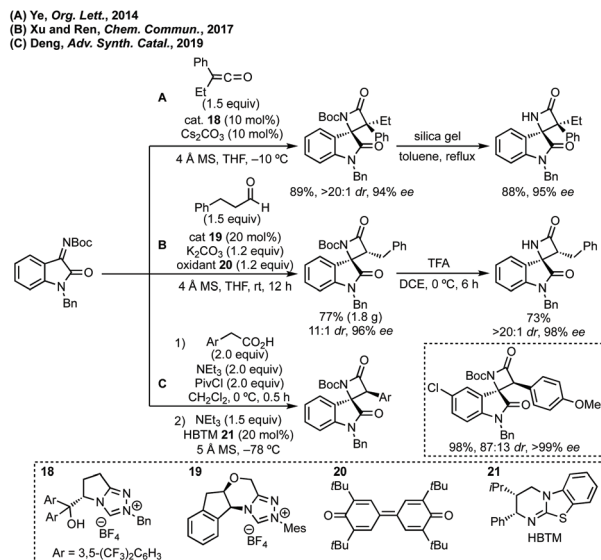


Fig. 4 Structure of chartelline A.



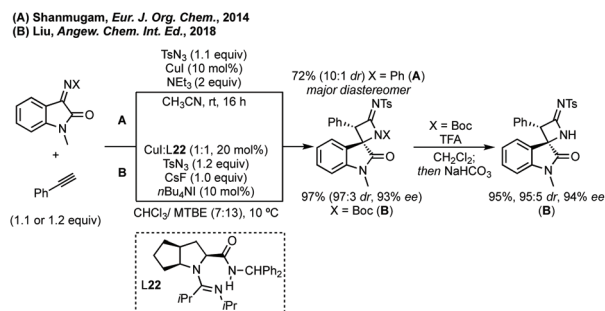


Scheme 19 Organocatalysed beta-lactam formation from isatin derived ketimines.

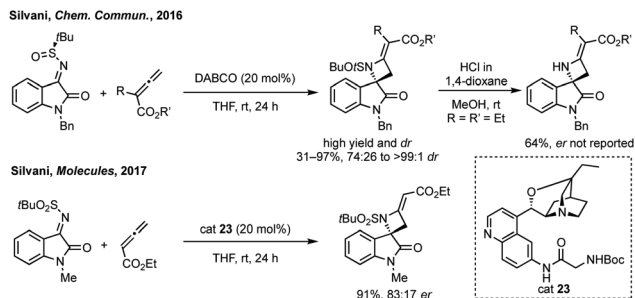
Deng's work does not use an NHC catalyst and uses a relatively more stable starting material while yielding the products in very high enantioselectivity.

Annulations using Cu/guanidinium catalysis. In 2014, Shanmugam reported a copper-catalysed one-pot, three-component diastereoselective synthesis of 3-spiroazetidinimine-2-oxindoles as masked β -lactams (Scheme 20A).⁹⁸ The spirocycle was built with high *anti*-diastereoselectivity.⁹⁹ In 2018, Liu advanced this type of reaction in a highly diastereoselective and enantioselective variant using a chiral guanidinium ligand L22 (Scheme 20B).¹⁰⁰

Azetidines from allene activation. The two main advances in the synthesis of spiroazetidine oxindoles (non-2-azetidinone structures) are from the Silvani lab in 2016 and 2017 involving allene activation. In 2016, Silvani reported a DABCO catalysed annulation of *tert*-butyl sulfinyl ketimines with allenes to form spiroazetidinyl oxindoles in high dr (Scheme 21).¹⁰¹ This could be followed by HCl mediated deprotection of the Ellman auxiliary affording the spiroazetidine in 64% yield. In 2017, Silvani published a follow up study using *cinchona* derived



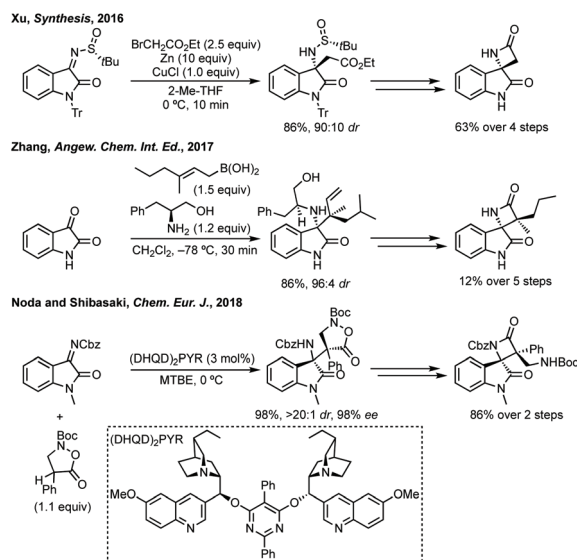
Scheme 20 Cu-Catalysed one-pot, three component synthesis of spiroazetidinimine oxindoles from isatin derived ketimines.



Scheme 21 Diastereoselective formal 2 + 2 annulation of *N*-sulfinylketimines and allenes by Silvani. Development of an enantioselective reaction employing a quinine derived nucleophilic catalyst with *N*-sulfonylketimines by the same authors.

organocatalyst 23 for the same reaction with a *t*Bus protecting group instead of the Ellman auxiliary and generating the spiroazetidine in up to 83 : 17 er (Scheme 21).¹⁰²

By nucleophilic addition. Other recent advances involve nucleophilic addition to isatin or isatin derived ketimines. In 2016, Xu developed an asymmetric Reformatsky reaction of *tert*-butyl sulfinyl isatin ketimines and ethyl bromoacetate to afford a disubstituted isatin in high yield with high diastereoselectivity (Scheme 22).¹⁰³ Zhang developed an asymmetric allylboration of isatin mediated by a chiral amino alcohol (Scheme 22).¹⁰⁴ Both Xu and Zhang showed how this diastereoselectivity could be converted to highly enantioenriched products in 4/5 steps. Noda and Shibasaki developed an asymmetric Mannich reaction mediated by a *cinchona* alkaloid dimer (Scheme 22).¹⁰⁵ The enantioenriched product could be converted to a spirocyclic β -lactam in 2 steps involving Zn mediated N–O bond cleavage followed by lactamisation mediated by HCTU.



Scheme 22 Examples of enantioselective addition to ketimines or isatins followed by elaboration to β -lactam spirocycles.



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).

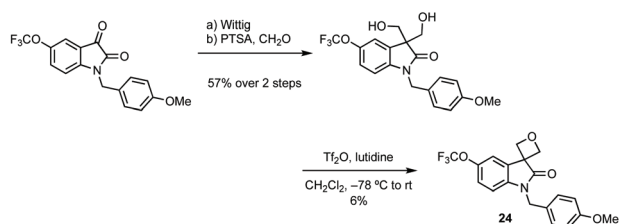
Non-stereoselective methods. As developments in stereoselective formation of spirooxetanes have been limited since 2012 (with the lowest number of hits out of any of the structures considered in this review), it is worthwhile mentioning papers that form spirooxetanes without stereoselectivity. Zhang 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).

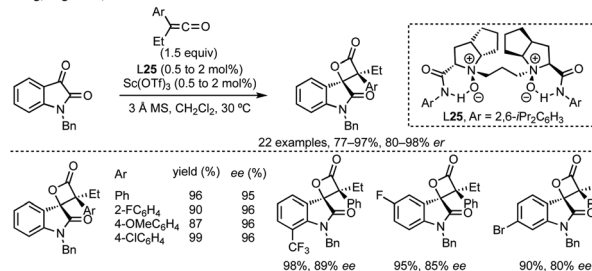
Five-membered rings

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.

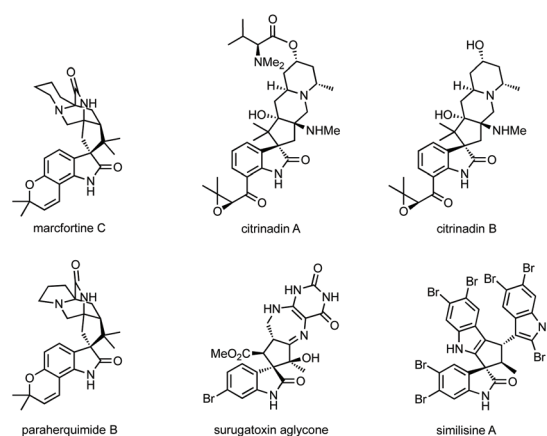
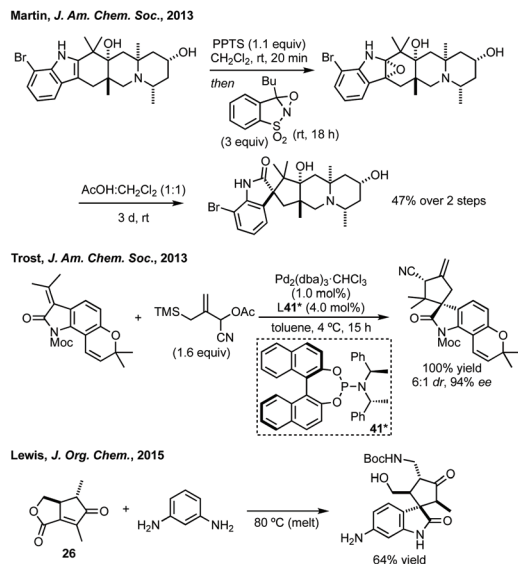


Fig. 5 Selected cyclopentane spiroindolones in nature.

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



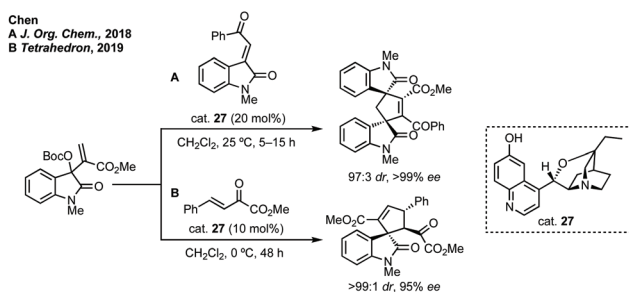


Scheme 25 Selected examples of spirocyclisation to cyclopentanes in total synthesis.

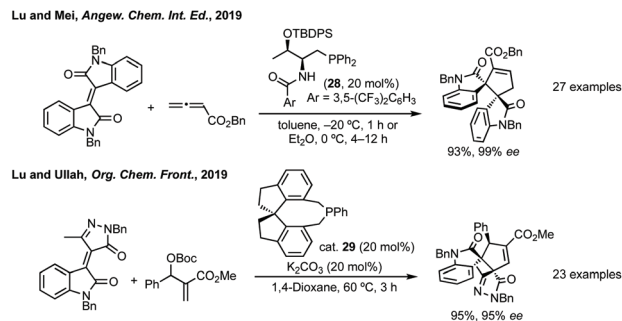
product see Fig. 5).¹¹⁷ Zhang and Jia recently described the total synthesis of similisines A and B (Fig. 5), enantiomeric tri-indole structures containing a spirocyclopentane oxindole core, through a key acid-mediated Friedel–Crafts cyclisation, though this was low yielding and non-stereoselective.¹¹⁸

[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.

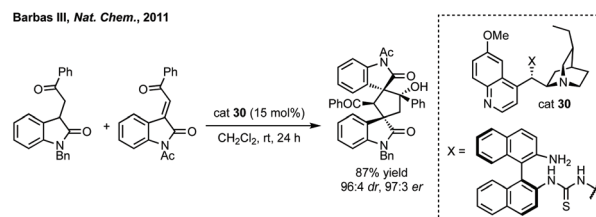


Scheme 27 Lu and coworkers' achievements in asymmetric phosphine catalysed activation of electrophiles to form spirocyclopentene scaffolds.

the highest yield and enantioselectivity in Et₂O for the [3 + 2] annulation of isoidindigos and allenes (Scheme 27).¹²⁶ Lu and Mei additionally showed unsymmetrical isoidindigos in this process with high regiocontrol, as well as the formal syntheses of a number of complex natural products. Lu, with Ullah, then reported the annulation of pyrazolonyldiene oxindoles with MBH carbonates using asymmetric phosphorus catalyst, SITCP 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.

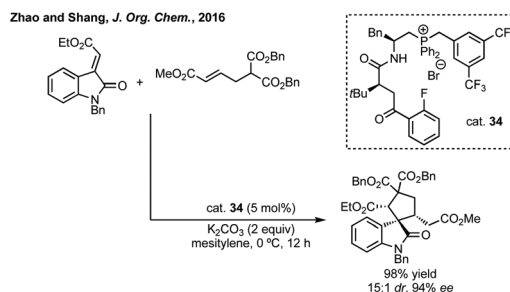


to form an enantioenriched spirocyclopentane with moderate dr.¹³² Shi has utilised asymmetric phosphoric acid catalysts to employ various vinyl indoles to react with 3-ylidene oxindoles, formed *in situ* from 3-indolylmethanol, in a Michael/alkylation cascade.¹³³

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 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

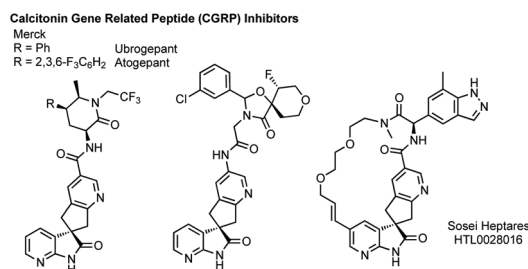
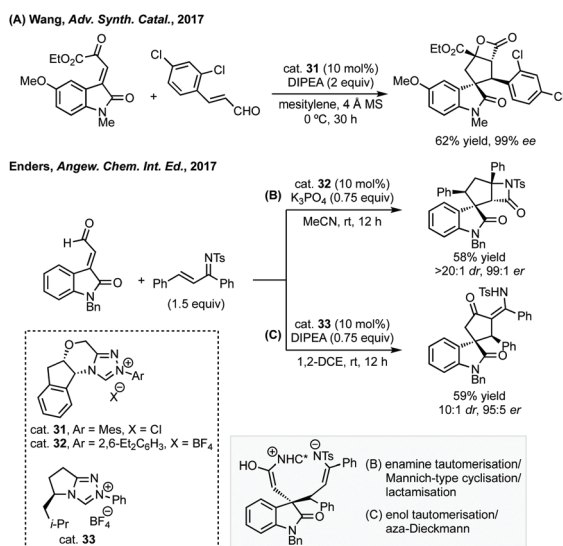
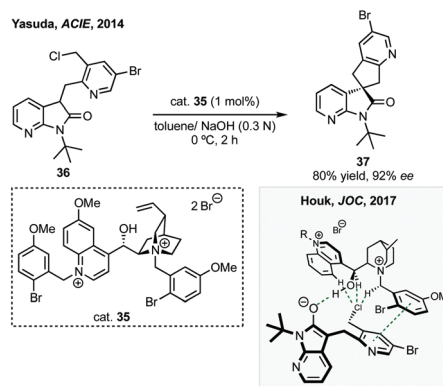


Fig. 6 Selected developments in structures of CGRP inhibitors.



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



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

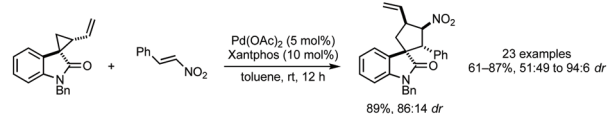


They proposed three key electrostatic interactions: (1) hydrogen bonding between the hydroxyl of the catalyst and the oxindole enolate; (2) a chloride-CH interaction activating the leaving group; (3) a π - π interaction between the pyridine of the formed cyclopentane and the quinuclidine benzyl group. 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.

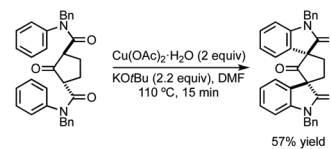
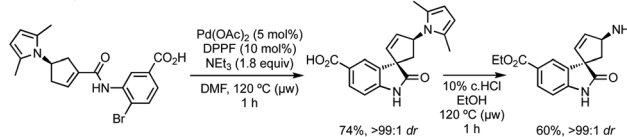
Metal/Lewis acid mediated approaches. Feng used a Mg/N, N'-dioxide catalyst system in a Michael/Friedel-Crafts/Mannich cascade of isocyanides to generate enantioenriched polycyclic spirocyclopentanes resembling strychnos alkaloids.¹⁴³ Franz recently used an Sc/pybox system for the [3 + 2]-cycloaddition 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.

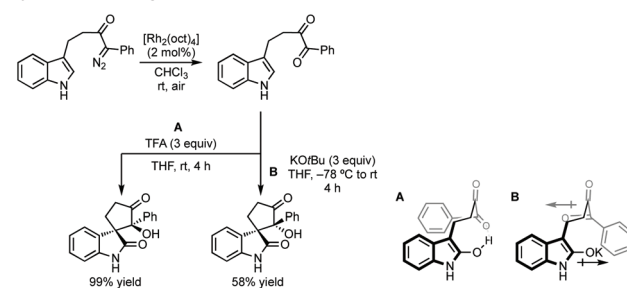
García-López and others have reported C-H activation and carbene insertion procedures to afford spirocyclopentanes.¹⁵³

Related to these C-H activation approaches is the stereo-selective 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.



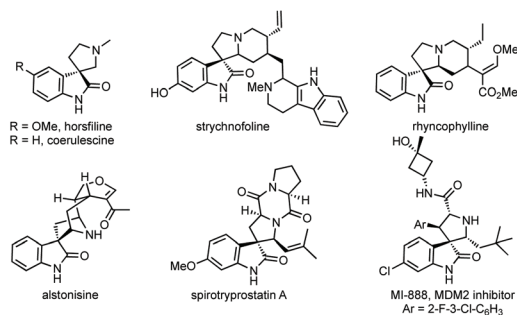


Fig. 7 Selected examples of bioactive 3,3'-spiropyrrolidinyl oxindoles.

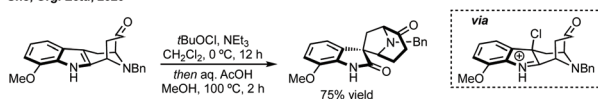
cancer,¹⁶¹ treatment for Alzheimer's,¹⁶² diabetes,¹⁶³ HIV¹⁶⁴ and tuberculosis.¹⁶⁵

Natural product synthesis. Spiropyrrolidinyl oxindoles, particularly spiro-3,3'-pyrrolidinyl oxindoles, have been the target and inspiration for many total syntheses.¹⁶⁶ Horsifilene and coerulescine (Fig. 7) are undoubtedly the simplest spiropyrrolidinyl oxindoles in nature and have been the focus of short, elegant total syntheses.¹⁶⁷ For more complex products, a general approach is to synthesise the corresponding annulated indole (termed a β -carboline, typically synthesised *via* a Pictet-Spengler reaction) and perform an oxidative rearrangement with *t*BuOCl. This reduces the problem down to the construction of the β -carboline (typically from tryptophan) and these products have received significant synthetic attention.¹⁶⁸ This was the strategy used by Cook in his total syntheses of (iso)affinisine oxindole and (iso)alstonisine,¹⁶⁹ Xu in the nine-step total synthesis of (–)-strychnofoline,¹⁷⁰ Zhang in the synthesis of multiple spirotryprostatins¹⁷¹ and more recently in She's total synthesis of (–)-gardmultimine A (for structures see Fig. 7 and Scheme 35).¹⁷² Rhynchophylline and isorhynchophylline have been synthesised formally by Amat and more recently totally by Ip and Tong (Scheme 40).¹⁷³

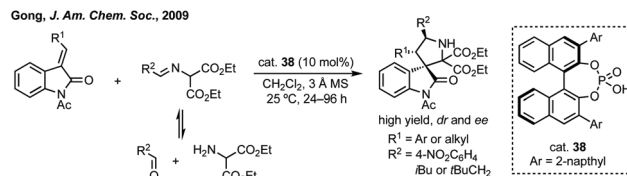
[3 + 2]-Cycloaddition

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

She, *Org. Lett.*, 2020



Scheme 35 Selected example from total synthesis of the application of an oxidative rearrangement of a β -carboline to a spirocyclopentane.

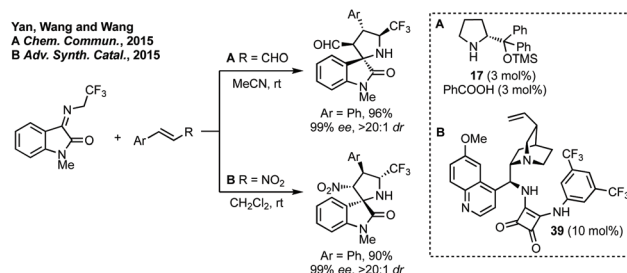


Scheme 36 Seminal report of catalytic enantioselective [3 + 2]-cycloaddition *via* azomethine ylides.

The utility of this approach by Gong has been demonstrated by the multitude of reports in this area since. These advances include the combination of an isatin derived dipole reacting with an external alkene dipolarophile,¹⁷⁶ or other dipolarophiles¹⁷⁷ such as alkynes¹⁷⁸ or allenes.¹⁷⁹ Often these dipoles are derived from aminooxindoles¹⁸⁰ or they could be malonitrile dipolarophiles,¹⁸¹ azomethine imines¹⁸² or pyridinium ylides.¹⁸³ There are also many applications of this methodology for the synthesis of bispirooxindoles.¹⁸⁴ Advances have also been made with related systems using copper catalysis.¹⁸⁵ This azomethine ylide cycloaddition has been used by Hoffman-La Roche to synthesise MDM2 antagonist MI-888 (Fig. 7, ref. 157), including >100 g scale synthesis of the final enantiopure product by chiral resolution.¹⁸⁶

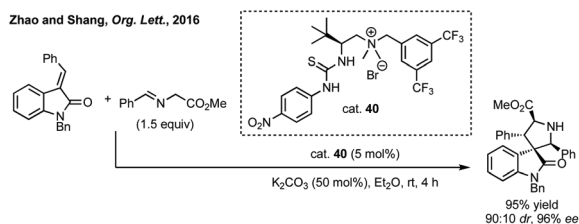
For the construction of 3,2'-spiropyrrolidinyl oxindoles, isatin derived ketimines can be used.¹⁸⁷ *N*-2,2,2-Trifluoroethylisatin ketimines are very popular as a starting material because of the resultant inclusion of a CF₃ group in the final product. In 2015, Yan, K. Wang and R. Wang demonstrated the first enantioselective [3 + 2]-cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines using prolinol cat. **17** (Scheme 37A).¹⁸⁸ The same authors subsequently reported a similar cycloaddition catalysed by a *cinchona* alkaloid derived squaramide catalyst (Scheme 37B).¹⁸⁹ These reports were followed by many diastereoselective¹⁹⁰ and enantioselective¹⁹¹ cycloadditions using *N*-2,2,2-trifluoroethylisatin ketimines as 1,3-dipole starting materials.

Zhao and Shang developed an asymmetric phase transfer catalysed [3 + 2]-cycloaddition using a thiourea containing ammonium salt **40** with K₂CO₃ as base to form polysubstituted 3,3'-spiropyrrolidinyl oxindoles in up to 99% ee (Scheme 38).¹⁹²



Scheme 37 Selected reports on the use of *N*-2,2,2-trifluoroethylisatin ketimines in [3 + 2]-cycloadditions.

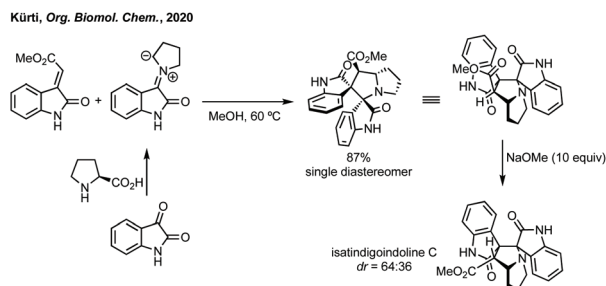




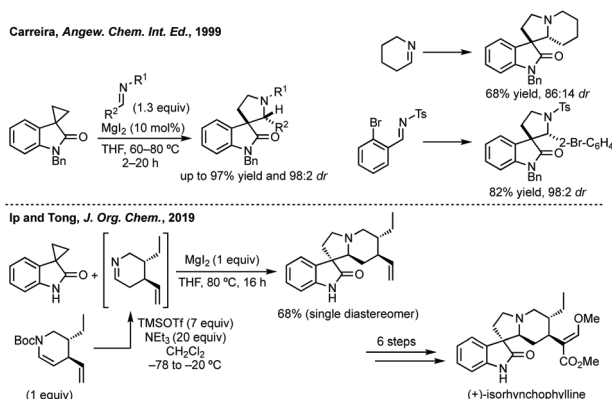
Scheme 38 Asymmetric phase-transfer catalysed [3 + 2]-cycloaddition.

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-



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



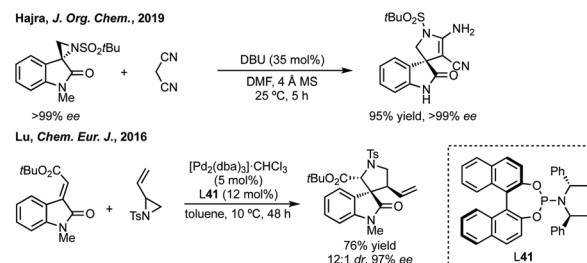
Scheme 40 Carreira's seminal ring expansion strategy and Ip and Tong's application of this methodology in total synthesis.

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 Isorynhynchophylline using a cyclic imine (Scheme 40).¹⁹⁷

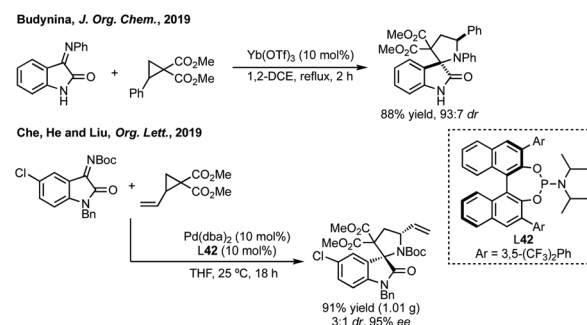
Budynina has performed a similar ring expansion in a sequential azide anion ring opening followed by a Staudinger/Wittig/Mannich reaction.¹⁹⁸ Whereas Hajra has ring expanded 3-spiroaziridinyl oxindoles using malonitrile (Scheme 41).¹⁹⁹ This type of ring expansion chemistry has also been carried out in 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

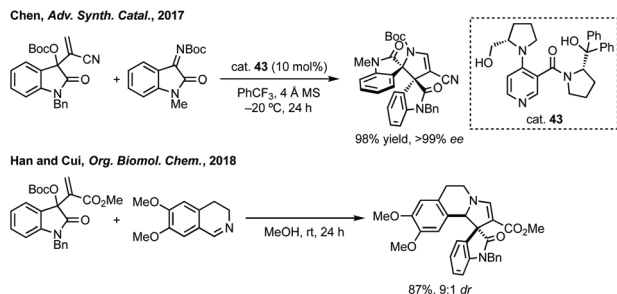


Scheme 41 3,3'-Spiropyrrolidine oxindoles synthesised by aziridine ring expansion.



Scheme 42 Selected examples of 3,2'-spirocyclopropyl oxindole 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

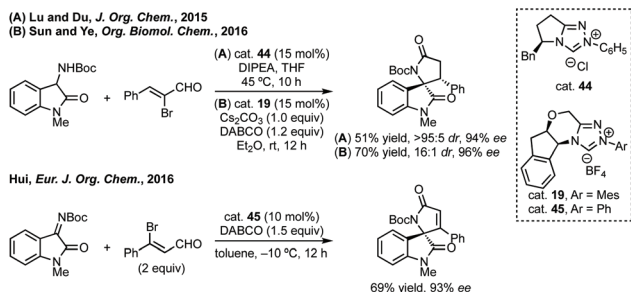
Conjugate addition/cyclisation is a common tactic employed to access spirocyclic oxindole scaffolds stereoselectively, and highlights the continuum between concerted [3 + 2]-annulation chemistry and stepwise sequences. Stepwise but simultaneous addition/cyclisation sequences will be dealt with first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

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

(A) 3-Isothiocyano oxindoles. The use of 3-isothiocyano 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-isothiocyano 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-isothiocyano 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-bromooxindoles in an enantioselective [4 + 1] annulation with azadienes using a *cinchona* alkaloid derived catalyst.²²³ As this strategy relies on the nucleophilic displacement by or with a component on the oxindole starting material it ultimately results in 3,2'-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



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



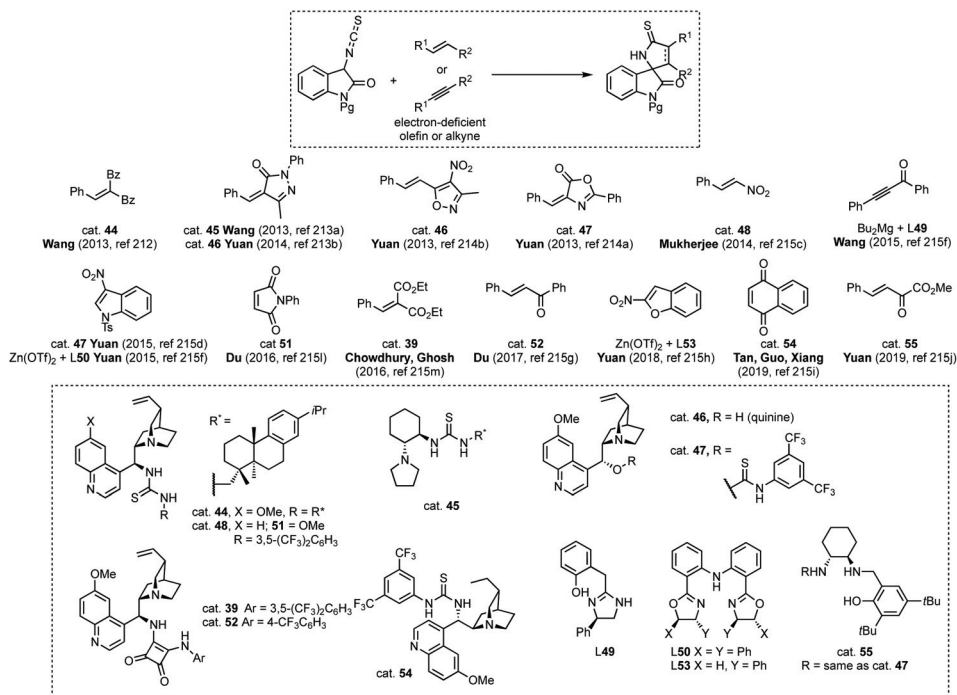
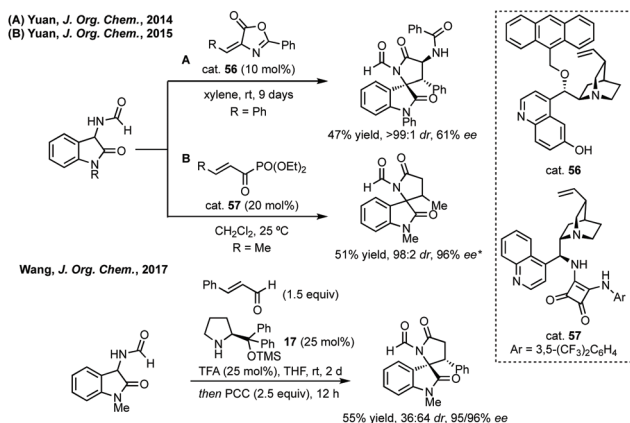
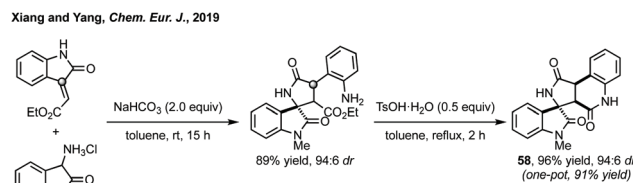


Fig. 8 Electrophiles and catalysts that have been developed for annulation of 3-isothiocyanato oxindoles.



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-aminoxindoles with 3-methylene oxindoles under basic conditions yielded a spirooxindole which upon treatment with TsOH in one-pot cyclised to spirooxindole 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-aminoxindoles and 3-methylene oxindoles to form bispirooxindoles and Enders showed a Mannich/deprotection/aza-Michael cascade between



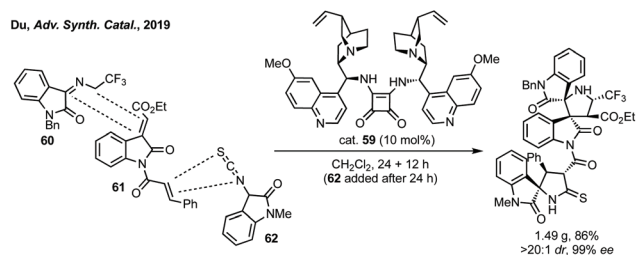
Scheme 46 Selected example of the combination of strategy B and C, using a nucleophilic C3 oxindole substituent and 3-ylidene oxindole.

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

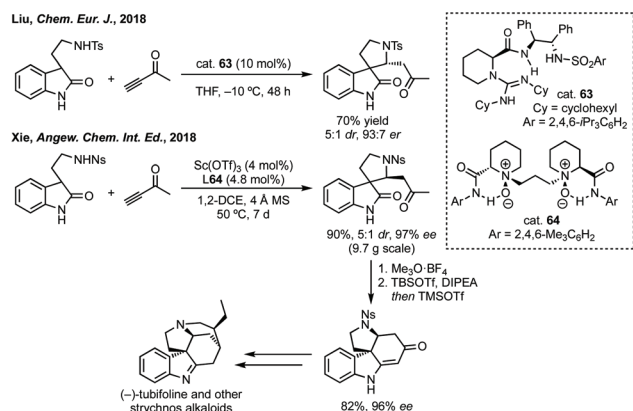
A remarkable extension of strategies A and C with dipolar cycloaddition has been developed by Du where compounds containing a spiropyrrolidine oxindole and bispirooxindole were formed by a dual Michael/Mannich and Michael/cyclisation sequence (Scheme 47).²²⁹ Using dimeric squaramide cat. 59 the reaction 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'-spiropyrrolidine oxindole synthesis was made by Liu and at a similar time by Xie. Both teams independently developed a double Michael addition between oxindoles and alkynones 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 stereocentres.

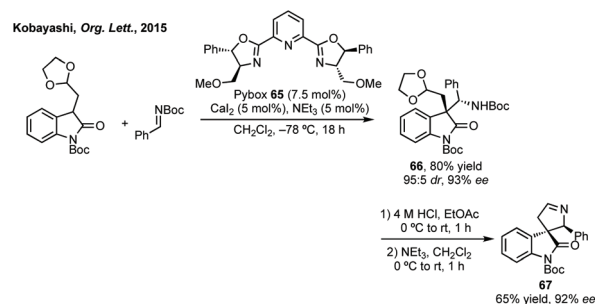


Scheme 48 Selected advances in Michael/Michael additions of alkynones.

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

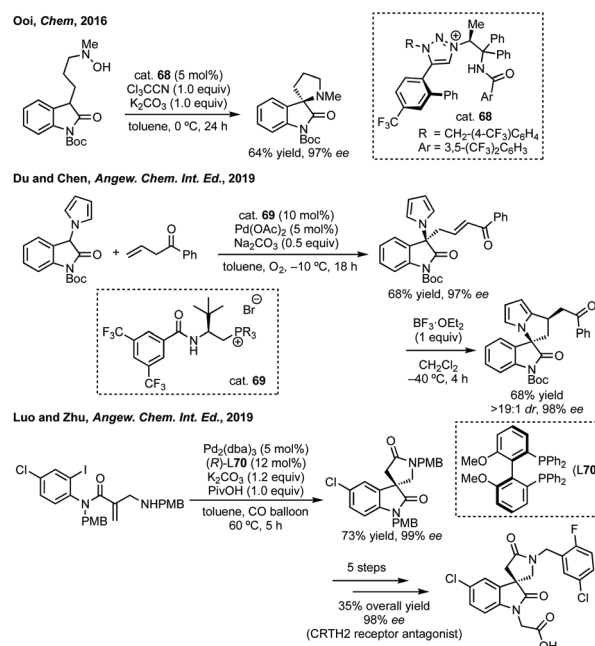
In this section strategies where a discrete coupling followed by cyclisation will be discussed. A common strategy towards spiropyrrolidine oxindoles is an asymmetric Mannich reaction using ketimines followed by cyclisation. In 2012, Lu and then Li and Wang reported significant advances in enantioselective Michael addition and allylic alkylation of nitroalkanes using *cinchona* alkaloid derived catalysts.²³⁵ Reductive cyclisation of the nitro group in the product then afforded spirolactams 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 CaI_2 with Pybox ligand **65** in CH_2Cl_2 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 NEt_3 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 $\text{Pd}(\text{OAc})_2$ with Na_2CO_3 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



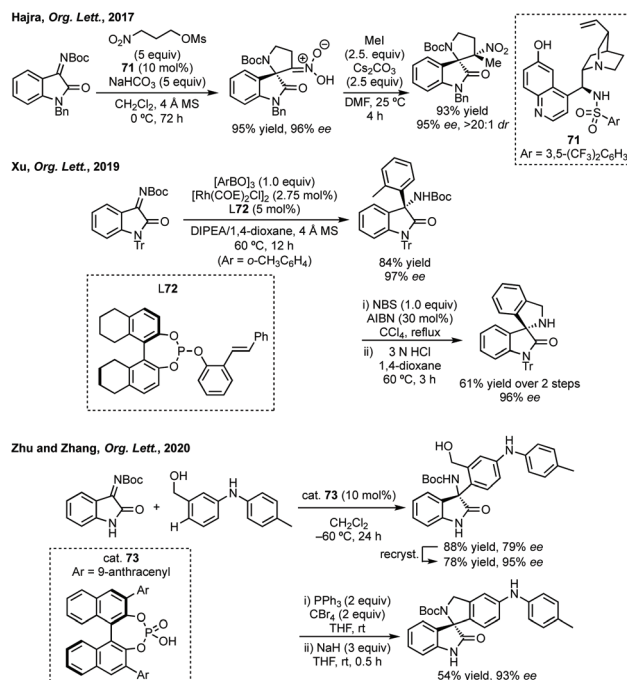
Scheme 50 Selected examples of phase transfer catalysed or metal-catalysed cross-coupling strategies to spiropyrrolidines. PMB = *para*-methoxybenzyl.

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).

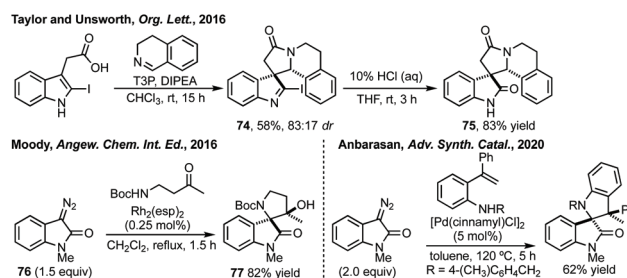
In a clearly distinct strategy Zhao and Xia developed a cross-dehydrogenative coupling of pyridines with 3-substituted oxindoles.²⁴² The pyridinium salts afforded could be reduced diastereoselectively with NaBH₄ in order to access racemic corynoxine in a rapid fashion (Scheme 51). Although the pyridine 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

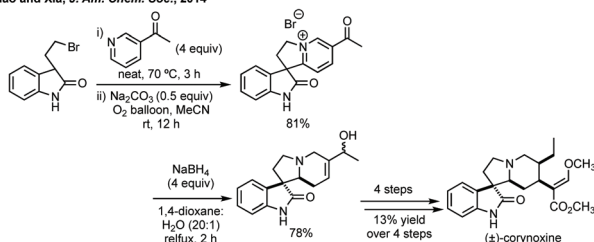


Scheme 52 Synthesis of 3,2'-spiropyrrolidine oxindoles following enantioselective additions to isatin derived ketimines.



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

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

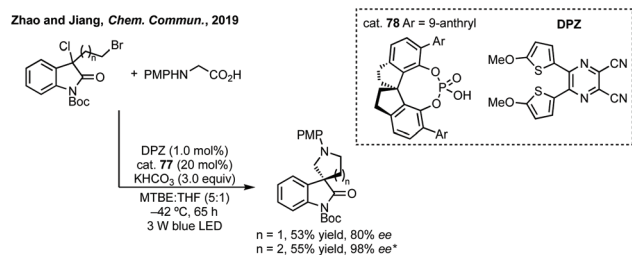


Scheme 51 Synthesis of spiropyrrolidine *via* pyridinium salts.

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.



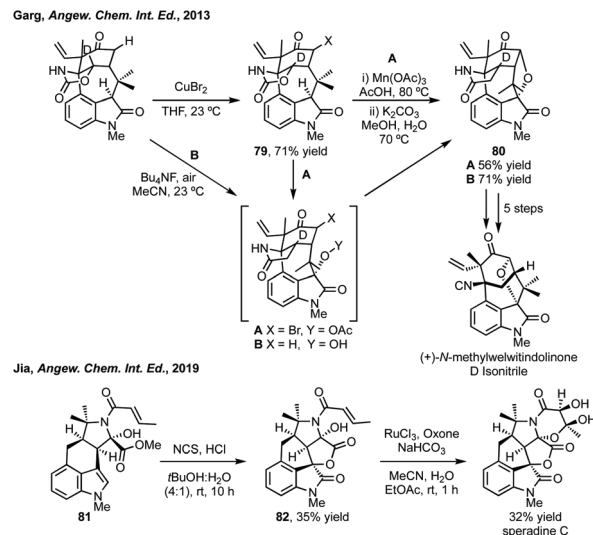


Scheme 54 Photoredox approach to enantioenriched 3,3'-spiropyrroli-dinyl oxindoles. * After recrystallisation, initial ee = 87%. PMP = *para*-methoxyphenyl.

Spirotetrahydrofuran oxindoles²⁵³

Applications. There are numerous bioactive spiroTHF oxindoles (Fig. 9). Of note is XEN402 (Funapide), developed by xenon and licensed by Teva (TV-45070) for treatment of pain (synthesis discussed below).²⁵⁴ Other applications of spiroTHFs include anti-tumour²⁵⁵ as well as antibacterial activity.²⁵⁶ Spring reported an example in a diversity-oriented synthesis of a library of drug-like macrocycles.²⁵⁷

Natural product synthesis. Garg demonstrated the importance of spirotetrahydrofuran oxindoles in the stereocontrolled total synthesis of *N*-methylwelwitindolinone D isonitrile.²⁵⁸ Late-stage installation of the key spiroTHF ring proved troublesome and an attempt to cyclise **79** (X = Br) under aerobic conditions afforded a spirocyclobutyl oxindole in high yield (Scheme 55). However, Garg and co-workers were able to develop two oxidative functionalisations of the oxindole C3 to afford the spirobutyrolactone **80** which was 5 steps from the natural product. The total synthesis of (±)-aspergilline A in 16 steps was developed by Wood and co-workers.²⁵⁹ More recently Jia reported a ten-step total synthesis of the related natural product Speradine C with a key oxidative spirocyclisation to form the spiroTHF ring at a late stage.²⁶⁰ Treatment of **81** with NCS formed a chloronium ion which was spontaneously attacked by the methyl ester to form **82** in 35% yield, which was one oxidative cyclisation step away from speradine C (Scheme 55). This use of the nucleophilicity of an indole is reminiscent of the strategy observed extensively for spiropyrrolidine synthesis (Scheme 35), indeed, Scheidt has synthesised (–)-coixspirolactam C (Fig. 9) from indole fused THPs (formed



Scheme 55 Selected examples of spiroTHF synthesis in total syntheses.

in an Oxa-Pictet–Spengler) by bromonium ion formation and rearrangement.²⁶¹ Dixon synthesised the spiroTHF oxindole core of the tryptoquivalines using a stereoselective aldol cyclisation/acidic hydrolysis (for the THF ring) and a Cu-catalysed Buchwald type C–N bond formation (for the oxindole).²⁶²

Cycloaddition

Iminium ion catalysis. In 2012, Melchiorre reported the reaction of 3-hydroxyoxindoles with enals under iminium ion catalysis for the synthesis of chiral butyrolactones and the preparation of maremycin A.²⁶³ In 2013, Melchiorre was able to further develop this chemistry with dienals to favour 1,6-addition in favour of 1,4-addition by using prolinol catalyst **17** with dienal **83**, where the β-substituent constrains the dienal in the *S-cis* conformation (Scheme 56).²⁶⁴

NHC catalysis. In seminal work, Ma reported an NHC catalysed [3 + 2] annulation of 3-bromo-enals and isatins for the synthesis of spirotetrahydrofuran oxindoles (Scheme 57).²⁶⁵ Using NHC cat. **84** Ma achieved high enantioselectivity of the spirobutenolide oxindole products. This reaction occurred through NHC activation of the aldehyde to form a Breslow intermediate. This intermediate can then react through the carbon alpha to the bromo substituent to afford the oxindole alcohol which undergoes spirocyclisation. At a similar time, Glorius reported a similar annulation between isatins and enals, providing spirocycles with two contiguous quaternary stereocentres, which was highly diastereoselective and enantioselective when cat. **85** was

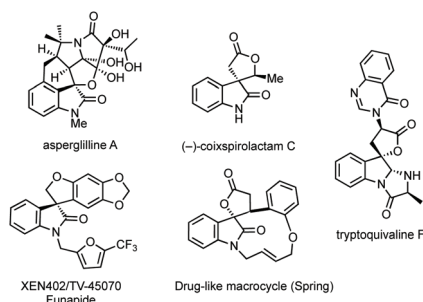
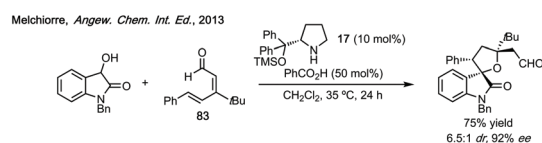
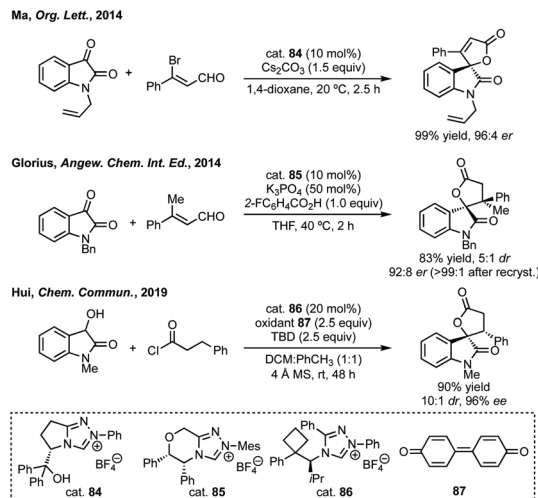


Fig. 9 Selected examples of bioactive spirotetrahydrofuran oxindoles.



Scheme 56 SpiroTHF synthesis using iminium ion catalysis by Melchiorre.

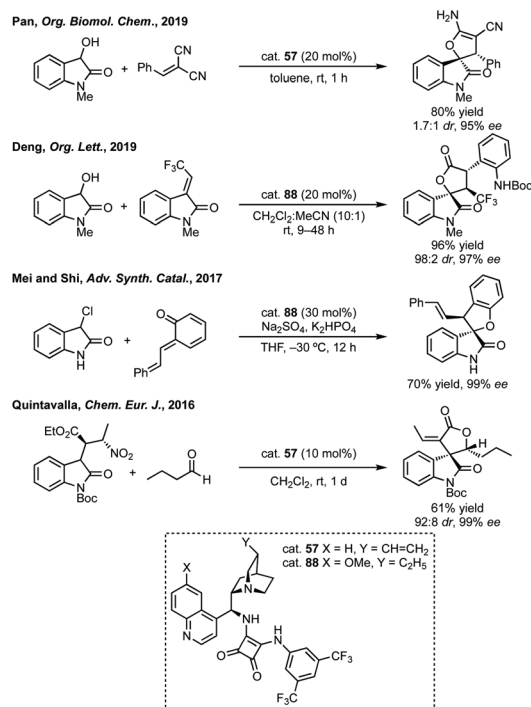




Scheme 57 Selected advances in NHC catalysed [3 + 2] annulations to spiroactones.

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 spiropyrrolidines, the use of cascade Michael/cyclisation procedures is also common for spiroTHF oxindoles.²⁷¹ Related to Yuan's use of phosphonates as leaving groups for the Michael addition/cyclisation (ref. 219), Du used *N*-acylated succinimides as leaving groups.²⁷² There are a number of reports of coupling of 3-hydroxyoxindoles and malonitriles,²⁷³ of note is Pan's highly enantioselective Michael/Pinner cascade reaction using cat. 57 (Scheme 58).²⁷⁴ Deng reported an asymmetric Michael/lactonization procedure between 3-hydroxyoxindoles and 3-methylene oxindoles which resulted in ring opening of the oxindole coupling partner (Scheme 58).^{275,276} Similar to ref. 227 (Scheme 46), Chen and Yang reported a Michael addition/ring opening/ring closing cascade, however, the resultant aniline formed cyclised with the ester of the 3-methylene oxindole in the final step.²⁷⁷ In a distinct reaction but using a similar catalyst, Mei and Shi reported an enantioselective [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



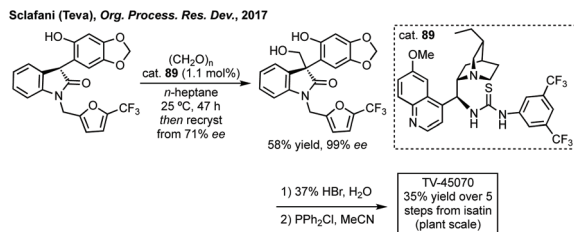
Scheme 58 Selected advances in annulations catalysed by bifunctional hydrogen bonding catalysts.

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

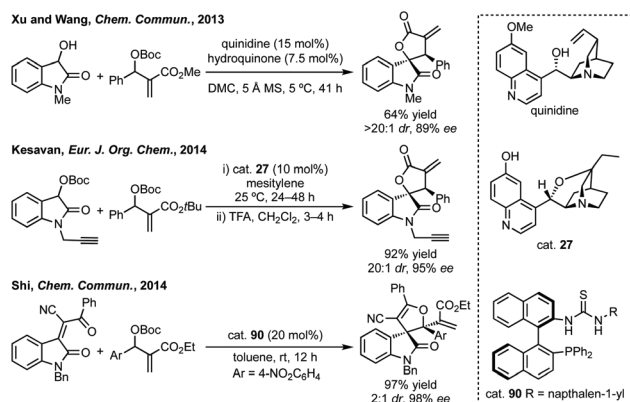
In 2016, Bisai reported an enantioselective aldol reaction of dimeric oxindoles which resulted in ring opening of one of the oxindoles, and in doing so developed a highly enantioselective thiourea catalysed aldol reaction with formaldehyde.²⁸¹ The first process scale synthesis of TV-45070 (Fig. 9) employed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





Scheme 59 Plant scale synthesis of TV-45070.

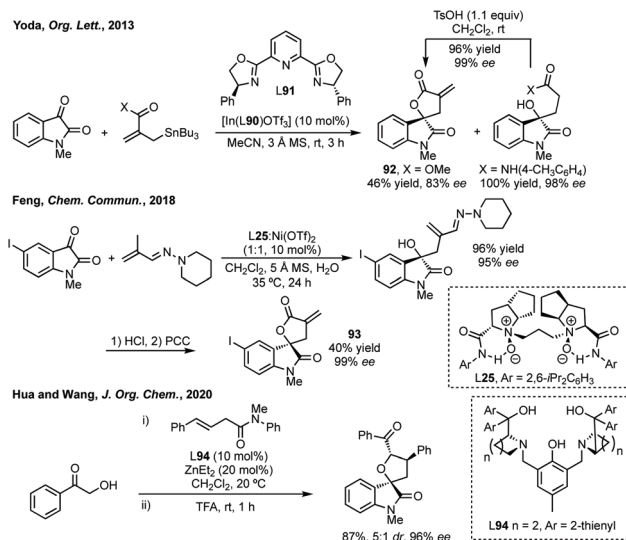


Scheme 60 Selected advances in the use of MBH carbonates to form spiro lactone and spiroTHF oxindoles.

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

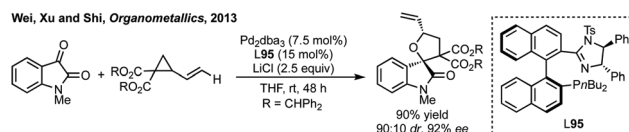
Yin has developed a Pd-catalysed cascade reaction involving dearomatisation of furans to form the THF core of the spirocycle.²⁹⁵ Other metal-mediated approaches include the use of Cu,²⁹⁶ Ti,²⁹⁷ Ru,²⁹⁸ or Ni-catalysed²⁹⁹ spirocyclisations. Trost has also applied his development of Pd-allyl complexes previously discussed in the spiropyrrolidine section to the synthesis of spiroTHFs.³⁰⁰ Similar to Moody's use of diazo compounds to synthesise spiropyrrolidines, 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



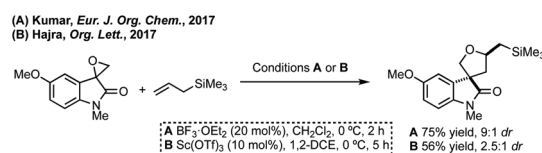
Scheme 61 Recent advances in metal-mediated spirocyclisation methods to spiroTHF oxindoles.

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 $\text{Pd}_2(\text{dba})_3$ 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 $\text{Pd}(\text{OAc})_2/\text{XantPhos}$ 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 2H-spirobenzofuran oxindoles.³⁰⁶

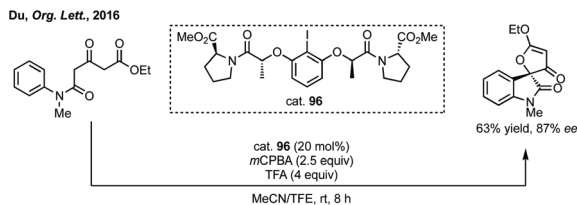


Scheme 62 Use of vinyl cyclopropanes to construct spiroTHFs.



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-ene reaction 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

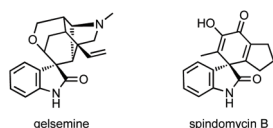
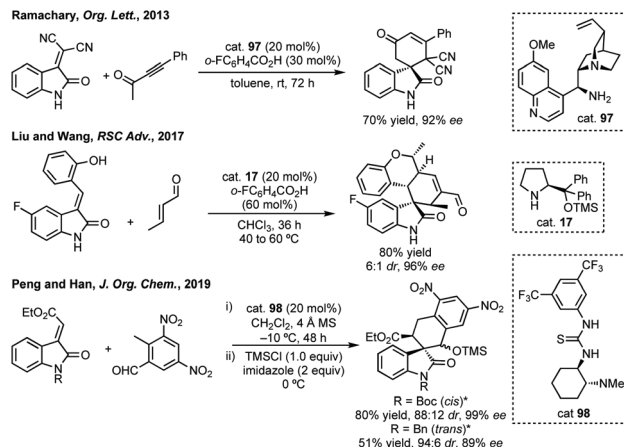


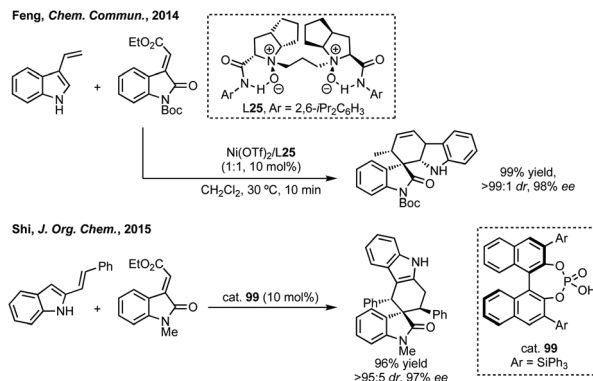
Fig. 10 Selected naturally occurring spirocyclohexane oxindole.



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

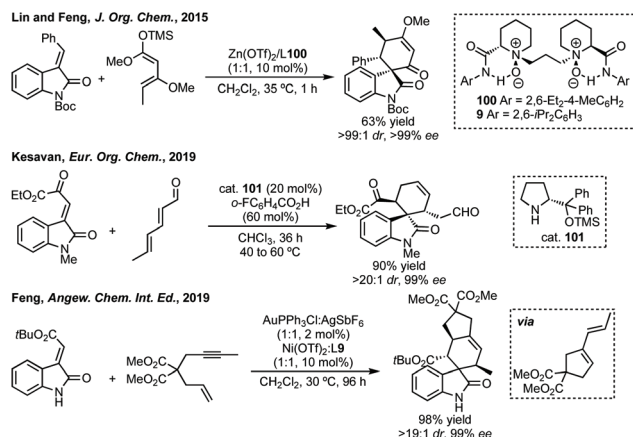
have been a number of reports of combining chromane scaffolds with spirocyclohexane oxindoles.³²² Of note is Liu and Wang's use of 3-methylene oxindoles with a phenol substituent undergoing an Michael/aldol/oxa-Michael cascade under iminium catalysis (Scheme 65).³²³ There have been many other developments 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.



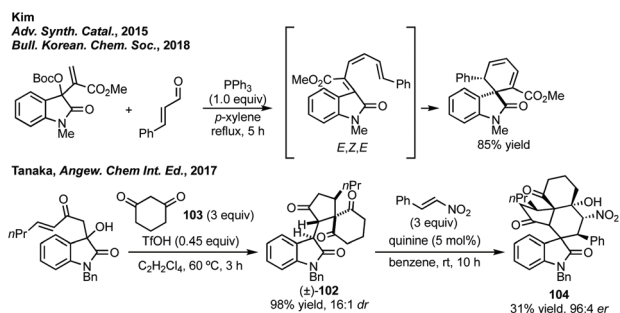


Scheme 67 Selected enantioselective Diels–Alder reactions to make spirooxindoles.

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.

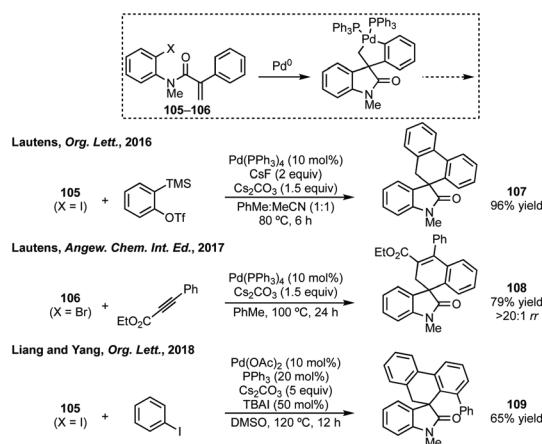
ketone **103** by treatment with TfOH (Scheme 68).³⁴⁰ In a Michael–Henry cascade reaction **102** could react with an electron-poor olefin (such as a nitroalkene) and form polycyclic spirocyclohexane oxindole containing product **104** with excellent enantioselectivity. The yields for these products 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**.

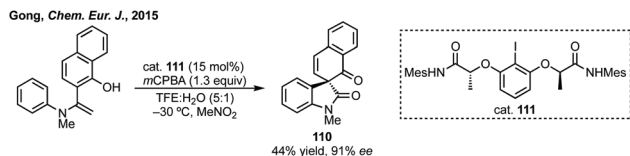
Spiropiperidiny oxindoles

Applications. In the last decade spiropiperidiny 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

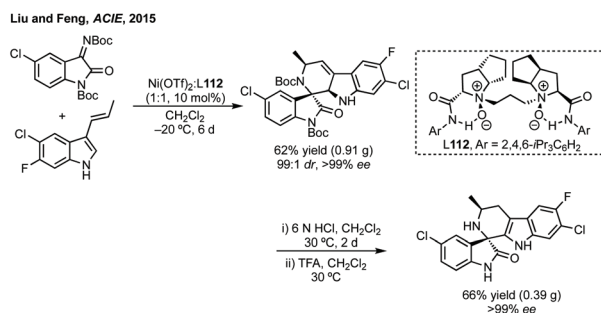


Scheme 69 Selected metal-mediated C–H activation approaches via alkyl-Pd^{II} intermediates.





Scheme 70 Chiral iodine mediated spirocyclohexene oxindole formation.



Scheme 71 Concise synthesis of anti-malarial cipargamin.

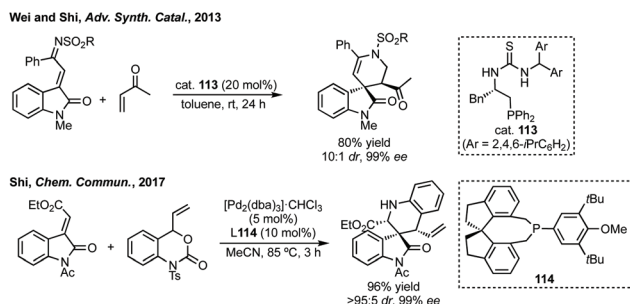
KAE609) has been developed as an anti-malarial agent.³⁵³ Shibasaki used a key asymmetric alkylation of an isatin ketimine to synthesise cipargamin.³⁵⁴ Liu and Feng synthesised cipargamin in an aza-Diels-Alder process employing 3-vinyl indoles and Ni catalysis (Scheme 71).³⁵⁵

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 spirocyclohexenes.³⁶⁰ More recently, Shi

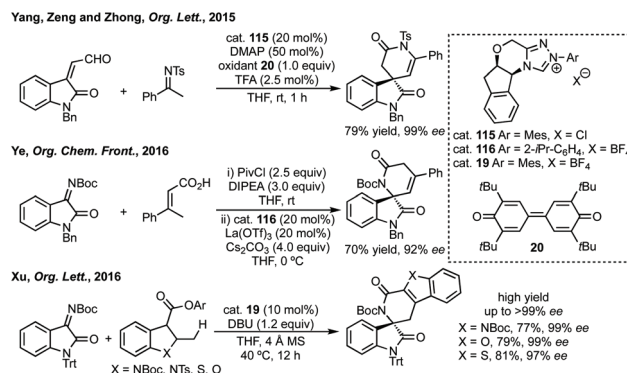
developed a Pd-catalysed decarboxylative [4 + 2] cycloaddition strategy using vinyl benzoxazinones and 3-methylene oxindoles (Scheme 72).³⁶¹

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'-spirocyclohexene 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'-spirocyclohexene 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'-spirocyclohexene 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'-spirocyclohexene oxindoles.³⁷² Related reactions include aza-Michael/Michael addition, Michael/Mannich reaction, Michael addition/Pictet-Spengler, Michael/aldol,

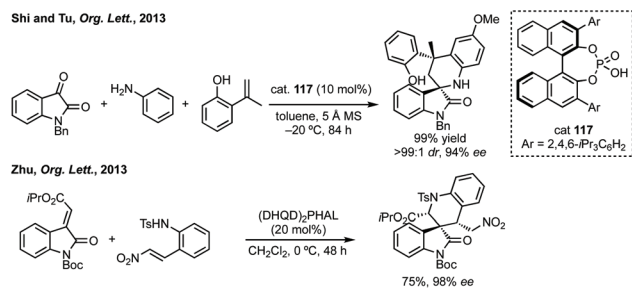


Scheme 72 Selected enantioselective [4 + 2]-cycloadditions.



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

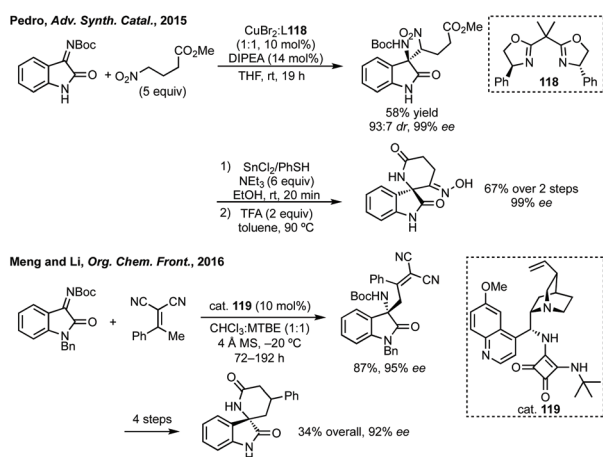




Scheme 74 Selected examples of phosphoric acid catalysed cascade reactions.

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.

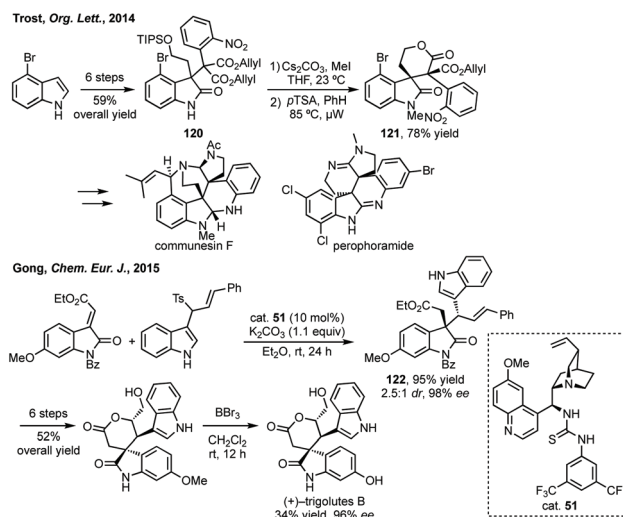
deprotected and cyclised to spiro lactam products (Scheme 75).³⁸¹ Han has also developed an enantioselective Mannich reaction which upon deprotection of the generated Boc-protected amine undergoes lactamisation to the six-membered spirocycle.³⁸²

Spirotetrahydropyranyl oxindoles

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

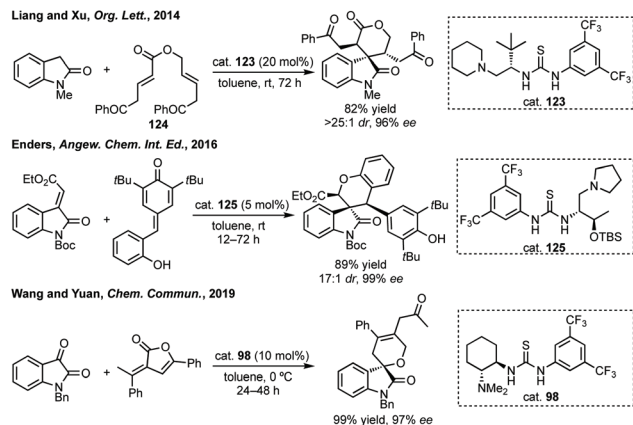
Natural product synthesis. Trost cyclised **120** to give cyclolactone **121** in 92% yield as one diastereomer as an intermediate for the total synthesis of communesin F and perophoramide (Scheme 76).³⁸⁶ Gong reported the first total synthesis of (+)-trigolutes B utilising an enantioselective substitution 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.



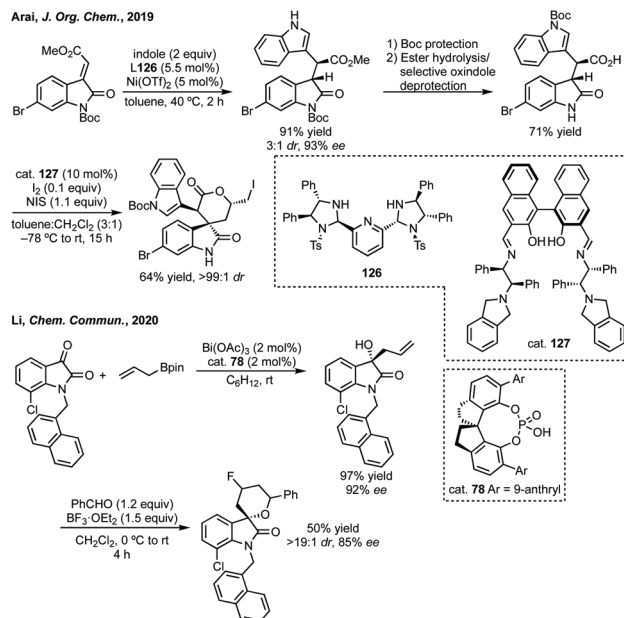


Scheme 77 Selected cascade reactions catalysed by thiourea catalysts.

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

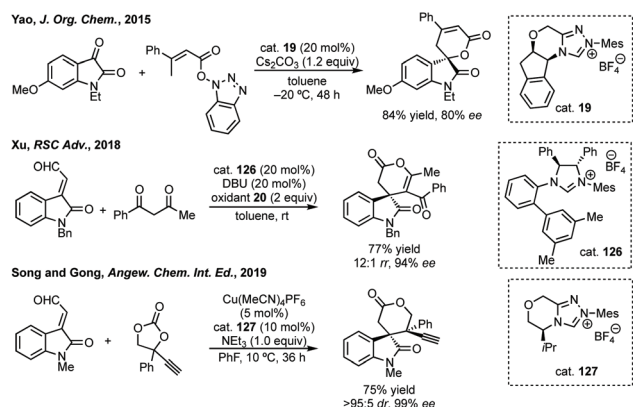
Stepwise approaches. Feng has employed a Mg/chiral N,N' -dioxide catalyst system for a hetero Diels–Alder reaction.⁴⁰⁵ Li has recently reported a Bi/chiral phosphoric acid 77 catalysed



Scheme 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-diazooxindoles 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



Scheme 78 Selected NHC catalysed cycloadditions.

Seven-membered rings

Applications

Natural products containing seven-membered spirocyclic oxindoles are predominantly bridged carbocyclic examples of gel-semium 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



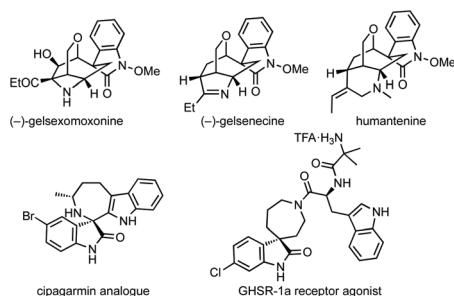


Fig. 11 Selected bioactive seven-membered rings.

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.

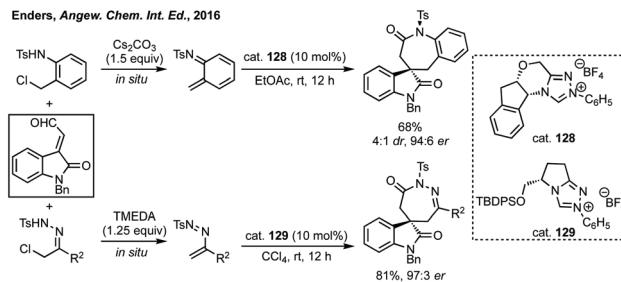
Natural product synthesis

Total synthesis efforts centre around the synthesis of gelsemium alkaloids. Carreira has described elegant approaches to gelsexomoxonine (see Fig. 11 for structure).⁴¹⁶ Ferreira constructed the oxindole of gelsenicine 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-hydroxygelsenicine and six other gelsemium alkaloids.⁴¹⁹ The spirooxindole was constructed in a diastereoselective Heck cyclisation (Scheme 80).

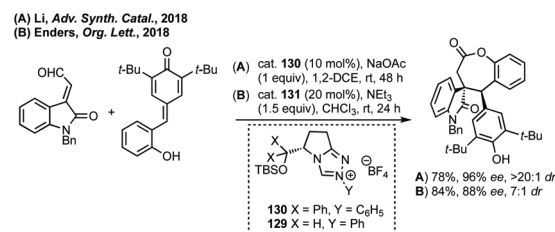
NHC catalysis

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



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



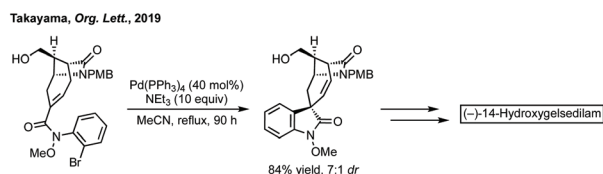
Scheme 82 Isatin-derived enals in [4 + 3] cycloaddition reactions.

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.

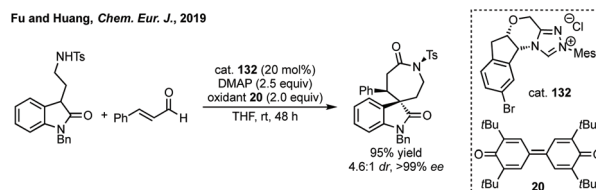
More recent advances include Fu and Huang's NHC catalysed [4 + 3]-annulation of α,β -unsaturated aldehydes and amine substituted oxindoles (oxotryptamines, Scheme 83).⁴²⁴ Song and Gong's previously discussed excellent Cu/NHC dual catalysis could be used with ethynyl benzoxazinanones to construct chiral 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

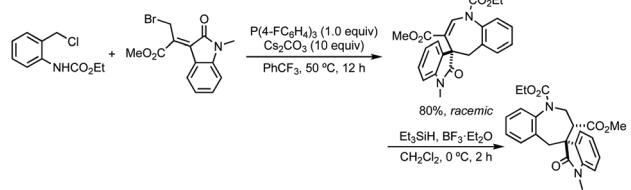


Scheme 80 Pd-Catalysed Heck reaction as key step in the total synthesis of (-)-14-hydroxygelsedilam.



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



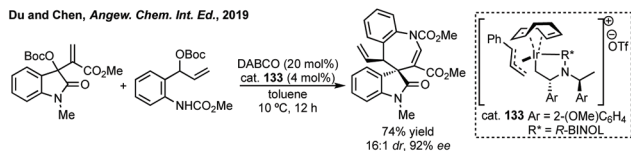
Chen, *Org. Lett.*, 2015Du, *Org. Lett.*, 2019

Scheme 84 Selected [4 + 3]-cycloadditions to 7-membered spirocycles using MBH carbonates or MBH precursors.

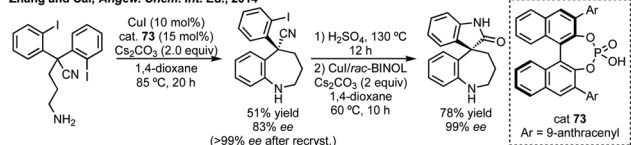
methide precursor to generate seven-membered spirocycles in good yields, including on gram-scale. In a similar fashion, Du recently employed *ortho*-quinone methides in combination with an isatin derived MBH precursor to affect a [4 + 3]-cycloaddition.⁴²⁷ Using DABCO as Lewis base catalyst in MeCN, high diastereoselectivity with electron-rich *ortho*-quinone methides was observed (Scheme 84).

Du and Chen have collaboratively reported an asymmetric Ir catalysed [4 + 3]-cycloaddition between an MBH carbonate and π -allyl precursor (Scheme 85).⁴²⁸ The π -allyl precursor includes a vinylogous leaving group *i.e.* vinyl-OBoc, ethylene oxazinones or vinyl aziridines (for six-membered rings) which forms an asymmetric Ir-allyl complex to react with the DABCO activated MBH carbonate.

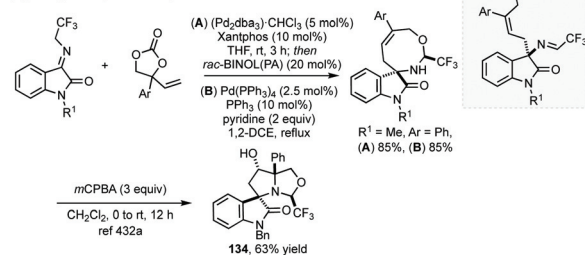
Other approaches to spiroazepanes include a desymmetrising Cu-catalysed C–N bond formation in high ee (Scheme 86).⁴²⁹ Budynina has used azide anion ring opening of spirocyclopropyl oxindoles (ref. 198) in a Staudinger, domino Michael/aza-Wittig and reduction sequence.⁴³⁰ Yang developed a Pd-NHC catalysed allylic alkylation, the products of which could readily be elaborated to a spiroazepinone.⁴³¹

Du and Chen, *Angew. Chem. Int. Ed.*, 2019

Scheme 85 Reaction of MBH carbonates with π -allyl precursors.

Zhang and Cai, *Angew. Chem. Int. Ed.*, 2014

Scheme 86 Cu-Catalysed desymmetrising cross-coupling reaction.

(A) Shi, *Org. Lett.*, 2019(B) Zhao, *Adv. Synth. Catal.*, 2019

Scheme 87 [5 + 3]-Cycloaddition towards 8-membered spiroindolones.

Eight-membered rings

As with seven-membered spiro-oxindoles there are very few examples of syntheses capable of accessing the eight-membered analogues. Shi and Zhao independently published the Pd-catalysed [5 + 3]-cycloaddition of *N*-2,2,2-trifluoromethylisatin ketimines and vinyl ethylene carbonates (Scheme 87).⁴³² Shi employed $(\text{Pd}_2\text{dba}_3)\cdot\text{CHCl}_3$ and Xantphos as a ligand for the decarboxylative allylic substitution and a racemic phosphoric acid catalyst to effect the cyclisation. Meanwhile, Zhao used $\text{Pd}(\text{PPh}_3)_4$ in combination with PPh_3 as ligand and pyridine as base for the cyclisation. Both procedures afford the *anti*-product as the major product in high yields and dr. Shi demonstrated a preliminary result for the enantioselective allylation using *t*Bu-RuPhos as ligand affording the eight-membered spirocycle in 63% ee. Furthermore, Shi showed that epoxidation of the endogenous double bond with *m*CPBA would lead to spontaneous epoxide ring opening to form spiropyrrolidine **134** (Scheme 87A).

Summary and conclusions

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

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

2. Spirooxindoles serve as a benchmark in asymmetric synthesis. Many of the methods reviewed here have made substantial advances in asymmetric catalysis. This may be due to the fused backbone of the indolone providing a flat and rigid plat-



form for construction of 3D spirocycles. These advances are doubly valuable because they fulfill the object of advancing asymmetric methodology while making biologically relevant scaffolds for screening against biologically relevant targets.

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

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

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

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

3. Small and larger ring spirocycles. As 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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Notes and references

- 1 Y. Zheng, C. M. Tice and S. B. Singh, The use of spirocyclic scaffolds in drug discovery, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673.
- 2 Y. J. Zheng and C. M. Tice, The utilization of spirocyclic scaffolds in novel drug discovery, *Expert Opin. Drug Discovery*, 2016, **11**, 831.
- 3 S. L. Degorce, M. S. Bodnarchuk and J. S. Scott, Lowering Lipophilicity by Adding Carbon: AzaSpiroHeptanes, a logD Lowering Twist, *ACS Med. Chem. Lett.*, 2019, **10**, 1198.
- 4 (a) G. Müller, T. Berkenbosch, J. C. J. Benningshof, D. Stumpfe and J. Bajorath, Charting Biologically Relevant Spirocyclic Compound Space, *Chem. – Eur. J.*, 2017, **23**, 703. For benefits of saturated heterocycles *vs.* aromatic cycles see: (b) T. J. Ritchie and S. J. F. Macdonald, The impact of aromatic ring count on compound developability - are too many aromatic rings a liability in drug design?, *Drug Discovery Today*, 2009, **14**, 1011; (c) T. J. Ritchie, S. J. F. MacDonald, R. J. Young and S. D. Pickett, The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types, *Drug Discovery Today*, 2011, **16**, 164.
- 5 E. M. Carreira and T. C. Fessard, Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities, *Chem. Rev.*, 2014, **114**, 8257.
- 6 G. S. Singh and Z. Y. Desta, Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks, *Chem. Rev.*, 2012, **112**, 6104.
- 7 T. L. Pavlovskaya, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, Molecular diversity of spirooxindoles. Synthesis and biological activity, *Mol. Diversity*, 2016, **20**, 299.
- 8 (a) B. Yu, D. Q. Yu and H. M. Liu, Spirooxindoles: Promising scaffolds for anticancer agents, *Eur. J. Med. Chem.*, 2015, **97**, 673; (b) B. Yu, Y.-C. Zheng, X.-J. Shi, P.-P. Qi and H.-M. Liu, Natural Product-Derived Spirooxindole Fragments Serve as Privileged Substructures for Discovery of New Anticancer agents, *Anticancer Agents Med. Chem.*, 2016, **16**, 1315.
- 9 N. Ye, H. Chen, E. A. Wold, P. Y. Shi and J. Zhou, Therapeutic Potential of Spirooxindoles. as Antiviral Agents, *ACS Infect. Dis.*, 2016, **2**, 382.



- 10 (a) M. M. M. Santos, Recent advances in the synthesis of biologically active spirooxindoles, *Tetrahedron*, 2014, **70**, 9735; (b) E. Sansinenea, E. F. Martínez and A. Ortiz, Organocatalytic Synthesis of Chiral Spirooxindoles with Quaternary Stereogenic Centers, *Eur. J. Org. Chem.*, 2020, 5101.
- 11 (a) B. M. Trost and M. K. Brennan, Asymmetric Syntheses of Oxindole and Indole Spirocyclic Alkaloid Natural Products, *Synthesis*, 2009, 3003; (b) F. Zhou, Y. L. Liu and J. Zhou, Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position, *Adv. Synth. Catal.*, 2010, **352**, 1381; (c) L. Hong and R. Wang, Recent Advances in Asymmetric Organocatalytic Construction of 3,3'-Spirocyclic Oxindoles, *Adv. Synth. Catal.*, 2013, **355**, 1023; (d) D. Cheng, Y. Ishihara, B. Tan and C. F. Barbas, Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles via Organocascade Strategies, *ACS Catal.*, 2014, **4**, 743; (e) R. Narayan, M. Potowski, Z. J. Jia, A. P. Antonchick and H. Waldmann, Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis, *Acc. Chem. Res.*, 2014, **47**, 1296; (f) R. Dalpozzo, Recent Catalytic Asymmetric Syntheses of 3,3-Disubstituted Indolin-2-ones and 2,2-Disubstituted Indolin-3-ones, *Adv. Synth. Catal.*, 2017, **359**, 1772; (g) G. J. Mei and F. Shi, Catalytic asymmetric synthesis of spirooxindoles: recent developments, *Chem. Commun.*, 2018, **54**, 6607.
- 12 (a) M. Xia and R.-Z. Ma, Recent Progress on Routes to Spirooxindole Systems Derived from Isatin, *J. Heterocycl. Chem.*, 2014, **51**, 539; (b) Y. Liu, H. Wang and J. Wan, Recent Advances in Diversity Oriented Synthesis through Isatin-based Multicomponent Reactions, *Asian J. Org. Chem.*, 2013, **2**, 374; (c) G. Mohammadi Ziarani, R. Moradi and N. Lashgari, Asymmetric synthesis of chiral oxindoles using isatin as starting material, *Tetrahedron*, 2018, **74**, 1323.
- 13 (a) S. Peddibhotla, 3-Substituted-3-hydroxy-2-oxindole, an Emerging New Scaffold for Drug Discovery with Potential Anti-Cancer and other Biological Activities, *Curr. Bioact. Compd.*, 2009, **5**, 20; (b) J. Kaur, B. P. Kaur and S. S. Chimni, Recent advances in the catalytic synthesis of 3-aminooxindoles: an update, *Org. Biomol. Chem.*, 2020, **18**, 4692.
- 14 (a) A. K. Franz, N. V. Hanhan and N. R. Ball-Jones, Asymmetric Catalysis for the Synthesis of Spirocyclic Compounds, *ACS Catal.*, 2013, **3**, 540; (b) A. Ding, M. Meazza, H. Guo, J. W. Yang and R. Rios, New development in the enantioselective synthesis of spiro compounds, *Chem. Soc. Rev.*, 2018, **47**, 5946; (c) J. Bariwal, L. G. Voskressensky and E. V. Van Der Eycken, Recent advances in spirocyclization of indole derivatives, *Chem. Soc. Rev.*, 2018, **47**, 3831.
- 15 Analysis carried out on SciFinder on 06/04/2020 and 07/04/2020. A general substructure search was carried out with each ring size and heteroatom position iteratively with the following restrictions placed: (1) exclude metal-containing results; (2) exclude isotope-containing results; (3) only include if hit has references; (4) only include if hit is a single component; (5) limit references to biological or preparative sources.
- 16 B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, *et al.*, Spirotetrahydro β -Carbolines (Spiroindolones): A New Class of Potent and Orally Efficacious Compounds for the Treatment of Malaria, *J. Med. Chem.*, 2010, **53**, 5155.
- 17 A. A. Akaev, M. Y. Melnikov and E. M. Budynina, Chameleon-Like Activating Nature of the Spirooxindole Group in Donor-Acceptor Cyclopropanes, *Org. Lett.*, 2019, **21**, 9795.
- 18 Z. Y. Cao and J. Zhou, Catalytic asymmetric synthesis of polysubstituted spirocyclopropyl oxindoles: organocatalysis versus transition metal catalysis, *Org. Chem. Front.*, 2015, **2**, 849.
- 19 E. P. Bacher and B. L. Ashfeld, Transition metal-free strategies for the stereoselective construction of spirocyclopropyl oxindoles, *Tetrahedron*, 2020, **76**, 130692.
- 20 B. Sampson, Y. Liu, N. K. Patel, M. Feher, B. Forrest, S.-W. Li, L. Edwards, R. Laufer, Y. Lang, F. Ban, *et al.*, The Discovery of Polo-Like Kinase 4 Inhibitors: Design and Optimization of Spiro[cyclopropane-1,3'[3H]indol]-2'(1'H)-ones as Orally Bioavailable Antitumor Agents, *J. Med. Chem.*, 2015, **58**, 130.
- 21 S. Chen, H. He, B. Lagu, H. Qin, C. Wu and Y. Xiao, Tricyclic Sulfonamide Derivatives, *PCT Int. Appl* WO2015102929A1, 2015.
- 22 D. Brunner, J. Malberg, B. G. Shankar, S. Kolczewski, A. Limberg, E. Prinssen, C. Riemer and T. Stoll, 2-Oxo-2,3-dihydro-indoles for the Treatment of CNS Disorders, *PCT Int. Appl* WO2014040969A1, 2014.
- 23 (a) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y. H. Wu and Y. He, Design, synthesis and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part 1, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2105; (b) T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Tuntland, K. Zhang, D. Karanewsky, *et al.*, Design, synthesis and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part 2, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2109; (c) B. Yu, Z. Yu, P. P. Qi, D. Q. Yu and H. M. Liu, Discovery of orally active anticancer candidate CFI-400945 derived from biologically promising spirooxindoles: Success and challenges, *Eur. J. Med. Chem.*, 2015, **95**, 35; (d) S. Cockerill, C. Pilkington, J. Lumley, R. Angell and N. Mathews, Pharmaceutical Compounds, *PCT Int. Appl* WO2013068769A1, 2013.
- 24 (a) F. C. Stevens, W. E. Bloomquist, A. G. Borel, M. L. Cohen, C. A. Droste, M. L. Heiman, A. Kriauciunas, D. J. Sall, F. C. Tinsley and C. D. Jesudason, Potent oxindole based human β_3 adrenergic receptor agonists,



- Bioorg. Med. Chem. Lett.*, 2007, **17**, 6270; (b) A. Nardi, F. Jakob, I. Konetzki, T. Craan, C. Hesslinger and R. Doodeman, Novel Substituted Pyrimidine Compounds, *PCT Int. Appl* WO2016008593A1, 2016. Also see ref. 25.
- 25 D. W. Robertson, J. H. Krushinski, G. D. Pollock, H. Wilson, R. F. Kauffman and J. S. Hayes, Dihydropyridazinone cardiotonics: synthesis and inotropic activity of 5'-(1,4,5,6-tetrahydro-6-oxo-3-pyridazinyl)-spiro[cycloalkane-1,3'-(3H)indol-2'(1'H)-ones], *J. Med. Chem.*, 1987, **30**, 824.
 - 26 M. Palomba, L. Rossi, L. Sancineto, E. Tramontano, A. Corona, L. Bagnoli, C. Santi, C. Pannecouque, O. Tabarrini and F. Marini, A new vinyl selenone-based domino approach to spirocyclopropyl oxindoles endowed with anti-HIV RT activity, *Org. Biomol. Chem.*, 2016, **14**, 2015.
 - 27 M. Zhou, K. En, Y. Hu, Y. Xu, H. C. Shen and X. Qian, Zinc triflate-mediated cyclopropanation of oxindoles with vinyl diphenyl sulfonium triflate: a mild reaction with broad functional group compatibility, *RSC Adv.*, 2017, **7**, 3741.
 - 28 H. Qin, Y. Miao, K. Zhang, J. Xu, H. Sun, W. Liu, F. Feng and W. Qu, A convenient cyclopropanation process of oxindoles via bromoethylsulfonium salt, *Tetrahedron*, 2018, **74**, 6809.
 - 29 S. Hajra, S. Roy and S. A. Saleh, Domino Corey-Chaykovsky Reaction for One-Pot Access to Spirocyclopropyl Oxindoles, *Org. Lett.*, 2018, **20**, 4540.
 - 30 (a) S. A. Bonderoff and A. Padwa, Rh(II)-Catalyzed Reactions of Differentially Substituted Bis(diazo) functionalities, *Org. Lett.*, 2013, **15**, 4114; (b) S. Muthusamy and R. Ramkumar, Solvent- and transition metal-free synthesis of spiro[cyclopropane-1,3-oxindoles] from cyclic diazoamides, *Tetrahedron Lett.*, 2014, **55**, 6389; (c) G. Karthik, T. Rajasekaran, B. Sridhar and B. V. S. Reddy, Catalyst and solvent-free cyclopropanation of electron-deficient olefins with cyclic diazoamides for the synthesis of spiro[cyclopropane-1,3'-indolin]-2'-one derivatives, *Tetrahedron Lett.*, 2014, **55**, 7064; (d) S. Muthusamy and R. Ramkumar, Highly Diastereoselective Synthesis of Spirocyclopropane-oxindoles Using InCl_3 as a Catalyst in Water, *Synlett*, 2015, **26**, 2156.
 - 31 A. Awata and T. Arai, Catalytic Asymmetric Cyclopropanation with Diazooxindole, *Synlett*, 2013, **24**, 29.
 - 32 Z. Y. Cao, F. Zhou, Y. H. Yu and J. Zhou, A Highly Diastereo- and Enantioselective Hg(II)-Catalyzed Cyclopropanation of Diazooxindoles and Alkenes, *Org. Lett.*, 2013, **15**, 42.
 - 33 Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou and K. Ding, Highly Stereoselective Olefin Cyclopropanation of Diazooxindoles Catalyzed by a C_2 -Symmetric Spiroketal Bisphosphine/Au(I) Complex, *J. Am. Chem. Soc.*, 2013, **135**, 8197.
 - 34 Y. Chi, L. Qiu and X. Xu, Highly enantioselective synthesis of spirocyclopropyloxindoles via a Rh(II)-catalyzed asymmetric cyclopropanation reaction, *Org. Biomol. Chem.*, 2016, **14**, 10357.
 - 35 Z. Y. Cao, W. Wang, K. Liao, X. Wang, J. Zhou and J. Ma, Catalytic enantioselective synthesis of cyclopropanes featuring vicinal all-carbon quaternary stereocenters with a CH_2F group; study of the influence of C-F...H-N interactions on reactivity, *Org. Chem. Front.*, 2018, **5**, 2960.
 - 36 M. Tone, Y. Nakagawa, S. Chanthamath, I. Fujisawa, N. Nakayama, H. Goto, K. Shibatomi and S. Iwasa, Highly stereoselective spirocyclopropanation of various diazooxindoles with olefins catalyzed using Ru(II)-complex, *RSC Adv.*, 2018, **8**, 39865.
 - 37 J. L. Meloche and B. L. Ashfeld, A Rhodium(II)-Catalyzed Formal [4 + 1]-Cycloaddition toward Spirooxindole Pyrrolone Construction Employing Vinyl Isocyanates as 1,4-Dipoles, *Angew. Chem., Int. Ed.*, 2017, **56**, 6604.
 - 38 T.-R. Li, S.-W. Duan, W. Ding, Y.-Y. Liu, J.-R. Chen, L.-Q. Lu and W.-J. Xiao, Synthesis of CF_3 -Containing 3,3'-Cyclopropyl Spirooxindoles by Sequential [3 + 2] Cycloaddition/Ring Contraction of Ylideneoxindoles with 2,2,2-Trifluorodiazooethane, *J. Org. Chem.*, 2014, **79**, 2296.
 - 39 B. Morandi and E. M. Carreira, Iron-Catalyzed Cyclopropanation with Trifluoroethylamine Hydrochloride and Olefins in Aqueous Media: In Situ Generation of Trifluoromethyl Diazomethane, *Angew. Chem., Int. Ed.*, 2010, **49**, 938.
 - 40 G. Ramu, N. Hari Krishna, G. Pawar, K. N. Visweswara Sastry, J. B. Nanubolu and B. Nagendra Babu, Solvent-Controlled, Tunable Domino Reaction of 3-Ylideneoxindoles with in Situ-Generated α -Aryldiazomethanes: A Facile Access to 3-Spirocyclopropyl-2-oxindole and Pyrazoloquinazolinone, *ACS Omega*, 2018, **3**, 12349.
 - 41 W. Y. Han, J. Zhao, J. S. Wang, B. D. Cui, N. W. Wan and Y. Z. Chen, Syntheses of CF_2H -containing spirocyclopropyloxindoles from in situ generated CF_2HCHN_2 and 3-ylideneoxindoles, *Tetrahedron*, 2017, **73**, 5806.
 - 42 N. Huang, L. Zou and Y. Peng, Enantioselective 1,3-Dipolar Cycloaddition of Methyleneindolinones with α -Diazomethylphosphonate to Access Chiral Spiro-phosphonylpyrazoline-oxindoles Catalyzed by Tertiary Amine Thiourea and 1,5-Diazabicyclo[4.3.0]non-5-ene, *Org. Lett.*, 2017, **19**, 5806.
 - 43 (a) R. Zhou, C. Yang, Y. Liu, R. Li and Z. He, Diastereoselective Synthesis of Functionalized Spirocyclopropyl Oxindoles via $\text{P}(\text{NMe}_2)_3$ -Mediated Reductive Cyclopropanation, *J. Org. Chem.*, 2014, **79**, 10709. For a further study see: (b) E. E. Wilson, K. X. Rodriguez and B. L. Ashfeld, Stereochemical implications in the synthesis of 3,3'-spirocyclopropyl oxindoles from β -aryl/alkyl-substituted alkylidene oxindoles, *Tetrahedron*, 2015, **71**, 5765.
 - 44 D. Yin, H. Liu, C. D. Lu and Y. J. Xu, Dialkyl Phosphite-Initiated Cyclopropanation of α,β -Unsaturated Ketones Using α -Ketoesters or Isatin Derivatives, *J. Org. Chem.*, 2017, **82**, 3252.



- 45 L. Zhang, H. Lu, G.-Q. Xu, Z.-Y. Wang and P.-F. Xu, PPh_3 Mediated Reductive Annulation Reaction between Isatins and Electron Deficient Dienes to Construct Spirooxindole Compounds, *J. Org. Chem.*, 2017, **82**, 5782.
- 46 (a) J. H. Li, T. F. Feng and D. M. Du, Construction of Spirocyclopropane-Linked Heterocycles Containing Both Pyrazolones and Oxindoles through Michael/Alkylation Cascade Reactions, *J. Org. Chem.*, 2015, **80**, 11369; (b) Y. X. Song and D. M. Du, Asymmetric synthesis of spirooxindole-fused spirothiazolones via squaramide-catalysed reaction of 3-chlorooxindoles with 5-alkenyl thiazolones, *Org. Biomol. Chem.*, 2019, **17**, 5375; (c) S. Wang, Z. Guo, Y. Wu, W. Liu, X. Liu, S. Zhang and C. Sheng, Organocatalytic asymmetric synthesis of highly functionalized spiro-thiazolone-cyclopropane-oxindoles bearing two vicinal spiro quaternary centers, *Org. Chem. Front.*, 2019, **6**, 1442; (d) Y. Zhu, T. Lu, A. Geng, H. Cui and L. Zhang, Ultrafast and Diastereoselective Synthesis of 3-Spirocyclopropyl-2-oxindoles Bearing Three Continuous All-Carbon Quaternary Centers, *Heterocycles*, 2019, **98**, 711; (e) J. B. Wen and D. M. Du, Squaramide-catalysed asymmetric cascade reactions of 2,3-dioxopyrrolidines with 3-chlorooxindoles, *Org. Biomol. Chem.*, 2020, **18**, 1647.
- 47 J. Guo, Y. Liu, X. Li, X. Liu, L. Lin and X. Feng, Nickel(II)-catalyzed enantioselective cyclopropanation of 3-alkenyl-oxindoles with phenyliodonium ylide via free carbene, *Chem. Sci.*, 2016, **7**, 2717.
- 48 (a) L. Wang, W. Cao, H. Mei, L. Hu and X. Feng, Catalytic Asymmetric Synthesis of Chiral Spiro-cyclopropyl Oxindoles from 3-Alkenyl-oxindoles and Sulfoxonium Ylides, *Adv. Synth. Catal.*, 2018, **360**, 4089; (b) For a related metal-free diastereoselective transformation (when using a chiral sulfur ylide in combination with an asymmetric hydrogen bonding catalyst achieved a maximum 39% ee see: J. W. Kang, X. Li, F. Y. Chen, Y. Luo, S. C. Zhang, B. Kang, C. Peng, X. Tian and B. Han, Protecting group-directed annulations of tetra-substituted oxindole olefins and sulfur ylides: regio- and chemoselective synthesis of cyclopropane- and dihydrofuran-fused spirooxindoles, *RSC Adv.*, 2019, **9**, 12255.
- 49 C. L. Ladd, D. Sustac Roman and A. B. Charette, Silver-Promoted, Palladium-Catalyzed Direct Arylation of Cyclopropanes: Facile Access to Spiro 3,3'-Cyclopropyl Oxindoles, *Org. Lett.*, 2013, **15**, 1350.
- 50 H. Li, X. Yan, J. Zhang, W. Guo, J. Jiang and J. Wang, Enantioselective Synthesis of C-N Axially Chiral N-Aryloxindoles by Asymmetric Rhodium-Catalyzed Dual C-H Activation, *Angew. Chem., Int. Ed.*, 2019, **58**, 6732.
- 51 J. Li, T. Du, G. Zhang and Y. Peng, 3-Bromooxindoles as nucleophiles in asymmetric organocatalytic Mannich reactions with N-Ts-imines, *Chem. Commun.*, 2013, **49**, 1330.
- 52 (a) M. A. Loreto, A. Migliorini, P. A. Tardella and A. Gambacorta, Novel Spiroheterocycles by Aziridination of α -methylene- γ - and - δ -lactams, *Eur. J. Org. Chem.*, 2007, 2365; (b) I. Ammetto, T. Gasperi, M. A. Loreto, A. Migliorini, F. Palmarelli and P. A. Tardella, Synthesis of Functionalized Spiroaziridine-oxindoles from 3-Ylideneoxindoles: An Easy Route to 3-(Aminoalkyl)oxindoles, *Eur. J. Org. Chem.*, 2009, 6189; (c) T. Gasperi, M. A. Loreto, A. Migliorini and C. Ventura, Synthesis of Aziridine- and Oxirane-2-phosphonates Spiro-Fused with Oxindoles, *Eur. J. Org. Chem.*, 2011, 385.
- 53 (a) Q. L. Wang, T. Cai, J. Zhou, F. Tian, X. Y. Xu and L. X. Wang, An unprecedented base-promoted domino reaction of methyleneindolinones and N-tosyloxycarbamates for the construction of bispirooxindoles and spiroaziridine oxindoles, *Chem. Commun.*, 2015, **51**, 10726; (b) Y. Y. Liu, S. W. Duan, R. Zhang, Y. H. Liu, J. R. Chen and W. J. Xiao, Base-catalyzed controllable reaction of 3-ylideneoxindoles with O-Boc hydroxycarbamates for the synthesis of amidoacrylates and spiroaziridine oxindoles, *Org. Biomol. Chem.*, 2016, **14**, 5224.
- 54 M. A. Marsini, J. T. Reeves, J. N. Desrosiers, M. A. Herbage, J. Savoie, Z. Li, K. R. Fandrick, C. A. Sader, B. McKibben, D. A. Gao, *et al.*, Diastereoselective Synthesis of α -Quaternary Aziridine-2-carboxylates via Aza-Corey-Chaykovsky Aziridination of N-tert-Butanesulfinyl Ketimino Esters, *Org. Lett.*, 2015, **17**, 5614.
- 55 (a) S. Hajra, S. M. Aziz, B. Jana, P. Mahish and D. Das, Synthesis of Chiral Spiro-Aziridine Oxindoles via Aza-Corey-Chaykovsky reaction of Isatin Derived N-tert-Butanesulfinyl Ketimines, *Org. Lett.*, 2016, **18**, 532; (b) S. Hajra and A. Biswas, Catalyst-Free Stereocontrolled Formal [3 + 2]-Cycloaddition of CO_2 for the Synthesis of Enantiopure Spiro[Indoline-3,5'-Oxazolidine]-2,2'-Diones under Aqueous and Ambient Conditions, *Org. Lett.*, 2020, **22**, 4990.
- 56 J. Chen, X. Wen, Y. Wang, F. Du, L. Cai and Y. Peng, Asymmetric Mannich Reaction of Isatin-Based Ketimines with α -Diazomethylphosphonates Catalyzed by Chiral Silver Phosphate, *Org. Lett.*, 2016, **18**, 4336.
- 57 J. Q. Zhao, D. F. Yue, X. M. Zhang, X. Y. Xu and W. C. Yuan, The organocatalytic asymmetric Neber reaction for the enantioselective synthesis of spirooxindole 2H-azirines, *Org. Biomol. Chem.*, 2016, **14**, 10946.
- 58 (a) K. Sharma, L. K. Sharma and R. Jain, Facile Synthesis of Spiro[3h-Indole-3,2'oxirane]-3'-(2-Oxo-2-(Thiophene-2-Yl-(2(1H)Ones and their Antibacterial Activity, *Heterocycl. Lett.*, 2015, **5**, 383; (b) M. Montana, F. Correard, O. Khoumeri, M. A. Esteve, T. Terme and P. Vanelle, Synthesis of New Quinoxalines Containing an Oxirane Ring by the TDAE Strategy and in Vitro Evaluation in Neuroblastoma Cell Lines, *Molecules*, 2014, **19**, 14987.
- 59 S. Monticelli, L. Castoldi, S. Touqeer, M. Miele, E. Urban and V. Pace, Recent Advances in the Synthesis and Reactivity of Spiro-Epoxyoxindoles, *Chem. Heterocycl. Compd.*, 2018, **54**, 389.
- 60 M. M. Lou, H. Wang, L. Song, H. Y. Liu, Z. Q. Li, X. S. Guo, F. G. Zhang and B. Wang, The Epoxidation of Carbonyl Compounds with a Benzyne-Triggered Sulfur Ylide, *J. Org. Chem.*, 2016, **81**, 5915.



- 61 V. Pace, L. Castoldi, A. D. Mamuye, T. Langer and W. Holzer, Chemoselective Addition of Halomethylolithiums to Functionalised Isatins: A Straightforward Access to Spiro-Epoxyoxindoles, *Adv. Synth. Catal.*, 2016, **358**, 172.
- 62 (a) D. Basavaiah, S. S. Badsara and B. C. Sahu, Baylis-Hillman Bromides as a Source of 1,3-Dipoles: Sterically Directed Synthesis of Oxindole-Fused Spirooxirane and Spirodihydrofuran Frameworks, *Chem. – Eur. J.*, 2013, **19**, 2961; (b) Q. Fu and C. G. Yan, Facile synthesis of functionalized spiro[indoline-3,2'-oxiran]-2-ones by Darzens reaction, *Beilstein J. Org. Chem.*, 2013, **9**, 918.
- 63 B. Cheng, B. Zu, Y. Li, C. Tao, C. Zhang, R. Wang, Y. Li and H. Zhai, Synthesis of CF₃-containing spiro-epoxyoxindoles via the Corey-Chaykovsky reaction of N-alkyl isatins with Ph₂S⁺CH₂CF₃OTf[−], *Org. Biomol. Chem.*, 2018, **16**, 3564.
- 64 K. Luo, X. Yu, P. Chen, K. He, J. Lin and Y. Jin, Visible-light-induced aerobic epoxidation in cyclic ether: Synthesis of spiroepoxyoxindole derivatives, *Tetrahedron Lett.*, 2020, **61**, 151578.
- 65 S. Crotti, N. Di Iorio, C. Artusi, A. Mazzanti, P. Righi and G. Bencivenni, Direct Access to Alkylideneoxindoles via Axially Enantioselective Knoevenagel Condensation, *Org. Lett.*, 2019, **21**, 3013.
- 66 V. Schulz, M. Davoust, M. Lemarié, J. F. Lohier, J. S. O. De Santos, P. Metzner and J. F. Brière, Straightforward Stereoselective Synthesis of Spiro-epoxyoxindoles, *Org. Lett.*, 2007, **9**, 1745.
- 67 C. Palumbo, G. Mazzeo, A. Mazziotta, A. Gambacorta, M. A. Loreto, A. Migliorini, S. Superchi, D. Tofani and T. Gasperi, Noncovalent Organocatalysis: A Powerful Tool for the Nucleophilic. Epoxidation of α -Ylideneoxindoles, *Org. Lett.*, 2011, **13**, 6248.
- 68 M. Miceli, A. Mazziotta, C. Palumbo, E. Roma, E. Tosi, G. Longhi, S. Abbate, P. Lupattelli, G. Mazzeo and T. Gasperi, Asymmetric Synthesis of Spirooxindoles via Nucleophilic Epoxidation Promoted by Bifunctional Organocatalysis, *Molecules*, 2018, **23**, 438.
- 69 A. Boucherif, Q.-Q. Yang, Q. Wang, J.-R. Chen, L.-Q. Lu and W.-J. Xiao, Enantio- and Diastereoselective Synthesis of Spiro-epoxyoxindoles, *J. Org. Chem.*, 2014, **79**, 3924.
- 70 Y. Kuang, Y. Lu, Y. Tang, X. Liu, L. Lin and X. Feng, Asymmetric Synthesis of Spiro-epoxyoxindoles by the Catalytic Darzens Reaction of Isatins with Phenacyl Bromides, *Org. Lett.*, 2014, **16**, 4244.
- 71 G.-L. Chai, J.-W. Han and H. N. C. Wong, Asymmetric Darzens Reaction of Isatins with Diazoacetamides Catalyzed by Chiral BINOL-Titanium Complex, *J. Org. Chem.*, 2017, **82**, 12647.
- 72 (a) G. Zhu, G. Bao, Y. Li, W. Sun, J. Li, L. Hong and R. Wang, Efficient Catalytic Kinetic Resolution of Spiro-epoxyoxindoles with Concomitant Asymmetric Friedel-Crafts Alkylation of Indoles, *Angew. Chem., Int. Ed.*, 2017, **56**, 5332; (b) G. Zhu, Y. Li, G. Bao, W. Sun, L. Huang, L. Hong and R. Wang, Catalytic Kinetic Resolution of Spiro-Epoxyoxindoles with 1-Naphthols: Switchable Asymmetric Tandem Dearomatization/Oxa-Michael Reaction and Friedel-Crafts Alkylation of 1-Naphthols at the C4 Position, *ACS Catal.*, 2018, **8**, 1810.
- 73 R. Zhou, H. Zhang, J. Liu, R. Liu, W. C. Gao, Y. Qiao and R. Li, Chemoselective P(NMe₂)₃-Mediated Reductive Epoxidation between Two Different Carbonyl Electrophiles: Synthesis of Highly Functionalized Unsymmetrical Epoxides, *J. Org. Chem.*, 2018, **83**, 8272.
- 74 M. Yoshikawa, H. Kamisaki, J. Kunitomo, H. Oki, H. Kokubo, A. Suzuki, T. Ikemoto, K. Nakashima, N. Kamiguchi, A. Harada, *et al.*, Design and synthesis of a novel 2-oxindole scaffold as a highly potent and brain-penetrant phosphodiesterase 10A inhibitor, *Bioorg. Med. Chem.*, 2015, **23**, 7138.
- 75 R. K. Ujjinamatada, S. Samajdar, C. Abbineni, S. Mukeherjee, T. Linnanen and G. Wohlfahrt, Spiro[cyclobutane-1,3'-indolin]-2'-one Derivatives as Bromodomain Inhibitors, *PCT Int. Appl* WO2016203112A1, 2016.
- 76 A. Fensome, R. Bender, J. Cohen, M. A. Collins, V. A. Mackner, L. L. Miller, J. W. Ullrich, R. Winneker, J. Wrobel, P. Zhang, *et al.*, New progesterone receptor antagonists: 3,3-disubstituted-5-aryloxindoles, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3487.
- 77 A. Tahri, S. M. H. Vendeville, T. H. M. Jonckers, P. J.-M. B. Raboisson, L. Hu, S. D. Demin and L. P. Cooy-Mans, RSV Antiviral Compounds, *PCT Int. Appl* WO2014060411A1, 2014.
- 78 (a) P. S. Baran and J. M. Richter, Enantioselective Total Syntheses of Welwitindolinone A and Fischerindoles I and G, *J. Am. Chem. Soc.*, 2005, **127**, 15394; (b) P. S. Baran, T. J. Maimone and J. M. Richter, Total synthesis of marine natural products without using protecting groups, *Nature*, 2007, **446**, 404; (c) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio and P. S. Baran, Enantiospecific Total Synthesis of the Hapalindoles, Fischerindoles, and Welwitindolinones via a Redox Economic Approach, *J. Am. Chem. Soc.*, 2008, **130**, 17938.
- 79 (a) J. M. Ready, S. E. Reisman, M. Hirata, M. M. Weiss, K. Tamaki, T. V. Ovaska and J. L. Wood, A Mild and Efficient Synthesis of Oxindoles: Progress Towards the Synthesis of Welwitindolinone A Isonitrile, *Angew. Chem., Int. Ed.*, 2004, **43**, 1270; (b) S. E. Reisman, J. M. Ready, A. Hasuoka, C. J. Smith and J. L. Wood, Total Synthesis of (±)-Welwitindolinone A Isonitrile, *J. Am. Chem. Soc.*, 2006, **128**, 1448; (c) S. E. Reisman, J. M. Ready, M. M. Weiss, A. Hasuoka, M. Hirata, K. Tamaki, T. V. Ovaska, C. J. Smith and J. L. Wood, Evolution of a Synthetic Strategy: Total Synthesis of (±)-Welwitindolinone A Isonitrile, *J. Am. Chem. Soc.*, 2008, **130**, 2087.
- 80 L. E. Overman and D. J. Poon, Asymmetric Heck Reactions via Neutral Intermediates: Enhanced Enantioselectivity with Halide Additives Gives Mechanistic Insights, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 518.
- 81 D. Katayev, Y. X. Jia, A. K. Sharma, D. Banerjee, C. Besnard, R. B. Sunoj and E. P. Kündig, Synthesis of 3,3-



- Disubstituted Oxindoles by Palladium-Catalyzed Asymmetric Intramolecular α -Arylation of Amides: Reaction Development and Mechanistic Studies, *Chem. – Eur. J.*, 2013, **19**, 11916.
- 82 R. Rocaboy, D. Dailler, F. Zellweger, M. Neuburger, C. Salomé, E. Clot and O. Baudoin, Domino Pd⁰-Catalyzed C(sp³)-H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates, *Angew. Chem., Int. Ed.*, 2018, **57**, 12131.
 - 83 Though non-stereoselective, Zhang and co-workers discovered an unexpected cascade reaction upon treatment of a spirocyclopropyl oxetane with boron trifluoride diethyl etherate to form a spirocyclobutyl oxindole via a carbocationic intermediate: D. D. Wu, C. M. Huang, Y. H. Wu, H. K. Fun, J. H. Xu and Y. Zhang, Acid-mediated transformation of spirocyclopropyl oxetanes: a facile approach to spirocyclopropyl butenolides and γ -butyrolactones, *RSC Adv.*, 2013, **3**, 7529.
 - 84 J. Q. Chen, Y. L. Wei, G. Q. Xu, Y. M. Liang and P. F. Xu, Intramolecular 1,5-H transfer reaction of aryl iodides through visible-light photoredox catalysis: a concise method for the synthesis of natural product scaffolds, *Chem. Commun.*, 2016, **52**, 6455.
 - 85 S. M. Hell, C. F. Meyer, G. Laudadio, A. Misale, M. C. Willis, T. Noël, A. A. Trabanco and V. Gouverneur, Silyl Radical-Mediated Activation of Sulfamoyl Chlorides Enables Direct Access to Aliphatic Sulfonamides from Alkenes, *J. Am. Chem. Soc.*, 2020, **142**, 720.
 - 86 L. W. Qi, Y. Yang, Y. Y. Gui, Y. Zhang, F. Chen, F. Tian, L. Peng and L. X. Wang, Asymmetric Synthesis of 3,3'-Spirooxindoles Fused with Cyclobutanes through Organocatalytic Formal [2 + 2] Cycloadditions under H-Bond-Directing Dienamine Activation, *Org. Lett.*, 2014, **16**, 6436.
 - 87 K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund and K. A. Jørgensen, Organocatalytic Enamine-Activation of Cyclopropanes for Highly Stereoselective Formation of Cyclobutanes, *J. Am. Chem. Soc.*, 2015, **137**, 1685.
 - 88 (a) Y. H. Jiang, R. Y. Yang, J. Sun and C. G. Yan, Diastereoselective synthesis of dispiro[indoline-3,1'-cyclobutane-2',3"-indolines] via visible light catalyzed cyclodimerization of 3-phenacylideneoxindoles, *Heterocycl. Commun.*, 2016, **22**, 151; (b) L. L. Wu, G. H. Yang, Z. Guan and Y. H. He, Metal-free visible-light-promoted intermolecular [2 + 2]-cycloaddition of 3-ylideneoxindoles, *Tetrahedron*, 2017, **73**, 1854.
 - 89 (a) J. W. Skiles and D. McNeil, Spiro indolinone beta-lactams, inhibitors of poliovirus and rhinovirus 3C-proteinases, *Tetrahedron Lett.*, 1990, **31**, 7277; (b) W. Shi, Z. Jiang, H. He, F. Xiao, F. Lin, Y. Sun, L. Hou, L. Shen, L. Han, M. Zeng, *et al.*, Discovery of 3,3'-Spiro[Azetidine]-2-oxo-indoline Derivatives as Fusion Inhibitors for Treatment of RSV Infection, *ACS Med. Chem. Lett.*, 2018, **9**, 94.
 - 90 G. S. Singh and P. Luntha, Synthesis and antimicrobial activity of new 1-alkyl/cyclohexyl-3,3-diaryl-1'-methylspiro[azetidine-2,3'-indoline]-2',4-diones, *Eur. J. Med. Chem.*, 2009, **44**, 2265.
 - 91 R. Kumar, S. Giri and N. Nizamuddin, Synthesis of some 1'-(substituted phenyl)spiro[indole-3,4'-azetidine]-2(3H),2'-diones as potential fungicides, *J. Agric. Food Chem.*, 1989, **37**, 1094.
 - 92 R. Jain, K. Sharma and D. Kumar, Green Synthesis of 1-(1,2,4-Triazol-4-yl)spiro[azetidine-2,3'-(3H)indole]-2'4'(1'H)-diones as Potential Insecticide Agents, *J. Heterocycl. Chem.*, 2013, **50**, 315.
 - 93 C. Sun, X. Lin and S. M. Weinreb, Explorations on the Total Synthesis of the Unusual Marine Alkaloid Chartelline A, *J. Org. Chem.*, 2006, **71**, 3159.
 - 94 Ref. 92 and (a) H. Deokar, J. Chaskar and A. Chaskar, Synthesis, Screening And Antimicrobial Activity Of Spiro Indolothiazolidinone, Oxazolidinone And Azetidine Derivatives Of Benzenesulfonyl Chloride, *Pharm. Chem. J.*, 2012, **46**, 429; (b) B. V. Subba Reddy, G. Karthik, T. Rajasekaran, A. Antony and B. Sridhar, Rh₂(OAc)₄ catalyzed substrate selective [4 + 2]/[2 + 2] cycloaddition of acylketenes: a highly chemo- and regioselective synthesis of spiro(oxindolyl)oxazinones and β -lactams, *Tetrahedron Lett.*, 2012, **53**, 2396.
 - 95 H. M. Zhang, Z. H. Gao and S. Ye, Bifunctional N-Heterocyclic Carbene-Catalyzed Highly Enantioselective Synthesis of Spirocyclic Oxindole- β -lactams, *Org. Lett.*, 2014, **16**, 3079.
 - 96 (a) J. Xu, S. Yuan, J. Peng, M. Miao, Z. Chen and H. Ren, Enantioselective [2 + 2] annulation of simple aldehydes with isatin-derived ketimines via oxidative N-heterocyclic carbene catalysis, *Chem. Commun.*, 2017, **53**, 3430. For further insights see: (b) X. Li, R. Duan, Y. Wang, L. B. Qu, Z. Li and D. Wei, Insights into N-Heterocyclic Carbene-Catalyzed Oxidative α -C(sp³)-H Activation of Aliphatic Aldehydes and Cascade [2 + 2] Cycloaddition with Ketimines, *J. Org. Chem.*, 2019, **84**, 6117.
 - 97 J. H. Jin, J. Zhao, W. L. Yang and W. P. Deng, Asymmetric Synthesis of Spirooxindole β -lactams via Isothiourea-catalyzed Mannich/lactamization Reaction of Aryl Acetic Acids with Isatin-derived Ketimines, *Adv. Synth. Catal.*, 2019, **361**, 1592.
 - 98 S. Periyaraja, P. Shanmugam and A. B. Mandal, A Copper-Catalyzed One-Pot, Three-Component Diastereoselective Synthesis of 3-Spiroazetidinimine-2-oxindoles and Their Synthetic Transformation into Fluorescent Conjugated Indolones, *Eur. J. Org. Chem.*, 2014, 954.
 - 99 Throughout this review the stereochemical relationship is, where applicable, defined between the aromatic group of the oxindole and the substituent on the ring.
 - 100 S. Guo, P. Dong, Y. Chen, X. Feng and X. Liu, Chiral Guanidine/Copper Catalyzed Asymmetric Azide-Alkyne Cycloaddition/[2 + 2] Cascade Reaction, *Angew. Chem., Int. Ed.*, 2018, **57**, 16852.
 - 101 G. Rainoldi, M. Faltracco, L. Lo Presti, A. Silvani and G. Lesma, Highly diastereoselective entry into chiral spirooxindole-based 4-methyleneazetidines via formal [2 + 2] annulation reaction, *Chem. Commun.*, 2016, **52**, 11575.



- 102 G. Rainoldi, M. Faltracco, C. Spatti, A. Silvani and G. Lesma, Organocatalytic Access to Enantioenriched Spirooxindole-Based 4-Methyleneazetidines, *Molecules*, 2017, **22**, 2016.
- 103 (a) L. Su and M. H. Xu, Asymmetric Reformatsky-Type Reaction of Isatin-Derived N-Sulfinyl Ketimines: Efficient and Practical Synthesis of Enantiopure Chiral 2-Oxoindolinyl- $\beta^{3,3}$ -Amino Esters, *Synthesis*, 2016, **48**, 2595; (b) In 2017 Hajra synthesised the same intermediates with high dr: S. Hajra, S. S. Bhosale and A. Hazra, An asymmetric acetate-Mannich reaction of chiral isatin derived ketimines and its applications, *Org. Biomol. Chem.*, 2017, **15**, 9217.
- 104 Q. Tan, X. Wang, Y. Xiong, Z. Zhao, L. Li, P. Tang and M. Zhang, Chiral Amino Alcohol Accelerated and Stereocontrolled Allylboration of Iminoisatins: Highly Efficient Construction of Adjacent Quaternary Stereogenic Centers, *Angew. Chem., Int. Ed.*, 2017, **56**, 4829.
- 105 J. S. Yu, H. Noda and M. Shibasaki, Exploiting β -Amino Acid Enolates in Direct Catalytic Diastereo- and Enantioselective C-C Bond-Forming Reactions, *Chem. - Eur. J.*, 2018, **24**, 15796.
- 106 C. Deutsch, D. Kuhn, T. Ross and L. Burgdorf, 8-Substituted 2-Amino-[1,2,4] Triazolo [1,5-A] Pyrazines as SYK Tryrosine Kinase Inhibitors and GCN2 Serin Kinase Inhibitors, *PCT Int. Appl* WO2013124026A1, 2013.
- 107 D. D. Wu, M. T. He, Q. Di Liu, W. Wang, J. Zhou, L. Wang, H. K. Fun, J. H. Xu and Y. Zhang, Photoinduced reactions of bicycloalkylidenes with isatin and isoquinolinetriene, *Org. Biomol. Chem.*, 2012, **10**, 3626.
- 108 M. Palomba, E. Scarcella, L. Sancineto, L. Bagnoli, C. Santi and F. Marini, Synthesis of Spirooxindole Oxetanes Through a Domino Reaction of 3-Hydroxyoxindoles and Phenyl Vinyl Selenone, *Eur. J. Org. Chem.*, 2019, 5396.
- 109 P. R. Gentry, T. M. Bridges, A. Lamsal, P. N. Vinson, E. Smith, P. Chase, P. S. Hodder, J. L. Engers, C. M. Niswender, J. Scott Daniels, *et al.*, Discovery of ML326: The first sub-micromolar, selective M5 PAM, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 2996.
- 110 X. Hao, X. Liu, W. Li, F. Tan, Y. Chu, X. Zhao, L. Lin and X. Feng, Chiral Lewis Acid Catalyzed Asymmetric Cycloadditions of Disubstituted Ketenes for the Synthesis of β -Lactones and δ -Lactones, *Org. Lett.*, 2014, **16**, 134.
- 111 E. Hayashi, M. Isogai, Y. Kagawa, N. Takayanagi and S. Yamada, Neosurugatoxin, a Specific Antagonist of Nicotinic Acetylcholine Receptors, *J. Neurochem.*, 1984, **42**, 1491.
- 112 Z. Bian, C. C. Marvin and S. F. Martin, Enantioselective Total Synthesis of (-)-Citridinadin A and Revision of Its Stereochemical Structure, *J. Am. Chem. Soc.*, 2013, **135**, 10886.
- 113 (a) D. A. Mundal and R. Sarpong, Synthetic Studies toward the Citridinadin A and B Core Architecture, *Org. Lett.*, 2013, **15**, 4952; (b) E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, *et al.*, Total synthesis and isolation of citridinadin and cyclopamine congeners, *Nature*, 2014, **509**, 318; (c) N. S. Simpkins, I. Pavlakos, M. D. Weller and L. Male, The cascade radical cyclisation approach to prenylated alkaloids: synthesis of stephacidin A and notoamide B, *Org. Biomol. Chem.*, 2013, **11**, 4957; (d) B. Zhang, W. Zheng, X. Wang, D. Sun and C. Li, Total Synthesis of Notoamides F, I, and R and Sclerotiamide, *Angew. Chem., Int. Ed.*, 2016, **55**, 10435.
- 114 A. E. Fraley, K. Caddell Haatveit, Y. Ye, S. P. Kelly, S. A. Newmister, F. Yu, R. M. Williams, J. L. Smith, K. N. Houk and D. H. Sherman, Molecular Basis for Spirocyclic Formation in the Paraherquamide Biosynthetic Pathway, *J. Am. Chem. Soc.*, 2020, **142**, 2244.
- 115 K. Kong, J. A. Enquist, M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz and J. L. Wood, An Enantioselective Total Synthesis and Stereochemical Revision of (+)-Citridinadin B, *J. Am. Chem. Soc.*, 2013, **135**, 10890.
- 116 B. M. Trost, D. A. Bringley, T. Zhang and N. Cramer, Rapid Access to Spirocyclic Oxindole Alkaloids: Application of the Asymmetric Palladium-Catalyzed [3 + 2] Trimethylenemethane Cycloaddition, *J. Am. Chem. Soc.*, 2013, **135**, 16720.
- 117 M. E. Hinze, J. L. Daughtry and C. A. Lewis, Access to the Surugatoxin Alkaloids: Chemo-, Regio-, and Stereoselective Oxindole Annulation, *J. Org. Chem.*, 2015, **80**, 11258.
- 118 L. Shi, L. Li, J. Wang, B. Huang, K. Zeng, H. Jin, Q. Zhang and Y. Jia, Total synthesis of natural spiro-trisindole enantiomers similisines A, B and their stereoisomers, *Tetrahedron Lett.*, 2017, **58**, 1934.
- 119 For a review see: Z. Chen, Z. Chen, W. Du and Y. Chen, Transformations of Modified Morita-Baylis-Hillman Adducts from Isatins Catalyzed by Lewis Bases, *Chem. Rec.*, 2020, **20**, 541.
- 120 For selected significant prior art in this area see: (a) B. M. Trost, N. Cramer and S. M. Silverman, Enantioselective Construction of Spirocyclic Oxindolic Cyclopentanes by Palladium-Catalyzed Trimethylenemethane-[3 + 2]-Cycloaddition, *J. Am. Chem. Soc.*, 2007, **129**, 12396; (b) J. Peng, X. Huang, L. Jiang, H. L. Cui and Y. C. Chen, Tertiary Amine-Catalyzed Chemoselective and Asymmetric [3 + 2] Annulation of Morita-Baylis-Hillman Carbonates of Isatins with Propargyl Sulfones, *Org. Lett.*, 2011, **13**, 4584; (c) B. Tan, N. R. Candeias and C. F. Barbas, Core-Structure-Motivated Design of a Phosphine-Catalyzed [3 + 2] Cycloaddition Reaction: Enantioselective Syntheses of Spirocyclopenteneoxindoles, *J. Am. Chem. Soc.*, 2011, **133**, 4672.
- 121 Y. Chen, B. D. Cui, Y. Wang, W. Y. Han, N. W. Wan, M. Bai, W. C. Yuan and Y. Z. Chen, Asymmetric [3 + 2] Cycloaddition Reaction of Isatin-Derived MBH Carbonates with 3-Methyleneoxindoles: Enantioselective Synthesis of 3,3'-Cyclopentenyl-dispirooxindoles Incorporating Two



- Adjacent Quaternary Spirostereocenters, *J. Org. Chem.*, 2018, **83**, 10465.
- 122 Y. Chen, B. D. Cui, M. Bai, W. Y. Han, N. W. Wan and Y. Z. Chen, Synthesis of chiral spiro-cyclopentene/cyclopentadiene-oxindoles through an asymmetric [3 + 2] cycloaddition of isatin-derived MBH carbonates and β,γ -unsaturated α -keto esters, *Tetrahedron*, 2019, **75**, 2971.
- 123 For related work see: (a) J. Peng, G. Y. Ran, W. Du and Y. C. Chen, Tertiary-Amine-Catalyzed Asymmetric [3 + 2] Annulations of Morita-Baylis-Hillman Carbonates of Isatins with Nitroolefins to Construct Spirooxindoles, *Synthesis*, 2015, **47**, 2538; (b) G. Y. Ran, P. Wang, W. Du and Y. C. Chen, α -Regioselective [3 + 2] annulations with Morita-Baylis-Hillman carbonates of isatins and 2-nitro-1,3-enynes, *Org. Chem. Front.*, 2016, **3**, 861; (c) G. Zhan, M.-L. Shi, Q. He, W.-J. Lin, Q. Ouyang, W. Du and Y.-C. Chen, Catalyst-Controlled Switch in Chemo- and Diastereoselectivities: Annulations of Morita-Baylis-Hillman Carbonates from Isatins, *Angew. Chem., Int. Ed.*, 2016, **55**, 2147; (d) Z. H. Wang, C. W. Lei, X. Y. Zhang, Y. You, J. Q. Zhao and W. C. Yuan, Asymmetric domino 1,6-addition/annulation reaction of 3-cyano-4-alkenyl-2H-chromen-2-ones with isatin-derived MBH cyclopentenyl-spirooxindoles bearing 2H-chromen-2-ones, *Org. Chem. Front.*, 2019, **6**, 3342; (e) J. Q. Zhao, L. Yang, X. J. Zhou, Y. You, Z. H. Wang, M. Q. Zhou, X. M. Zhang, X. Y. Xu and W. C. Yuan, Organocatalyzed Dearomative Cycloaddition of 2-Nitrobenzofurans and Isatin-Derived Morita-Baylis-Hillman Carbonates: Highly Stereoselective Construction of Cyclopenta[b]benzofuran Scaffolds, *Org. Lett.*, 2019, **21**, 660.
- 124 F. Zhong, X. Han, Y. Wang and Y. Lu, Highly Enantioselective [3 + 2] Annulation of Morita-Baylis-Hillman Adducts Mediated by L-Threonine-Derived Phosphines: Synthesis of 3-Spirocyclopentene-2-oxindoles having Two Contiguous Quaternary Centers, *Angew. Chem., Int. Ed.*, 2011, **50**, 7837.
- 125 Work by Miao and co-workers on phosphorus promoted [3 + 2] cycloaddition of alkynes and 3-methylene oxindoles with moderate enantioselectivity achieved: (a) J. Zhang, C. Cheng, D. Wang and Z. Miao, Regio- and Diastereoselective Construction of Spirocyclopenteneoxindoles through Phosphine-Catalyzed [3 + 2] Annulation of Methyleneindolinone with Alkynoate Derivatives, *J. Org. Chem.*, 2017, **82**, 10121. For related non-stereoselective activation by phosphorus catalysts see: (b) L. Zhang, H. Lu, G.-Q. Xu, Z.-Y. Wang and P.-F. Xu, PPh₃ Mediated Reductive Annulation Reaction between Isatins and Electron Deficient Dienes to Construct Spirooxindole Compounds, *J. Org. Chem.*, 2017, **82**, 5782. Also see: (c) D. B. Ramachary, C. Venkaiah and P. M. Krishna, Stereoselective Synthesis of Five-Membered Spirooxindoles through Tomita Zipper Cyclization, *Org. Lett.*, 2013, **15**, 4714; (d) C. Gomez, M. Gicquel, J. C. Carry, L. Schio, P. Retailleau, A. Voituriez and A. Marinetti, Phosphine-Catalyzed Synthesis of 3,3-Spirocyclopenteneoxindoles from g-Substituted Allenates: Systematic Studies and Targeted Applications, *J. Org. Chem.*, 2013, **78**, 1488.
- 126 W. L. Chan, X. Tang, F. Zhang, G. Quek, G. J. Mei and Y. Lu, Phosphine-Catalyzed (3 + 2) Annulation of Isoindigos with Allenes: Enantioselective Formation of Two Vicinal Quaternary Stereogenic Centers, *Angew. Chem., Int. Ed.*, 2019, **58**, 6260.
- 127 J. Zhang, W.-L. Chan, L. Chen, N. Ullah and Y. Lu, Creation of bispiro[pyrazoline-3,3'-oxindoles] via a phosphine-catalyzed enantioselective [3 + 2] annulation of the Morita-Baylis-Hillman carbonates with pyrazoloneyldiene, *Org. Chem. Front.*, 2019, **6**, 2210.
- 128 S. Su, C. Li, X. Jia and J. Li, Isocyanide-Based Multicomponent Reactions: Concise Synthesis of Spirocyclic Oxindoles with Molecular Complexity by Using a [1,5]-Hydrogen Shift as the Key Step, *Chem. – Eur. J.*, 2014, **20**, 5905.
- 129 B. Tan, N. R. Candeias and C. F. Barbas, Construction of bispirooxindoles containing three quaternary stereocentres in a cascade using a single multifunctional organo-catalyst, *Nat. Chem.*, 2011, **3**, 473.
- 130 (a) X. Li, Y. M. Li, F. Z. Peng, S. T. Wu, Z. Q. Li, Z. W. Sun, H. Bin Zhang and Z. H. Shao, Highly Enantioselective One-Pot Synthesis of Spirocyclopentaneoxindoles Containing the Oxime Group by Organocatalyzed Michael Addition/ISOC/Fragmentation Sequence, *Org. Lett.*, 2011, **13**, 6160; (b) K. Albertshofer, K. E. Anderson and C. F. Barbas, Assembly of Spirooxindole Derivatives via Organocatalytic Iminium-Enamine Cascade Reactions, *Org. Lett.*, 2012, **14**, 5968; (c) W. Sun, G. Zhu, C. Wu, L. Hong and R. Wang, An Organocatalytic Cascade Strategy for the Enantioselective Construction of Spirocyclopentane Bioxindoles Containing Three Contiguous Stereocenters and Two Spiro Quaternary Centers, *Chem. – Eur. J.*, 2012, **18**, 6737; (d) W. Sun, G. Zhu, C. Wu, L. Hong and R. Wang, 'Organo-Metal' Synergistic Catalysis: The 1 + 1 > 2 Effect for the Construction of Spirocyclopentane oxindoles, *Chem. – Eur. J.*, 2012, **18**, 13959; (e) J. Sun, Y. J. Xie and C. G. Yan, Construction of Dispirocyclopentanebisoxindoles via Self-Domino Michael-Aldol Reactions of 3-Phenacylideneoxindoles, *J. Org. Chem.*, 2013, **78**, 8354; (f) W. Sun, L. Hong, G. Zhu, Z. Wang, X. Wei, J. Ni and R. Wang, An Organocatalytic Michael-Michael Cascade for the Enantioselective Construction of Spirocyclopentane Bioxindoles: Control of Four Contiguous Stereocenters, *Org. Lett.*, 2014, **16**, 544; (g) L. Z. Ding, T. S. Zhong, H. Wu and Y. M. Wang, Highly Enantioselective Construction of Spirocyclopentaneoxindoles Containing Four Consecutive Stereocenters through an Organocatalytic Iminium-Enamine Cascade Reaction, *Eur. J. Org. Chem.*, 2014, 5139; (h) J. Zhou, Q. L. Wang, L. Peng, F. Tian, X. Y. Xu and L. X. Wang, An organocatalytic domino Michael-alkylation reaction: highly enantioselective construction of spiro-



- cyclopentaneoxindoles and tetronic acid scaffolds, *Chem. Commun.*, 2014, **50**, 14601; (i) K. Suman and S. Thennarasu, Base catalysed domino and self-domino Michael-Aldol reactions: one-pot synthesis of dispirocyclopentaneoxindoles containing multiple chiral stereocenters, *RSC Adv.*, 2015, **5**, 23291; (j) B. L. Zhao and D. M. Du, Organocatalytic cascade Michael/Michael reaction for the asymmetric synthesis of spirooxindoles containing five contiguous stereocenters, *Chem. Commun.*, 2016, **52**, 6162; (k) Y. Du, J. Li, K. Chen, C. Wu, Y. Zhou and H. Liu, Construction of highly enantioenriched spirocyclopentaneoxindoles containing four consecutive stereocenters via thiourea-catalyzed asymmetric Michael-Henry cascade reactions, *Beilstein J. Org. Chem.*, 2017, **13**, 1342; (l) R.-Y. Yang, J. Sun, G. Jin and C.-G. Yan, Synthesis of functionalized dispiro[indoline-3,1'-cyclopentane-3',3''-indolines] via cyclo-dimerization of 3-phenacylideneoxindolines with benzoylhydrazides and arylhydrazines, *Mol. Diversity*, 2018, **22**, 21; (m) B. L. Zhao, Y. Lin and D. M. Du, Enantioselective Construction of Bispirooxindoles via Squaramide-Catalysed Cascade Michael/Cyclization Reaction, *Adv. Synth. Catal.*, 2019, **361**, 3387; (n) Y. Lin, B.-L. Zhao and D.-M. Du, Bifunctional Squaramide-Catalyzed Asymmetric [3 + 2] Cyclization of 2-(1-Methyl-2-oxoindolin-3-yl)malonitriles with Unsaturated Pyrazolones To Construct Spirooxindole-Fused Spiropyrazolones, *J. Org. Chem.*, 2019, **84**, 10209; (o) S. Xu, X. Liu, X. Zuo, G. Zhou, Y. Gong, X. Liu and Y. Zhou, Oxindole-chromones C3 Synthons Directed Stereocontrolled Construction of Five Contiguous Stereocenters on Spiro[tetrahydrocyclopenta[b]chromanone-oxindole]s, *Adv. Synth. Catal.*, 2019, **361**, 5328; (p) S. S. Vagh, P. Karanam, C. Liao, T. Lin, Y. Liou, A. Edukondalu, Y. Chen and W. Lin, Enantioselective Construction of Spirooxindole-Fused Cyclopenta[c]chromen-4-ones Bearing Five Contiguous Stereocenters via a Stepwise (3 + 2) Cycloaddition, *Adv. Synth. Catal.*, 2020, **362**, 1679.
- 131 (a) A. Noole, K. Ilmarinen, I. Järving, M. Lopp and T. Kanger, Asymmetric Synthesis of Congested Spiro-cyclopentaneoxindoles via an Organocatalytic Cascade Reaction, *J. Org. Chem.*, 2013, **78**, 8117. Also see for 5- and 6-membered rings: (b) M. Monari, E. Montroni, A. Nitti, M. Lombardo, C. Trombini and A. Quintavalla, Highly Stereoselective [4 + 2] and [3 + 2] Spiroannulations of 2-(2-Oxoindolin-3-ylidene)acetic Esters Catalyzed by Bifunctional Thioureas, *Chem. – Eur. J.*, 2015, **21**, 11038.
 - 132 L. Deiana, Y. Jiang, C. Palo-Nieto, S. Afewerki, C. A. Incerti-Pradillos, O. Verho, C. W. Tai, E. V. Johnston and A. Córdova, Combined Heterogeneous Metal/Chiral Amine: Multiple Relay Catalysis for Versatile Eco-Friendly Synthesis, *Angew. Chem., Int. Ed.*, 2014, **53**, 3447.
 - 133 (a) F. Shi, H. H. Zhang, X. X. Sun, J. Liang, T. Fan and S. J. Tu, Organocatalytic Asymmetric Cascade Reactions of 7-Vinylindoles: Diastereo- and Enantioselective Synthesis of C7-Functionalized Indoles, *Chem. – Eur. J.*, 2015, **21**, 3465; (b) T. Fan, H. H. Zhang, C. Li, Y. Shen and F. Shi, The Application of N-Protected 3-Vinylindoles in Chiral Phosphoric Acid-Catalyzed [3 + 2] Cyclization with 3-Indolylmethanols: Monoactivation of the Catalyst to Vinyliminium, *Adv. Synth. Catal.*, 2016, **358**, 2017.
 - 134 J. Q. Zhang, N. K. Li, S. J. Yin, B. B. Sun, W. T. Fan and X. W. Wang, Chiral N-Heterocyclic Carbene-Catalyzed Asymmetric Michael-Intramolecular Aldol-Lactonization Cascade for Enantioselective Construction of β -Propiolactone-Fused Spiro[cyclopentane-oxindoles], *Adv. Synth. Catal.*, 2017, **359**, 1541.
 - 135 For earlier work using NHC catalysis see: A. Patra, A. Bhunia, S. R. Yetra, R. G. Gonnade and A. T. Biju, Diastereoselective synthesis of cyclopentanone-fused spirooxindoles by N-heterocyclic carbene-catalyzed homoenolate annulation with isatidenes, *Org. Chem. Front.*, 2015, **2**, 1584.
 - 136 L. Wang, S. Li, M. Blümel, R. Puttreddy, A. Peuronen, K. Rissanen and D. Enders, Switchable Access to Different Spirocyclopentane Oxindoles by N-Heterocyclic Carbene Catalyzed Reactions of Isatin-Derived Enals and N-Sulfonyl Ketimines, *Angew. Chem., Int. Ed.*, 2017, **56**, 8516.
 - 137 J. Zhang, D. Cao, H. Wang, C. Zheng, G. Zhao and Y. Shang, Enantioselective Construction of Spirocyclic Oxindoles via Tandem Michael/Michael Reactions Catalyzed by Multifunctional Quaternary Phosphonium Salt, *J. Org. Chem.*, 2016, **81**, 10558.
 - 138 Q. Jin, C. Zheng, G. Zhao and G. Zou, Bifunctional Quaternary Ammonium Salts Catalyzed Stereoselective Conjugate Addition of Oxindoles to Electron-Deficient β -Haloalkanes, *J. Org. Chem.*, 2017, **82**, 4840.
 - 139 (a) G. M. Dubowchik, C. M. Conway and A. W. Xin, Blocking the CGRP Pathway for Acute and Preventive Treatment of Migraine: The Evolution of Success, *J. Med. Chem.*, 2020, **63**, 6600; (b) B. M. Crowley, C. A. Stump, D. N. Nguyen, C. M. Potteiger, M. A. McWherter, D. V. Paone, A. G. Quigley, J. G. Bruno, D. Cui, J. C. Culberson, *et al.*, Novel oxazolidinone calcitonin gene-related (CGRP) receptor antagonists for the acute treatment of migraine, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4777.
 - 140 B. Xiang, K. M. Belyk, R. A. Reamer and N. Yasuda, Discovery and Application of Doubly Quaternized Cinchona-Alkaloid-Based Phase-Transfer Catalysts, *Angew. Chem., Int. Ed.*, 2014, **53**, 8375.
 - 141 C. Q. He, A. Simon, Y.-H. Lam, A. P. J. Brunskill, N. Yasuda, J. Tan, A. M. Hyde, E. C. Sherer and K. N. Houk, Model for the Enantioselectivity of Asymmetric Intramolecular Alkylations by Bis-Quaternized Cinchona Alkaloid-Derived Catalysts, *J. Org. Chem.*, 2017, **82**, 8645.
 - 142 J. A. Daponte, Y. Guo, R. T. Ruck and J. E. Hein, Using an Automated Monitoring Platform for Investigations of Biphasic Reactions, *ACS Catal.*, 2019, **9**, 11484.
 - 143 X. Zhao, X. Liu, Q. Xiong, H. Mei, B. Ma, L. Lin and X. Feng, The asymmetric synthesis of polycyclic 3-spiroox-



- indole alkaloids via the cascade reaction of 2-isocyanoethylindoles, *Chem. Commun.*, 2015, **51**, 16076.
- 144 A. A. Cobo, B. M. Armstrong, J. C. Fettinger and A. K. Franz, Catalytic Asymmetric Synthesis of Cyclopentene-spirooxindoles Bearing Vinylsilanes Capable of Further Transformations, *Org. Lett.*, 2019, **21**, 8196.
 - 145 (a) J. A. Xiao, X. L. Cheng, Y. C. Li, Y. M. He, J. L. Li, Z. P. Liu, P. J. Xia, W. Su and H. Yang, Palladium-catalysed ring-opening [3 + 2]-annulation of spirovinylcyclopropyl oxindole to diastereoselectively access spirooxindoles, *Org. Biomol. Chem.*, 2019, **17**, 103. For metal-free approach using cyclopropanes see: (b) D. Pan, C. Mou, N. Zan, Y. Lv, B. A. Song, Y. R. Chi and Z. Jin, NaOH-Promoted Chemoselective Cascade Cyclization of Cyclopropyl Esters with Unsaturated Imines: Access to Bioactive Cyclopenta [c]pyridine derivatives, *Org. Lett.*, 2019, **21**, 6624. For Mg catalysed approach: (c) K. Singh, S. Pramanik, T. A. Hamlin, B. Mondal, D. Das and J. Saha, Lewis acid catalyzed annulation of spirocyclic donor-acceptor cyclopropanes with exo-heterocyclic olefins: access to highly functionalized bis-spirocyclopentane oxindole frameworks, *Chem. Commun.*, 2019, **55**, 7069.
 - 146 M. Meazza and R. Rios, Synergistic Catalysis: Enantioselective Ring Expansion of Vinyl Cyclopropanes Combining Four Catalytic Cycles for the Synthesis of Highly Substituted Spirocyclopentanes Bearing up to Four Stereocenters, *Chem. – Eur. J.*, 2016, **22**, 9923.
 - 147 For examples see: (a) J. N. Desrosiers, L. Hie, S. Biswas, O. V. Zatolochnaya, S. Rodriguez, H. Lee, N. Grinberg, N. Haddad, N. K. Yee, N. K. Garg, *et al.*, Construction of Quaternary Stereocenters by Nickel-Catalyzed Heck Cyclization Reactions, *Angew. Chem., Int. Ed.*, 2016, **55**, 11921; (b) W. Ji, Y. A. Liu and X. Liao, Transition-Metal-Free Synthesis of N-Hydroxy Oxindoles by an Aza-Nazarov-Type Reaction Involving Azaoxyallyl Cations, *Angew. Chem., Int. Ed.*, 2016, **55**, 13286; (c) W. Kong, Q. Wang and J. Zhu, Water as a Hydride Source in Palladium-Catalyzed Enantioselective Reductive Heck Reactions, *Angew. Chem., Int. Ed.*, 2017, **56**, 3987.
 - 148 S. Afewerki, G. Ma, I. Ibrahim, L. Liu, J. Sun and A. Córdova, Highly Enantioselective Control of Dynamic Cascade Transformations by Dual Catalysis: Asymmetric Synthesis of Polysubstituted Spirocyclic Oxindoles, *ACS Catal.*, 2015, **5**, 1266.
 - 149 (a) B. M. Trost, D. Zell, C. Hohn, G. Mata and A. Maruniak, Enantio- and Diastereoselective Synthesis of Chiral Allenes by Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition Reactions, *Angew. Chem., Int. Ed.*, 2018, **57**, 12916; (b) B. M. Trost, Y. Wang and C.-I. (Joey) Hung, Use of α -trifluoromethyl carbanions for palladium-catalysed asymmetric cycloadditions, *Nat. Chem.*, 2020, **12**, 294.
 - 150 P. Drouhin, T. E. Hurst, A. C. Whitwood and R. J. K. Taylor, Copper-Mediated Construction of Spirocyclic Bis-oxindoles via a Double C-H, Ar-H Coupling Process, *Org. Lett.*, 2014, **16**, 4900.
 - 151 A. Wetzel, J. Bergman, P. Brandt, M. Larhed and J. Bräñalt, Regio- and Stereoselective Synthesis of Functionalized Cyclopentene Derivatives via Mizoroki-Heck Reactions, *Org. Lett.*, 2017, **19**, 1602.
 - 152 T. Roy, P. Brandt, A. Wetzel, J. Bergman, J. Bräñalt, J. Sävmarker and M. Larhed, Selective Synthesis of Spirooxindoles by an Intramolecular Heck-Mizoroki Reaction, *Org. Lett.*, 2017, **19**, 2738.
 - 153 (a) M. Pérez-Gómez, S. Hernández-Ponte, D. Bautista and J. A. García-López, Synthesis of spiro-oxindoles through Pd-catalyzed remote C-H alkylation using α -diazocarbonyl compounds, *Chem. Commun.*, 2017, **53**, 2842. Also see: (b) X. Liu, X. Ma, Y. Huang and Z. Gu, Pd-Catalyzed Heck-Type Cascade Reactions with N-Tosyl Hydrazones: An Efficient Way to Alkenes via in Situ Generated Alkylpalladium, *Org. Lett.*, 2013, **15**, 4814; (c) C. Shao, Z. Wu, X. Ji, B. Zhou and Y. Zhang, An approach to spirooxindoles via palladium-catalyzed remote C-H activation and dual alkylation with CH_2Br_2 , *Chem. Commun.*, 2017, **53**, 10429.
 - 154 (a) J. R. Frost, S. M. Huber, S. Breitenlechner, C. Bannwarth and T. Bach, Enantiotopos-Selective C-H Oxygenation Catalyzed by a Supramolecular Ruthenium Complex, *Angew. Chem., Int. Ed.*, 2015, **54**, 691; (b) B. Qiu, D. Xu, Q. Sun, J. Lin and W. Sun, Manganese-Catalyzed Asymmetric Oxidation of Methylene C-H of Spirocyclic Oxindoles and Dihydroquinolinones with Hydrogen Peroxide, *Org. Lett.*, 2019, **21**, 618.
 - 155 (a) M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, Selective Synthesis of Six Products from a Single Indolyl α -Diazocarbonyl Precursor, *Angew. Chem., Int. Ed.*, 2016, **55**, 9671. For a related reaction in total synthesis of spirobacillenes A and B see: (b) H. Yang, J. Feng and Y. Tang, Biomimetic total syntheses of spirobacillenes A and B, *Chem. Commun.*, 2013, **49**, 6442.
 - 156 R. Paniagua-Pérez, E. Madrigal-Bujaidar, D. Molina-Jasso, S. Reyes-Cadena, I. Álvarez-González, L. Sánchez-Chapul and J. Pérez-Gallaga, Antigenotoxic, Antioxidant and Lymphocyte Induction Effects Produced by Pteropodine, *Basic Clin. Pharmacol. Toxicol.*, 2009, **104**, 222.
 - 157 (a) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, *et al.*, Structure-Based Design of Potent Non-Peptide MDM2 Inhibitors, *J. Am. Chem. Soc.*, 2005, **127**, 10130; (b) Y. Zhao, S. Yu, W. Sun, L. Liu, J. Lu, D. McEachern, S. Shargary, D. Bernard, X. Li, T. Zhao, *et al.*, A Potent Small-Molecule Inhibitor of the MDM2-p53 Interaction (MI-888) Achieved Complete and Durable Tumor Regression in Mice, *J. Med. Chem.*, 2013, **56**, 5553; (c) Y. Zhao, L. Liu, W. Sun, J. Lu, D. McEachern, X. Li, S. Yu, D. Bernard, P. Ochsenbein, V. Ferey, *et al.*, Diastereomeric Spirooxindoles as Highly Potent and Efficacious MDM2 Inhibitors, *J. Am. Chem. Soc.*, 2013, **135**, 7223; (d) A. K. Gupta, M. Bharadwaj, A. Kumar and R. Mehrotra, Spiro-oxindoles as a Promising Class of Small Molecule Inhibitors of p53-MDM2 Interaction



- Useful in Targeted Cancer Therapy, *Top. Curr. Chem.*, 2017, **375**, 3.
- 158 (a) A. Kumar, G. Gupta, A. K. Bishnoi, R. Saxena, K. S. Saini, R. Konwar, S. Kumar and A. Dwivedi, Design and synthesis of new bioisosteres of spirooxindoles (MI-63/219) as anti-breast cancer agents, *Bioorg. Med. Chem.*, 2015, **23**, 839; (b) A. Gollner, D. Rudolph, H. Arnhof, M. Bauer, S. M. Blake, G. Boehmelt, X. L. Cockcroft, G. Dahmann, P. Ettmayer, T. Gerstberger, *et al.*, Discovery of Novel Spiro[3H-indole-3,2'-pyrrolidin]-2 (1H)-one Compounds as Chemically Stable and Orally Active Inhibitors of the MDM2-p53 Interaction, *J. Med. Chem.*, 2016, **59**, 10147; (c) A. Aguilar, J. Lu, L. Liu, D. Du, D. Bernard, D. McEachern, S. Przybranowski, X. Li, R. Luo, B. Wen, *et al.*, Discovery of 4-((3'R,4'S,5'R)-6"-Chloro-4'-(3-chloro-2-fluorophenyl)-1'-ethyl-2"-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indoline]-5'-carboxamido)-bicyclo[2.2.2]octane-1-carboxylic Acid (AA-115/APG-115): A Potent and Orally Active Murine Double Minute 2 (MDM2) Inhibitor in Clinical Development, *J. Med. Chem.*, 2017, **60**, 2819; (d) A. Barakat, M. S. Islam, H. M. Ghawas, A. M. Al-Majid, F. F. El-Senduny, F. A. Badria, Y. A. M. M. Elshaier and H. A. Ghabbour, Design and synthesis of new substituted spirooxindoles as potential inhibitors of the MDM2-p53 interaction, *Bioorg. Chem.*, 2019, **86**, 598.
 - 159 (a) Y. Li, J. Yang, A. Aguilar, D. McEachern, S. Przybranowski, L. Liu, C. Y. Yang, M. Wang, X. Han and S. Wang, Discovery of MD-224 as a First-in-Class, Highly Potent, and Efficacious Proteolysis Targeting Chimera Murine Double Minute 2 Degradable Capable of Achieving Complete and Durable Tumor Regression, *J. Med. Chem.*, 2019, **62**, 448; (b) R. P. Wurz and V. J. Cee, Targeted Degradation of MDM2 as a New Approach to Improve the Efficacy of MDM2-p53 Inhibitors, *J. Med. Chem.*, 2019, **62**, 445.
 - 160 J. Yang, Y. Li, A. Aguilar, Z. Liu, C. Y. Yang and S. Wang, Simple Structural Modifications Converting a Bona fide MDM2 PROTAC Degradable into a Molecular Glue Molecule: A Cautionary Tale in the Design of PROTAC Degradable, *J. Med. Chem.*, 2019, **62**, 9471.
 - 161 Y. Arun, G. Bhaskar, C. Balachandran, S. Ignacimuthu and P. T. Perumal, Facile one-pot synthesis of novel dispirooxindole-pyrrolidine derivatives and their antimicrobial and anticancer activity against A549 human lung adenocarcinoma cancer cell line, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 1839.
 - 162 I. V. Efremov, F. F. Vajdos, K. A. Borzilleri, S. Capetta, H. Chen, P. H. Dorff, J. K. Dutra, S. W. Goldstein, M. Mansour, A. McColl, *et al.*, Discovery and Optimization of a Novel Spiropyrrolidine Inhibitor of β -Secretase (BACE1) through Fragment-Based Drug Design, *J. Med. Chem.*, 2012, **55**, 9069.
 - 163 R. Murugan, S. Anbazhagan and S. Sriman Narayanan, Synthesis and in vivo antidiabetic activity of novel dispiropyrrolidines through [3 + 2] cycloaddition reactions with thiazolidinedione and rhodanine derivatives, *Eur. J. Med. Chem.*, 2009, **44**, 3272.
 - 164 K. Hagiwara, T. Murakami, G. Xue, Y. Shimizu, E. Takeda, Y. Hashimoto, K. Honda, Y. Kondoh, H. Osada, Y. Tsunetsugu-Yokota, *et al.*, Identification of a novel Vpr-binding compound that inhibits HIV-1 multiplication in macrophages by chemical array, *Biochem. Biophys. Res. Commun.*, 2010, **403**, 40.
 - 165 S. V. Karthikeyan, B. D. Bala, V. P. A. Raja, S. Perumal, P. Yogeewari and D. Sriram, A highly atom economic, chemo-, regio- and stereoselective synthesis and evaluation of spiro-pyrrolothiazoles as antitubercular agents, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 350.
 - 166 (a) C. Marti and E. M. Carreira, Construction of Spiro[pyrrolidine-3,3'-oxindoles] – Recent Applications to the Synthesis of Oxindole Alkaloids, *Eur. J. Org. Chem.*, 2003, 2209; (b) C. V. Galliford and K. A. Scheidt, Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.
 - 167 (a) T. Mukaiyama, K. Ogata, I. Sato and Y. Hayashi, Asymmetric Organocatalyzed Michael Addition of Nitromethane to a 2-Oxindoline-3-ylidene Acetaldehyde and the Three One-Pot Sequential Synthesis of (–)-Horsifoline and (–)-Coerulescine, *Chem. – Eur. J.*, 2014, **20**, 13583; (b) S. De, M. K. Das, S. Bhunia and A. Bisai, Unified Approach to the Spiro(pyrrolidinyl-oxindole) and Hexahydropyrrolo[2,3-b]indole Alkaloids: Total Syntheses of Pseudophrynamines 270 and 272A, *Org. Lett.*, 2015, **17**, 5922.
 - 168 (a) S. G. Wang, Z. L. Xia, R. Q. Xu, X. J. Liu, C. Zheng and S. L. You, Construction of Chiral Tetrahydro- β -Carbolines: Asymmetric Pictet-Spengler Reaction of Indolyl Dihydropyridines, *Angew. Chem., Int. Ed.*, 2017, **56**, 7440; (b) V. Srinivasulu, P. Schilf, S. Ibrahim, M. A. Khanfar, S. M. Sieburth, H. Omar, A. Sebastian, R. A. AlQawasmeh, M. J. O'Connor and T. H. Al-Tel, Multidirectional desymmetrization of pluripotent building block en route to diastereoselective synthesis of complex nature-inspired scaffolds, *Nat. Commun.*, 2018, **9**, 4989.
 - 169 (a) G. O. Fonseca, Z. J. Wang, O. A. Namjoshi, J. R. Deschamps and J. M. Cook, First stereospecific total synthesis of (–)-affinisine oxindole as well as facile entry into the C(7)-diastereomeric chitosenine stereochemistry, *Tetrahedron Lett.*, 2015, **56**, 3052; (b) M. R. Stephen, M. T. Rahman, V. V. N. P. B. Tiruveedhula, G. O. Fonseca, J. R. Deschamps and J. M. Cook, Concise Total Synthesis of (–)-Affinisine Oxindole, (+)-Isoalstonisine, (+)-Alstofoline, (–)-Macrogentine, (+)-N_a-Demethylalstonisine, (–)-Alstonoxine A, and (+)-Alstonisine, *Chem. – Eur. J.*, 2017, **23**, 15805.
 - 170 Q. Yu, P. Guo, J. Jian, Y. Chen and J. Xu, Nine-step total synthesis of (–)-strychnofoline, *Chem. Commun.*, 2018, **54**, 1125.
 - 171 Y. K. Xi, H. Zhang, R. X. Li, S. Y. Kang, J. Li and Y. Li, Total Synthesis of Spirotryprostatins through



- Organomediated Intramolecular Umpolung Cyclization, *Chem. – Eur. J.*, 2019, **25**, 3005.
- 172 P. Chen, H. Yang, H. Zhang, W. Chen, Z. Zhang, J. Zhang, H. Li, X. Wang, X. Xie and X. She, Total Synthesis of (–)-Gardmultimine A, *Org. Lett.*, 2020, **5**, 2022–2025.
- 173 (a) M. Amat, C. Ramos, M. Pérez, E. Molins, P. Florindo, M. M. M. Santos and J. Bosch, Enantioselective formal synthesis of ent-rhynchophylline and ent-isorhynchophylline, *Chem. Commun.*, 2013, **49**, 1954. Also see: (b) M. Pérez, C. Ramos, L. Massi, S. Gazzola, C. Taglienti, N. Yayik, E. Molins, A. Viayna, F. J. Luque, J. Bosch, *et al.*, Enantioselective Synthesis of Spiro[indolizidine-1,3'-oxindoles], *Org. Lett.*, 2017, **19**, 4050.
- 174 (a) X.-H. Chen, Q. Wei, S.-W. Luo, H. Xiao and L.-Z. Gong, Organocatalytic Synthesis of Spiro[pyrrolidin-3,3'-oxindoles] with High Enantiopurity and Structural Diversity, *J. Am. Chem. Soc.*, 2009, **131**, 13819. For 3,2'-spiropyrrolidines see: (b) F. Shi, Z. L. Tao, S. W. Luo, S. J. Tu and L. Z. Gong, Scaffold-Inspired Enantioselective Synthesis of Biologically Important Spiro[pyrrolidin-3,2'-oxindoles] with Structural Diversity through Catalytic Isatin-Derived 1,3-Dipolar Cycloadditions, *Chem. – Eur. J.*, 2012, **18**, 6885.
- 175 For a related chiral auxiliary approach see: (a) P. R. Sebahar and R. M. Williams, The Asymmetric Total Synthesis of (+)- and (–)-Spirotryprostatin B, *J. Am. Chem. Soc.*, 2000, **122**, 5666; (b) T. Onishi, P. R. Sebahar and R. M. Williams, Concise, Asymmetric Total Synthesis of Spirotryprostatin A, *Org. Lett.*, 2003, **5**, 3135.
- 176 (a) J. Li, J. Wang, Z. Xu and S. Zhu, Combinatorial Synthesis of Functionalized Spirooxindole-Pyrrolidine/Pyrrolizidine/Pyrrolothiazole Derivatives via Three-Component 1,3-Dipolar Cycloaddition Reactions, *ACS Comb. Sci.*, 2014, **16**, 506; (b) L. Cui, G. Zhu, S. Liu, X. Bao, X. Zhao, J. Qu and B. Wang, Construction of indolenine-substituted spiro[pyrrolidine-2,3'-oxindoles] from 2-alkenylindolenines and isatin-derived azomethine ylides, *Tetrahedron*, 2018, **74**, 2369; (c) J. Yue, S. Chen, X. Zuo, X. L. Liu, S. W. Xu and Y. Zhou, Diversity-oriented one-pot multicomponent synthesis of chromanone-based 3,3'-pyrrolidinyl-spirooxindoles via a 1,3-dipolar cycloaddition reaction, *Tetrahedron Lett.*, 2019, **60**, 137; (d) M. S. Islam, H. M. Ghawas, F. F. El-Senduny, A. M. Al-Majid, Y. A. M. M. Elshaier, F. A. Badria and A. Barakat, Synthesis of new thiazolo-pyrrolidine(spirooxindole) tethered to 3-acylindole as anticancer agents, *Bioorg. Chem.*, 2019, **82**, 423; (e) L. Wang, X. M. Shi, W. P. Dong, L. P. Zhu and R. Wang, Efficient construction of highly functionalized spiro[γ -butyrolactone-pyrrolidin-3,3'-oxindole] tricyclic skeletons via an organocatalytic 1,3-dipolar cycloaddition, *Chem. Commun.*, 2013, **49**, 3458; (f) F. Salahi, M. J. Taghizadeh, H. Arvinnezhad, M. Moemeni, K. Jadidi and B. Notash, An efficient, one-pot, three-component procedure for the synthesis of chiral spirooxindolopyrrolizidines via catalytic highly enantioselective 1,3-dipolar cycloaddition, *Tetrahedron Lett.*, 2014, **55**, 1515; (g) X. Meng, Y. Du, Q. Zhang, A. Yu, Y. Zhang, J. Jia and X. Liu, Direct Functionalization of Azepane via Azomethine Ylides: A Highly Efficient Synthesis of Spirooxindoles Bearing a 1-Azabicyclo[5.3.0]decane Moiety, *Asian J. Org. Chem.*, 2017, **6**, 1719; (h) Y. Du, A. Yu, J. Jia, Y. Zhang and X. Meng, Direct N-H/ $\alpha,\alpha,\beta,\beta$ -C(sp³)-H functionalization of piperidine via an azomethine ylide route: synthesis of spirooxindoles bearing 3-substituted oxindoles, *Chem. Commun.*, 2017, **53**, 1684; (i) X. Zhang, M. Liu, W. Qiu, J. Evans, M. Kaur, J. P. Jasinski and W. Zhang, One-Pot Synthesis of Polycyclic Spirooxindoles via Montmorillonite K10-Catalyzed C-H Functionalization of Cyclic Amines, *ACS Sustainable Chem. Eng.*, 2018, **6**, 5574.
- 177 (a) Y. Huang, H. L. Fang, Y. X. Huang, J. Sun and C. G. Yan, Synthesis of 7'-Arylidenespiro[indoline-3,1'-pyrrolizines] and 7'-Arylidenespiro[indene-2,1'-pyrrolizines] via [3 + 2] Cycloaddition and β -C-H Functionalized Pyrrolidine, *J. Org. Chem.*, 2019, **84**, 12437; (b) I. B. Kutyashev, M. V. Ulitko, A. Y. Barkov, N. S. Zimmitskiy, V. Y. Korotaev and V. Y. Sosnovskikh, A regio- and stereocontrolled approach to the synthesis of 4-CF₃-substituted spiro[chromeno[3,4-c]pyrrolidine-oxindoles] via reversible [3 + 2] cycloaddition of azomethine ylides generated from isatins and sarcosine to 3-nitro-2-(trifluoromethyl)-2H-chromenes, *New J. Chem.*, 2019, **43**, 18495; (c) Z. Zhang, W. Sun, G. Zhu, J. Yang, M. Zhang, L. Hong and R. Wang, Chiral phosphoric acid catalyzed enantioselective 1,3-dipolar cycloaddition reaction of azlactones, *Chem. Commun.*, 2016, **52**, 1377; (d) W. Sun, G. Zhu, C. Wu, G. Li, L. Hong and R. Wang, Organocatalytic Diastereo- and Enantioselective 1,3-Dipolar Cycloaddition of Azlactones and Methyleneindolinones, *Angew. Chem., Int. Ed.*, 2013, **52**, 8633; (e) A. S. Filatov, N. A. Knyazev, A. P. Molchanov, T. L. Panikorovsky, R. R. Kostikov, A. G. Larina, V. M. Boitsov and A. V. Stepanov, Synthesis of Functionalized 3-Spiro[cyclopropa[a]pyrrolizine]- and 3-Spiro[3-azabicyclo[3.1.0]hexane]oxindoles from Cyclopropenes and Azomethine Ylides via [3 + 2]-Cycloaddition, *J. Org. Chem.*, 2017, **82**, 959; (f) X.-C. Yang, J.-Y. Liu, Z. Liu, X.-Q. Hu and P.-F. Xu, Quaternary Carbon Center Forming [3 + 2] Cyclization Reaction by Adjusting the Substituents of Substrates, *J. Org. Chem.*, 2019, **84**, 13871.
- 178 (a) P. Wu, H. Gao, J. Sun and C. G. Yan, Isatin hybrids and their anti-tuberculosis activity, *Chin. Chem. Lett.*, 2017, **28**, 329; (b) Y. Huang, Y. X. Huang, J. Sun and C. G. Yan, A [3 + 2] cycloaddition reaction for the synthesis of spiro[indoline-3,3'-pyrrolidines] and evaluation of cytotoxicity towards cancer cells, *New J. Chem.*, 2019, **43**, 8903.
- 179 C. S. Wang, R. Y. Zhu, J. Zheng, F. Shi and S. J. Tu, Enantioselective Construction of Spiro[indoline-3,2'-pyrrole] Framework via Catalytic Asymmetric 1,3-Dipolar Cycloadditions Using Allenes as Equivalents of Alkynes, *J. Org. Chem.*, 2015, **80**, 512.



- 180 (a) G. Zhu, B. Wang, X. Bao, H. Zhang, Q. Wei and J. Qu, Catalytic asymmetric construction of spiro[pyrrolidine-2,3'-oxindole] scaffolds through chiral phosphoric acid-catalyzed 1,3-dipolar cycloaddition involving 3-amino oxindoles, *Chem. Commun.*, 2015, **51**, 15510–15513; (b) Q. Wei, G. Zhu, H. Zhang, J. Qu and B. Wang, 1,3-Dipolar Cycloaddition of Azomethine Ylides Involving 3-Aminooxindoles: Versatile Construction of Dispiro[pyrrolidine-2,3'-oxindole] Scaffolds, *Eur. J. Org. Chem.*, 2016, 5335; (c) G. Zhu, S. Liu, S. Wu, L. Peng, J. Qu and B. Wang, Assembly of Indolenines, 3-Amino Oxindoles, and Aldehydes into Indolenine-Substituted Spiro[pyrrolidine-2,3'-oxindoles] via 1,3-Dipolar Cycloaddition with Divergent Diastereoselectivities, *J. Org. Chem.*, 2017, **82**, 4317; (d) G. Zhu, Q. Wei, H. Chen, Y. Zhang, W. Shen, J. Qu and B. Wang, Asymmetric [3 + 2] Cycloaddition of 3-Amino Oxindole-Based Azomethine Ylides and α,β -Enones with Divergent Diastereocontrol on the Spiro [pyrrolidine-oxindoles], *Org. Lett.*, 2017, **19**, 1862; (e) G. Zhu, S. Wu, X. Bao, L. Cui, Y. Zhang, J. Qu, H. Chen and B. Wang, Asymmetric [3 + 2] cycloaddition of 3-amino oxindole-based azomethine ylides with α,β -ynones: a straightforward approach to spirooxindoles incorporating 2,5-dihydropyrroles and pyrroles, *Chem. Commun.*, 2017, **53**, 4714; (f) J. He, R.-G. Sun, L. Fan, S.-Y. Tian, T.-P. Huang, Z. Chen and L. Chen, 4-(N,N-Dimethylamino) pyridine (DMAP)-Catalyzed 1,3-Dipolar Cycloaddition of 3-Aminooxindole-Based Azomethine Ylides with α,β -Unsaturated Acyl Phosphonates for the Construction of Spiropyrrolidinyl-2,3'-oxindoles, *Synthesis*, 2019, **51**, 1353; (g) T. Huang, L. Liu, Q. Wang, M. Wu and D. Kong, 1,3-Dipolar Cycloaddition of 3-Amino Oxindole-Based Azomethine Ylides and O-Vinylphosphonylated Salicylaldehydes for Diastereoselective Synthesis of Oxindole Spiro-P,N-polycyclic Heterocycles, *Synthesis*, 2020, **52**, 1387.
- 181 (a) J. Sun, G. L. Shen, Y. Huang and C. G. Yan, Formation of diverse polycyclic spirooxindoles via three-component reaction of isoquinolinium salts, isatins and malononitrile, *Sci. Rep.*, 2017, **7**, 41024; (b) Y. Huang, W. Min, Q. W. Wu, J. Sun, D. H. Shi and C. G. Yan, Facile one-pot synthesis of spirooxindole-pyrrolidine derivatives and their antimicrobial and acetylcholinesterase inhibitory activities, *New J. Chem.*, 2018, **42**, 16211.
- 182 (a) X. Wang, P. Yang, Y. Zhang, C. Z. Tang, F. Tian, L. Peng and L. X. Wang, Isatin, N,N'-Cyclic Azomethine Imine 1,3-Dipole and Abnormal [3 + 2]-Cycloaddition with Maleimide in the Presence of 1,4-Diazabicyclo[2.2.2] octane, *Org. Lett.*, 2017, **19**, 646; (b) X.-J. Song, H.-X. Ren, M. Xiang, C.-Y. Li, F. Tian and L.-X. Wang, Base Catalyzed Abnormal [3 + 2]-Cycloaddition between Isatin N,N'-Cyclic Azomethine Imine 1,3-Dipole and 3-Methyleneoxindole for the One-Step Construction of Tetracyclic Bispirooxindoles, *J. Org. Chem.*, 2020, **85**, 3921.
- 183 J. Day, M. Uroos, R. A. Castledine, W. Lewis, B. McKeever-Abbas and J. Dowden, Alkaloid inspired spirocyclic oxindoles from 1,3-dipolar cycloaddition of pyridinium ylides, *Org. Biomol. Chem.*, 2013, **11**, 6502.
- 184 (a) J. A. Xiao, H. G. Zhang, S. Liang, J. W. Ren, H. Yang and X. Q. Chen, Synthesis of Pyrrolo(spiro-[2.3']-oxindole)-spiro-[4.3'']-oxindole via 1,3-Dipolar Cycloaddition of Azomethine Ylides with 3-Acetylidenoxindole, *J. Org. Chem.*, 2013, **78**, 11577; (b) Y. L. Qian, B. Li, P. J. Xia, J. Wang, H. Y. Xiang and H. Yang, Diastereospecific entry to pyrrolidinyl-dispirooxindole skeletons via three-component 1,3-dipolar cycloadditions, *Tetrahedron*, 2018, **74**, 6821; (c) T. T. Feng, Y. Gong, Q. Di Wei, G. L. Wang, H. H. Liu, M. Y. Tian, X. L. Liu, Z. Y. Chen and Y. Zhou, Diversity-oriented Construction of Chromanone-fused Polycyclic Pyrrolidinyl-dispirooxindoles, *J. Heterocycl. Chem.*, 2018, **55**, 1136; (d) Y. Huang, Y. X. Huang, J. Sun and C. G. Yan, Diastereoselective synthesis of dispirooxindoles via, [3 + 2] cycloaddition of azomethine ylides to 3-phenacylidenoxindoles and evaluation of their cytotoxicity, *RSC Adv.*, 2018, **8**, 23990; (e) J. Guo, Y. Zhao, D. Fang, Q. Wang and Z. Bu, Diastereoselective construction of pyrrolo[2,1-a]isoquinoline-based bispirooxindoles through a three-component [3 + 2] cycloaddition, *Org. Biomol. Chem.*, 2018, **16**, 6025; (f) S. Bhandari, S. Sana, B. Sridhar and N. Shankaraiah, Microwave-Assisted One-Pot [3 + 2] Cycloaddition of Azomethine Ylides and 3-Alkenyl Oxindoles: A Facile Approach to Pyrrolidine-Fused Bis-Spirooxindoles, *ChemistrySelect*, 2019, **4**, 1727; (g) W. Dai, X. L. Jiang, Q. Wu, F. Shi and S. J. Tu, Diastereo- and Enantioselective Construction of 3,3'-Pyrrolidinyl-dispirooxindole Framework via Catalytic Asymmetric 1,3-Dipolar Cycloadditions, *J. Org. Chem.*, 2015, **80**, 5737; (h) K. Suman, L. Srinu and S. Thennarasu, Lewis Acid Catalyzed Unprecedented [3 + 2] Cycloaddition Yields 3,3'-Pyrrolidinyl-dispirooxindoles Containing Four Contiguous Chiral Stereocenters with Two Contiguous Quaternary Spirostereocenters, *Org. Lett.*, 2014, **16**, 3732; (i) D. Shukla and S. A. Babu, Pd-Catalyzed Diastereoselective Intramolecular Amide α -C–H Arylation in Sterically Hindered Monospirooxindole Motifs, *Adv. Synth. Catal.*, 2019, **361**, 2075; (j) N. Shahrestani, K. Tovfighmadar, M. Eskandari, K. Jadidi, B. Notash and P. Mirzaei, Synthesis of Highly Enantioenriched Bis-spirooxindole Pyrrolizidine/Pyrrolidines through Asymmetric [3 + 2] Cycloaddition Reaction, *Asian J. Org. Chem.*, 2020, **9**, 822.
- 185 (a) T. Arai, H. Ogawa, A. Awata, M. Sato, M. Watabe and M. Yamanaka, PyBidine-Cu(OTf)₂-Catalyzed Asymmetric [3 + 2] Cycloaddition with Imino Esters: Harmony of Cu-Lewis Acid and Imidazolidine-NH Hydrogen Bonding in Concerto Catalysis, *Angew. Chem., Int. Ed.*, 2015, **54**, 1595; (b) W. L. Yang, Y. Z. Liu, S. Luo, X. Yu, J. S. Fossey and W. P. Deng, The copper-catalyzed asymmetric construction of a dispiropyrrolidine skeleton via 1,3-dipolar cycloaddition of azomethine ylides to α -alkylidene succinimides, *Chem. Commun.*, 2015, **51**, 9212.
- 186 L. Shu, Z. Li, C. Gu and D. Fishlock, Synthesis of a Spiroindolinone Pyrrolidinecarboxamide MDM2 Antagonist, *Org. Process Res. Dev.*, 2013, **17**, 247.



- 187 J. P. Macdonald, B. H. Shupe, J. D. Schreiber and A. K. Franz, Counterion effects in the catalytic stereoselective synthesis of 2,3'-pyrrolidiny spirooxindoles, *Chem. Commun.*, 2014, **50**, 5242.
- 188 M. Ma, Y. Zhu, Q. Sun, X. Li, J. Su, L. Zhao, Y. Zhao, S. Qiu, W. Yan, K. Wang, *et al.*, The asymmetric synthesis of CF₃-containing spiro[pyrrolidin-3,2'-oxindole] through the organocatalytic 1,3-dipolar cycloaddition reaction, *Chem. Commun.*, 2015, **51**, 8789.
- 189 Q. Sun, X. Li, J. Su, L. Zhao, M. Ma, Y. Zhu, Y. Zhao, R. Zhu, W. Yan, K. Wang, *et al.*, The Squaramide-Catalyzed 1,3-Dipolar Cycloaddition of Nitroalkenes with N-2,2,2-Trifluoroethylisatin Ketimines: An Approach for the Synthesis of 5'-Trifluoromethyl-spiro[pyrrolidin-3,2'-oxindoles], *Adv. Synth. Catal.*, 2015, **357**, 3187.
- 190 (a) A. Ponce, I. Alonso, J. Adrio and J. C. Carretero, Stereoselective Ag-Catalyzed 1,3-Dipolar Cycloaddition of Activated Trifluoromethyl-Substituted Azomethine Ylides, *Chem. – Eur. J.*, 2016, **22**, 4952; (b) H. Z. Gui, Y. N. Gao, Y. Wei and M. Shi, Highly Efficient and Diastereoselective Construction of Trifluoromethyl-Containing Spiro[pyrrolidin-3,2'-oxindole] by a Catalyst-free Mutually Activated [3 + 2] Cycloaddition Reaction, *Chem. – Eur. J.*, 2018, **24**, 10038; (c) X. Y. Wu, Y. N. Gao and M. Shi, Phosphine-Catalyzed [3 + 2] Annulation of N-2,2,2-Trifluoroethylisatin Ketimines with γ -Substituted Allenates: Synthesis of Spiro[indoline-3,2'-pyrrole], *Eur. J. Org. Chem.*, 2019, 1620.
- 191 (a) Z. H. Wang, Z. J. Wu, D. F. Yue, W. F. Hu, X. M. Zhang, X. Y. Xu and W. C. Yuan, Organocatalytic asymmetric [3 + 2] cycloaddition of N-2,2,2-trifluoroethylisatin ketimines with 3-alkenyl-5-aryl-furan-2(3H)-ones, *Chem. Commun.*, 2016, **52**, 11708; (b) C. Wang, D. Wen, H. Chen, Y. Deng, X. Liu, X. Liu, L. Wang, F. Gao, Y. Guo, M. Sun, *et al.*, The catalytic asymmetric synthesis of CF₃-containing spiro-oxindole-pyrrolidine-pyrazolone compounds through squaramide-catalyzed 1,3-dipolar cycloaddition, *Org. Biomol. Chem.*, 2019, **17**, 5514; (c) C. Zou, Y. Han, C. Zeng, T. Y. Zhang, J. Ye and G. Song, Remote regioselective organocatalytic asymmetric [3 + 2] cycloaddition of N-2,2,2-trifluoroethyl isatin ketimines with cyclic 2,4-dienones, *Chin. Chem. Lett.*, 2020, **31**, 377; (d) Y. Yi, Y. Hua, H. Lu, L. Liu and M. Wang, Brønsted Base and Lewis Acid Cooperatively Catalyzed Asymmetric exo'-Selective [3 + 2] Cycloaddition of Trifluoromethylated Azomethine Ylides and Methyleneindolinones, *Org. Lett.*, 2020, **22**, 2527; (e) B. Li, F. Gao, X. Feng, M. Sun, Y. Guo, D. Wen, Y. Deng, J. Huang, K. Wang and W. Yan, Highly efficient enantioselective synthesis of bispiro[benzofuran-oxindole-pyrrolidine]s through organocatalytic cycloaddition, *Org. Chem. Front.*, 2019, **6**, 1567; (f) X. Liu, D. Lu, J.-H. Wu, J.-P. Tan, C. Jiang, G. Gao and T. Wang, Stereoselective Synthesis of CF₃-Containing Spirooxindoles via 1,3-Dipolar Cycloaddition by Dipeptide-Based Phosphonium Salt Catalysis, *Adv. Synth. Catal.*, 2020, **362**, 1490; (g) Y. Zhi, K. Zhao, C. Von Essen, K. Rissanen and D. Enders, Thiourea-Catalyzed Domino Michael-Mannich [3 + 2] Cycloadditions: A Strategy for the Asymmetric Synthesis of 3,3'-Pyrrolidiny-dispirooxindoles, *Synlett*, 2017, **28**, 2876; (h) T. L. An and D. M. Du, Chiral Squaramide Catalyzed Asymmetric [3 + 2] Cycloaddition Reaction for Synthesis of Trifluoromethylated Barbituric Acid Derivatives, *ChemistrySelect*, 2019, **4**, 11302; (i) F.-Y. Chen, L. Xiang, G. Zhan, H. Liu, B. Kang, S.-C. Zhang, C. Peng and B. Han, Highly stereoselective organocatalytic synthesis of pyrrolidiny spirooxindoles containing halogenated contiguous quaternary carbon stereocenters, *Tetrahedron Lett.*, 2020, **61**, 151806.
- 192 J. X. Zhang, H. Y. Wang, Q. W. Jin, C. W. Zheng, G. Zhao and Y. J. Shang, Thiourea-Quaternary Ammonium Salt Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Imino Esters To Construct Spiro[pyrrolidin-3,3'-oxindoles], *Org. Lett.*, 2016, **18**, 4774.
- 193 J. H. Siitonen, S. Lira, M. Yousufuddin and L. Kürti, Total synthesis of isatindigotindoline C, *Org. Biomol. Chem.*, 2020, **18**, 2051.
- 194 P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, Facile, Novel Methodology for the Synthesis of Spiro[pyrrolidin-3,3'-oxindoles]: Catalyzed Ring Expansion Reactions of Cyclopropanes by Aldimines, *Angew. Chem., Int. Ed.*, 1999, **38**, 3186.
- 195 (a) A. Lerchner and E. M. Carreira, First Total Synthesis of (±)-Strychnofoline via a Highly Selective Ring-Expansion Reaction, *J. Am. Chem. Soc.*, 2002, **124**, 14826; (b) A. Lerchner and E. M. Carreira, Synthesis of (±)-Strychnofoline via a Highly Convergent Selective Annulation Reaction, *Chem. – Eur. J.*, 2006, **12**, 8208; (c) C. Meyers and E. M. Carreira, Total Synthesis of (–)-Spirotryprostatin B, *Angew. Chem., Int. Ed.*, 2003, **42**, 694; (d) C. Marti and E. M. Carreira, Total Synthesis of (–)-Spirotryprostatin B: Synthesis and Related Studies, *J. Am. Chem. Soc.*, 2005, **127**, 11505–11515; (e) C. P. Seath, J. W. B. Fyfe, J. J. Molloy and A. J. B. Watson, Synthesis of Oxindoles and Benzofuranones via Oxidation of 2-Heterocyclic BMIDAs, *Synthesis*, 2017, **49**, 891.
- 196 (a) V. Helan, A. Mills, D. Drewry and D. Grant, A Rapid Three-Component MgI₂-Mediated Synthesis of 3,3'-Pyrrolidiny Spirooxindoles, *J. Org. Chem.*, 2010, **75**, 6693; (b) E. M. Buev, V. S. Moshkin and V. Y. Sosnovskikh, Reactivity of spiroanthraceneoxazolidines with cyclopropanes: An approach to the oxindole alkaloid scaffold, *Tetrahedron Lett.*, 2018, **59**, 3409.
- 197 Z. Zhang, W. Zhang, F. Kang, F. C. F. Ip, N. Y. Ip and R. Tong, Asymmetric Total Syntheses of Rhynchophylline and Isorhynchophylline, *J. Org. Chem.*, 2019, **84**, 11359.
- 198 A. A. Akaev, E. V. Villemson, N. S. Vorobyeva, A. G. Majouga, E. M. Budynina and M. Y. Melnikov, 3-(2-Azidoethyl)oxindoles: Advanced Building Blocks for One-Pot Assembly of Spiro[pyrrolidine-3,3'-oxindoles], *J. Org. Chem.*, 2017, **82**, 5689.
- 199 S. Hajra, S. K. Abu Saleh, A. Hazra and M. S. Singh, Organocatalytic Domino Reaction of Spiroaziridine



- Oxindoles and Malononitrile for the Enantiopure Synthesis of Spiro[dihydropyrrole-3,3'-oxindoles], *J. Org. Chem.*, 2019, **84**, 8194.
- 200 T. R. Li, B. Y. Cheng, S. Q. Fan, Y. N. Wang, L. Q. Lu and W. J. Xiao, Highly Stereoselective [3 + 2] Cycloadditions of Chiral Palladium-Containing N^1 -1,3-Dipoles: A Divergent Approach to Enantioenriched Spirooxindoles, *Chem. – Eur. J.*, 2016, **22**, 6243.
- 201 S. Hajra, S. S. Bhosale, A. Hazra and N. Kanaujia, The one pot asymmetric synthesis of 3,3'-pyrrolidonyl spirooxindoles via a regio- and stereoselective domino reaction, *Org. Biomol. Chem.*, 2019, **17**, 8140.
- 202 A. A. Akaev, S. I. Bezzubov, V. G. Desyatkin, N. S. Vorobyeva, A. G. Majouga, M. Y. Melnikov and E. M. Budynina, Stereocontrolled [3 + 2] Cycloaddition of Donor-Acceptor Cyclopropanes to Iminooxindoles: Access to Spiro[oxindole-3,2'-pyrrolidines], *J. Org. Chem.*, 2019, **84**, 3340.
- 203 X. B. Huang, X. J. Li, T. T. Li, B. Chen, W. D. Chu, L. He and Q. Z. Liu, Palladium-Catalyzed Highly Enantioselective Cycloaddition of Vinyl Cyclopropanes with Imines, *Org. Lett.*, 2019, **21**, 1713.
- 204 P. Yuvaraj and B. S. R. Reddy, Synthesis of 3-spiropyrrolidine-3-spirooxindoles from Baylis-Hillman adducts of chromone with azomethine ylides via [3 + 2] cycloaddition reaction, *Tetrahedron Lett.*, 2013, **54**, 821.
- 205 Q. He, W. Du and Y. C. Chen, Asymmetric [3 + 2] Annulations to Construct 1,2-Bispirooxindoles Incorporating a Dihydropyrrolidine Motif, *Adv. Synth. Catal.*, 2017, **359**, 3782.
- 206 X. Tang, Y. J. Gao, H. Q. Deng, J. J. Lei, S. W. Liu, L. Zhou, Y. Shi, H. Liang, J. Qiao, L. Guo, *et al.*, Catalyst-free [3 + 2] cyclization of dihydroisoquinoline imines and isatin-derived Morita-Baylis-Hillman carbonates via 1,5-electrocyclization: synthesis of tetrahydroisoquinoline-fused spirooxindoles, *Org. Biomol. Chem.*, 2018, **16**, 3362.
- 207 D. Jiang, S. Dong, W. Tang, T. Lu and D. Du, N-Heterocyclic, Carbene-Catalyzed Formal [3 + 2] Annulation of α -Bromoaldehydes with 3-Aminooxindoles: A Stereoselective Synthesis of Spirooxindole γ -Butyrolactams, *J. Org. Chem.*, 2015, **80**, 11593.
- 208 K.-Q. Chen, Y. Li, C.-L. Zhang, D.-Q. Sun and S. Ye, N-Heterocyclic, carbene-catalyzed [3 + 2] annulation of bromoaldehydes with 3-aminooxindoles: highly enantioselective synthesis of spirocyclic oxindole- γ -lactams, *Org. Biomol. Chem.*, 2016, **14**, 2007.
- 209 (a) C. Wang, S. Zhu, G. Wang, Z. Li and X. P. Hui, Enantioselective Synthesis of Spiro[indoline-3,2'-pyrroles] through N-Heterocyclic-Carbene-Catalyzed Formal [3 + 2] Annulation, *Eur. J. Org. Chem.*, 2016, 5653. For detailed mechanistic study see: (b) Y. Li, Z. Zhang and C. Liang, Understanding the mechanism and stereoselectivity of NHC-catalyzed [3 + 2] cycloaddition of 3-bromoaldehydes and isatin N-Boc ketimines, *Org. Biomol. Chem.*, 2018, **16**, 9251.
- 210 X. Y. Chen, J. W. Xiong, Q. Liu, S. Li, H. Sheng, C. von Essen, K. Rissanen and D. Enders, Control of N-Heterocyclic Carbene Catalyzed Reactions of Enals: Asymmetric Synthesis of Oxindole- γ -Amino Acid Derivatives, *Angew. Chem., Int. Ed.*, 2018, **57**, 300.
- 211 For a review see: W. Y. Han, J. Q. Zhao, J. Zuo, X. Y. Xu, X. M. Zhang and W. C. Yuan, Recent Advances of α -Isothiocyanato Compounds in the Catalytic Asymmetric Reaction, *Adv. Synth. Catal.*, 2015, **357**, 3007.
- 212 Y. M. Cao, F. F. Shen, F. T. Zhang and R. Wang, Catalytic Asymmetric Michael Addition/Cyclization of Isothiocyanato Oxindoles: Highly Efficient and Versatile Approach for the Synthesis of 3,2'-Pyrrolidinyl Mono- and Bi-spirooxindole Frameworks, *Chem. – Eur. J.*, 2013, **19**, 1184.
- 213 (a) Q. Chen, J. Liang, S. Wang, D. Wang and R. Wang, An asymmetric approach toward chiral multicyclic spirooxindoles from isothiocyanato oxindoles and unsaturated pyrazolones by a chiral tertiary amine thiourea catalyst, *Chem. Commun.*, 2013, **49**, 1657; (b) In 2014, Yuan showed an example of the same reaction catalysed by quinine: B. D. Cui, S. W. Li, J. Zuo, Z. J. Wu, X. M. Zhang and W. C. Yuan, Quinine-catalyzed asymmetric domino Michael-cyclization reaction for the synthesis of spirocyclic oxindoles bearing two spiro quaternary centers and three consecutive stereocenters, *Tetrahedron*, 2014, **70**, 1895.
- 214 (a) W. Y. Han, S. W. Li, Z. J. Wu, X. M. Zhang and W. C. Yuan, 3-Isothiocyanato Oxindoles Serving as Powerful and Versatile Precursors to Structurally Diverse Dispirocyclic Thiopyrrolidineoxindoles through a Cascade Michael/Cyclization Process with Amino-Thiocarbamate Catalysts, *Chem. – Eur. J.*, 2013, **19**, 5551; (b) X. L. Liu, W. Y. Han, X. M. Zhang and W. C. Yuan, Highly Efficient and Stereocontrolled Construction of 3,3'-Pyrrolidonyl Spirooxindoles via Organocatalytic Domino Michael/Cyclization Reaction, *Org. Lett.*, 2013, **15**, 1246.
- 215 (a) Z. K. Fu, J. Y. Pan, D. C. Xu and J. W. Xie, Organocatalytic domino Michael/cyclization reaction: efficient synthesis of multi-functionalized tetracyclic spirooxindoles with multiple stereocenters, *RSC Adv.*, 2014, **4**, 51548; (b) F. Tan, L. Q. Lu, Q. Q. Yang, W. Guo, Q. Bian, J. R. Chen and W. J. Xiao, Enantioselective Cascade Michael Addition/Cyclization Reactions of 3-Nitro-2H-Chromenes with 3-Isothiocyanato Oxindoles: Efficient Synthesis of Functionalized Polycyclic Spirooxindoles, *Chem. – Eur. J.*, 2014, **20**, 3415; (c) S. Kayal and S. Mukherjee, Catalytic Asymmetric Michael Addition/Cyclization Cascade Reaction of 3-Isothiocyanatooxindoles with Nitro Olefins, *Eur. J. Org. Chem.*, 2014, 6696; (d) J. Q. Zhao, M. Q. Zhou, Z. J. Wu, Z. H. Wang, D. F. Yue, X. Y. Xu, X. M. Zhang and W. C. Yuan, Asymmetric Michael/Cyclization Cascade Reaction of 3-Isothiocyanato Oxindoles and 3-Nitroindoles with Amino-Thiocarbamate Catalysts: Enantioselective Synthesis of Polycyclic Spirooxindoles, *Org. Lett.*, 2015, **17**, 2238; (e) J. Q. Zhao, Z. J. Wu, M. Q. Zhou, X. Y. Xu, X. M. Zhang and W. C. Yuan, Zn-Catalyzed Diastereo- and Enantioselective Cascade



- Reaction of 3-Isothiocyanato Oxindoles and 3-Nitroindoles: Stereocontrolled Syntheses of Polycyclic Spirooxindoles, *Org. Lett.*, 2015, **17**, 5020; (f) L. Wang, D. Yang, D. Li, X. Liu, Q. Zhao, R. Zhu, B. Zhang and R. Wang, Catalytic Asymmetric [3 + 2] Cyclization Reactions of 3-Isothiocyanato Oxindoles and Alkynyl Ketones Via an in Situ Generated Magnesium Catalyst, *Org. Lett.*, 2015, **17**, 4260; (g) Y. Lin, L. Liu and D. M. Du, Squaramide-catalyzed asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with chalcones for synthesis of pyrrolidinyl spirooxindoles, *Org. Chem. Front.*, 2017, **4**, 1229; (h) J. Q. Zhao, X. J. Zhou, Y. Zhou, X. Y. Xu, X. M. Zhang and W. C. Yuan, Diastereo- and Enantioselective Dearomative [3 + 2] Cycloaddition Reaction of 2-Nitrobenzofurans with 3-Isothiocyanato Oxindoles, *Org. Lett.*, 2018, **20**, 909; (i) L. L. Zhang, B. C. Da, S. H. Xiang, S. Zhu, Z. Y. Yuan, Z. Guo and B. Tan, Organocatalytic double arylation of 3-isothiocyanato oxindoles: Stereocontrolled synthesis of complex spirooxindoles, *Tetrahedron*, 2019, **75**, 1689; (j) H. Gui, X. Wu, Y. Wei and M. Shi, A Formal Condensation and [4 + 1] Annulation Reaction of 3-Isothiocyanato Oxindoles with Aza-o-Quinone Methides, *Adv. Synth. Catal.*, 2019, **361**, 5466; (k) M. Bai, Y. Z. Chen, B. D. Cui, X. Y. Xu and W. C. Yuan, Thiourea-catalyzed asymmetric domino Michael-cyclization reaction of 3-isothiocyanato oxindoles with β,γ -unsaturated α -keto esters for the synthesis of spirocyclic oxindoles, *Tetrahedron*, 2019, **75**, 2155; (l) L. Liu, B. L. Zhao and D. M. Du, Organocatalytic Asymmetric Michael/Cyclization Cascade Reaction of 3-Isothiocyanato Oxindoles with Maleimides for the Efficient Construction of Pyrrolidinyl Spirooxindoles, *Eur. J. Org. Chem.*, 2016, 4711; (m) R. Chowdhury, M. Kumar and S. K. Ghosh, Organocatalyzed enantioselective Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles with arylidene malonates, *Org. Biomol. Chem.*, 2016, **14**, 11250; (n) H.-W. Zhao, T. Tian, B. Li, Z. Yang, H.-L. Pang, W. Meng, X.-Q. Song and X.-Q. Chen, Diastereoselective Synthesis of Dispirobarbiturates through Et_3N -Catalyzed [3 + 2] Cycloaddition of Barbiturate-Based Olefins with 3-Isothiocyanato Oxindoles, *J. Org. Chem.*, 2015, **80**, 10380; (o) S. Chen, G. L. Wang, S. W. Xu, M. Y. Tian, M. Zhang, X. L. Liu and W. C. Yuan, Regio- and stereoselective [3 + 2] cycloaddition reaction: access to isoxazole-dispirobisoxindoles featuring three contiguous stereocenters, *Org. Biomol. Chem.*, 2019, **17**, 6551.
- 216 See ref. 212; (a) H. Wu, L. L. Zhang, Z. Q. Tian, Y. D. Huang and Y. M. Wang, Highly Efficient Enantioselective Construction of Bispirooxindoles Containing Three Stereocenters through an Organocatalytic Cascade Michael-Cyclization Reaction, *Chem. – Eur. J.*, 2013, **19**, 1747; (b) F. Tan, H. G. Cheng, B. Feng, Y. Q. Zou, S. W. Duan, J. R. Chen and W. J. Xiao, Highly Enantioselective Organocatalytic Michael Addition/Cyclization Cascade Reaction of Ylideneoxindoles with Isothiocyanato Oxindoles: A Formal [3 + 2] Cycloaddition Approach to Optically Active Bispirooxindole Derivatives, *Eur. J. Org. Chem.*, 2013, 2071; (c) W. R. Zhu, Q. Chen, N. Lin, K. Bin Chen, Z. W. Zhang, G. Fang, J. Weng and G. Lu, Organocatalytic Michael/cyclization cascade reactions of 3-isothiocyanato oxindoles with 3-trifluoroethylidene oxindoles: an approach for the synthesis of 3'-trifluoromethyl substituted 3,2'-pyrrolidinyl-bispirooxindoles, *Org. Chem. Front.*, 2018, **5**, 1375.
- 217 M. Monecke and T. Lindel, Tackling the Spiro Tetracyclic Skeleton of Cyanogramide: Incorporation of a Hydantoin Moiety, *Org. Lett.*, 2018, **20**, 7969.
- 218 B. D. Cui, J. Zuo, J. Q. Zhao, M. Q. Zhou, Z. J. Wu, X. M. Zhang and W. C. Yuan, Tandem Michael Addition-Ring Transformation Reactions of 3-Hydroxyoxindoles/3-Aminooxindoles with Olefinic Azlactones: Direct Access to Structurally Diverse Spirocyclic Oxindoles, *J. Org. Chem.*, 2014, **79**, 5305.
- 219 L. Chen, Z. J. Wu, M. L. Zhang, D. F. Yue, X. M. Zhang, X. Y. Xu and W. C. Yuan, Organocatalytic Asymmetric Michael/Cyclization Cascade Reactions of 3-Hydroxyoxindoles/3-Aminooxindoles with α,β -Unsaturated Acyl Phosphonates for the Construction of Spirocyclic Oxindole- γ -lactones/lactams, *J. Org. Chem.*, 2015, **80**, 12668.
- 220 For a related reaction see: B. Cui, Y. Chen, J. Shan, L. Qin, C. Yuan, Y. Wang, W. Han, N. Wan and Y. Chen, An enantioselective synthesis of spiro-oxindole-based 3,4-dihydropyrroles via a Michael/cyclization cascade of 3-aminooxindoles with 2-enoylpyridines, *Org. Biomol. Chem.*, 2017, **15**, 8518.
- 221 P. Yang, X. Wang, F. Chen, Z. B. Zhang, C. Chen, L. Peng and L. X. Wang, Organocatalytic Enantioselective Michael/Cyclization Domino Reaction between 3-Amideoxindoles and α,β -Unsaturated Aldehydes: One-Pot Preparation of Chiral Spirocyclic Oxindole- γ -lactams, *J. Org. Chem.*, 2017, **82**, 3908.
- 222 X. C. Yang, M. M. Liu, F. Mathey, H. Yang, Y. Z. Hua and M. C. Wang, Access to Chiral 2,5-Pyrrolidinyl Dispirooxindoles via Dinuclear Zinc-Catalyzed Asymmetric Cascade Reactions, *J. Org. Chem.*, 2019, **84**, 7762.
- 223 P. F. Zheng, Q. Ouyang, S. L. Niu, L. Shuai, Y. Yuan, K. Jiang, T. Y. Liu and Y. C. Chen, Enantioselective [4 + 1] Annulation Reactions of α -Substituted Ammonium Ylides To Construct Spirocyclic Oxindoles, *J. Am. Chem. Soc.*, 2015, **137**, 9390.
- 224 R. Le Goff, M. Sanselme, A. M. Lawson, A. Daïch and S. Comesse, Highly Stereoselective Domino Oxa-Michael/Aza-Michael/Cyclization: Synthesis of Bicyclic Lactams and Spiroox-indole Skeleton, *Eur. J. Org. Chem.*, 2015, 7244.
- 225 X. Huang, M. Liu, K. Pham, X. Zhang, W. Bin Yi, J. P. Jasinski and W. Zhang, Organocatalytic One-Pot Asymmetric Synthesis of Thiolated Spiro- γ -lactam Oxindoles Bearing Three Stereocenters, *J. Org. Chem.*, 2016, **81**, 5362.



- 226 H. Xu, H. W. Liu, H. S. Lin and G. W. Wang, Solvent-free iodine-promoted synthesis of 3,2'-pyrrolinyl spirooxindoles from alkylidene oxindoles and enamino esters under ball-milling conditions, *Chem. Commun.*, 2017, **53**, 12477.
- 227 J. W. Ren, Q. L. Zhao, J. A. Xiao, P. J. Xia, H. Y. Xiang, X. Q. Chen and H. Yang, A One-Pot Ring-Opening/Ring-Closure Sequence for the Synthesis of Polycyclic Spirooxindoles, *Chem. – Eur. J.*, 2019, **25**, 4673.
- 228 (a) Y. Lin, B. L. Zhao and D. M. Du, Organocatalytic Asymmetric Synthesis of 3,3'-Pyrrolidinyl-bispirooxindoles via Michael/N-Hemiketalization Cascade Reaction between 3-Aminooxindoles and Isatin-Derived β,γ -Unsaturated α -Keto Esters, *J. Org. Chem.*, 2018, **83**, 7741; (b) K. Zhao, Y. Zhi, X. Li, R. Puttreddy, K. Rissanen and D. Enders, Asymmetric synthesis of 3,3'-pyrrolidinyl-dispirooxindoles via a one-pot organocatalytic Mannich/deprotection/aza-Michael sequence, *Chem. Commun.*, 2016, **52**, 2249.
- 229 B. L. Zhao and D. M. Du, Asymmetric Synthesis of Spirooxindoles with Seven Stereocenters via Organocatalyzed One-pot Three-component Sequential Cascade Reactions, *Adv. Synth. Catal.*, 2019, **361**, 3412.
- 230 (a) T. Kang, P. Zhao, J. Yang, L. Lin, X. Feng and X. Liu, Asymmetric Catalytic Double Michael Additions for the Synthesis of Spirooxindoles, *Chem. – Eur. J.*, 2018, **24**, 3703; (b) W. He, J. Hu, P. Wang, L. Chen, K. Ji, S. Yang, Y. Li, Z. Xie and W. Xie, Highly Enantioselective Tandem Michael Addition of Tryptamine-Derived Oxindoles to Alkynones: Concise Synthesis of Strychnos Alkaloids, *Angew. Chem., Int. Ed.*, 2018, **57**, 3806.
- 231 H. Sasai, S. Takizawa, M. Kusaba, K. Kishi, B. Jianfei and T. Suzuki, Facile Synthesis of Spirooxindoles via an Enantioselective Organocatalyzed Sequential Reaction of Oxindoles with Ynone, *Heterocycles*, 2017, **95**, 761.
- 232 T. Cong, H. Wang, X. Li, H. H. Wu and J. Zhang, Chiral bifunctional bisphosphine enabled enantioselective tandem Michael addition of tryptamine-derived oxindoles to ynones, *Chem. Commun.*, 2019, **55**, 9176.
- 233 F. Beltran, I. Fabre, I. Ciofini and L. Miesch, Direct Spirocyclization from Keto-sulfonamides: An Approach to Azaspiro Compounds, *Org. Lett.*, 2017, **19**, 5042.
- 234 T. Zha, X. Tong, Y. Deng, F. Peng and Z. Shao, Catalytic Asymmetric and Divergent Synthesis of Tricyclic and Tetracyclic Spirooxindoles: Controllable Site-Selective Electrophilic Halocyclization of 1,6-Enynes, *Org. Lett.*, 2019, **21**, 6068.
- 235 (a) G. Y. Chen, F. Zhong and Y. Lu, Asymmetric Allylic Alkylation of Isatin-Derived Morita-Baylis-Hillman Carbonates with Nitroalkanes, *Org. Lett.*, 2012, **14**, 3955; (b) L. Liu, D. Wu, S. Zheng, T. Li, X. Li, S. Wang, J. Li, H. Li and W. Wang, Synthesis of Highly Functionalized Chiral 3,3'-Disubstituted Oxindoles via an Organocatalytic Enantioselective Michael Addition of Nitroalkanes to Indolyldenecyanoacetates, *Org. Lett.*, 2012, **14**, 134.
- 236 S. Shimizu, T. Tsubogo, P. Xu and S. Kobayashi, Calcium-Catalyzed Asymmetric Synthesis of 3-Tetrasubstituted Oxindoles: Efficient Construction of Adjacent Quaternary and Tertiary Chiral Centers, *Org. Lett.*, 2015, **17**, 2006.
- 237 For a related reaction of in situ derived imines in a domino aza-Michael/lactamisation including a preliminary asymmetric example see: J. Zhu, S. Fang, S. Jin, R. Ma, T. Lu and D. Du, Application of isatin-derived saturated esters in the synthesis of 3,3'-spirooxindole γ -butyrolactams, *Org. Biomol. Chem.*, 2019, **17**, 8745.
- 238 K. Ohmatsu, Y. Ando, T. Nakashima and T. Ooi, A Modular Strategy for the Direct Catalytic Asymmetric α -Amination of Carbonyl Compounds, *Chem*, 2016, **1**, 802.
- 239 G.-Y. Ran, X.-X. Yang, J.-F. Yue, W. Du and Y.-C. Chen, Asymmetric Allylic Alkylation with Deconjugated Carbonyl Compounds: Direct Vinylogous Umpolung Strategy, *Angew. Chem., Int. Ed.*, 2019, **58**, 9210.
- 240 H. Hu, F. Teng, J. Liu, W. Hu, S. Luo and Q. Zhu, Enantioselective Synthesis of 2-Oxindole Spirofused Lactones and Lactams by Heck/Carbonylative Cyclization Sequences: Method Development and Applications, *Angew. Chem., Int. Ed.*, 2019, **58**, 9225.
- 241 (a) S. Crosignani, P. Page, M. Missotten, V. Colovray, C. Cleva, J.-F. Arrighi, J. Atherall, J. Macritchie, T. Martin, Y. Humbert, *et al.*, Discovery of a New Class of Potent, Selective, and Orally Bioavailable CRTH2 (DP2) Receptor Antagonists for the Treatment of Allergic Inflammatory Diseases, *J. Med. Chem.*, 2008, **51**, 2227; (b) S. Crosignani, C. Jorand-Lebrun, P. Page, G. Campbell, V. Colovray, M. Missotten, Y. Humbert, C. Cleva, J. F. Arrighi, M. Gaudet, *et al.*, Optimization of the Central Core of Indolinone-Acetic Acid-Based CRTH2 (DP2) Receptor Antagonists, *ACS Med. Chem. Lett.*, 2011, **2**, 644.
- 242 J. Xu, L. D. Shao, D. Li, X. Deng, Y. C. Liu, Q. S. Zhao and C. Xia, Construction of Tetracyclic 3-Spirooxindole through Cross-Dehydrogenation of Pyridinium: Applications in Facile Synthesis of ($\pm$)-Corynoxine and ($\pm$)-Corynoxine B, *J. Am. Chem. Soc.*, 2014, **136**, 17962.
- 243 X. Chen, H. Chen, X. Ji, H. Jiang, Z. J. Yao and H. Liu, Asymmetric One-Pot Sequential Mannich/Hydroamination Reaction by Organo- and Gold Catalysts: Synthesis of Spiro [pyrrolidin-3,2'-oxindole] Derivatives, *Org. Lett.*, 2013, **15**, 1846.
- 244 X. P. Yin, X. P. Zeng, Y. L. Liu, F. M. Liao, J. S. Yu, F. Zhou and J. Zhou, Asymmetric Triple Relay Catalysis: Enantioselective Synthesis of Spirocyclic Indolines through a One-Pot Process Featuring an Asymmetric 6π Electrocyclization, *Angew. Chem., Int. Ed.*, 2014, **53**, 13740.
- 245 S. Hajra and B. Jana, Quinine-Based Trifunctional Organocatalyst for Tandem Aza-Henry Reaction-Cyclization: Asymmetric Synthesis of Spirooxindole-Pyrrolidine/Piperidines, *Org. Lett.*, 2017, **19**, 4778.
- 246 C. Liu, F.-X. Tan, J. Zhou, H.-Y. Bai, T.-M. Ding, G.-D. Zhu, S.-Y. Zhang and H. Chemo-, Site-, and Enantioselective para C-H Aminoalkylation of N-Monosubstituted Aniline Derivatives Affording 3-Amino-2-oxindoles, *Org. Lett.*, 2020, **22**, 2173.
- 247 N. Sharma, Z. Li, U. K. Sharma and E. V. Van Der Eycken, Facile Access to Functionalized Spiro[indoline-3,2'-



- pyrrole]-2,5'-diones via Post-Ugi Domino Buchwald-Hartwig/Michael Reaction, *Org. Lett.*, 2014, **16**, 3884.
- 248 S. J. Chambers, G. Coulthard, W. P. Unsworth, P. O'Brien and R. J. K. Taylor, From Heteroaromatic Acids and Imines to Azaspirocycles: Stereoselective Synthesis and 3D Shape Analysis, *Chem. – Eur. J.*, 2016, **22**, 6496.
- 249 (a) J. T. R. Liddon, A. K. Clarke, R. J. K. Taylor and W. P. Unsworth, Preparation and Reactions of Indoleninyl Halides: Scaffolds for the Synthesis of Spirocyclic Indole Derivatives, *Org. Lett.*, 2016, **18**, 6328. (Also includes the synthesis of racemic spirocyclopentane oxindoles). For related recent work see: (b) C. Li, L. Xue, J. Zhou, Y. Zhao, G. Han, J. Hou, Y. Song and Y. Liu, Copper-Catalyzed Trifluoromethylation of Ynones Coupled with Dearomatizing Spirocyclization of Indoles: Access to CF₃-Containing Spiro[cyclopentane-1,3'-indole], *Org. Lett.*, 2020, **22**, 3291.
- 250 S. M. Nicolle, W. Lewis, C. J. Hayes and C. J. Moody, Stereoselective Synthesis of Functionalized Pyrrolidines by the Diverted N–H Insertion Reaction of Metallocarbenes with β -Aminoketone Derivatives, *Angew. Chem., Int. Ed.*, 2016, **55**, 3749.
- 251 A. C. S. Reddy, P. M. Reddy and P. Anbarasan, Diastereoselective Palladium Catalyzed Carbenylation Amination of ortho-Vinylanilines with 3-Diazoindolin-2-ones, *Adv. Synth. Catal.*, 2020, **362**, 801.
- 252 G. Zeng, Y. Li, B. Qiao, X. Zhao and Z. Jiang, Photoredox asymmetric catalytic enantioconvergent substitution of 3-chlorooxindoles, *Chem. Commun.*, 2019, **55**, 11362.
- 253 There are a number of works where 5-membered oxygen spirocycles are synthesised as well as nitrogen heterocycles, these will be referenced again in the appropriate section but not further discussed.
- 254 (a) S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu and J. A. Cadieux, Discovery of XEN907, a spirooxindole blocker of Na_v1.7 for the treatment of pain, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 3676; (b) Y. P. Goldberg, N. Price, R. Namdari, C. J. Cohen, M. H. Lamers, C. Winters, J. Price, C. E. Young, H. Verschoof, R. Sherrington, *et al.*, Treatment of Na_v1.7-mediated pain in inherited erythromelalgia using a novel sodium channel blocker, *Pain*, 2012, **153**, 80–85; (c) S. K. Bagal, M. L. Chapman, B. E. Marron, R. Prime, R. I. Storer and N. A. Swain, Recent progress in sodium channel modulators for pain, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3690.
- 255 (a) A. K. Franz, P. D. Dreyfuss and S. L. Schreiber, Synthesis and Cellular Profiling of Diverse Organosilicon Small Molecules, *J. Am. Chem. Soc.*, 2007, **129**, 1020; (b) R. T. Moon, T. L. Biechele, S. Haggarty and D. Fass, Molecular Inhibitors of the WNT/Beta-Catenin Pathway, *PCT Int. Appl* WO2010075282A1, 2010; (c) S. Rana, E. C. Blowers, C. Tebbe, J. I. Contreras, P. Radhakrishnan, S. Kizhake, T. Zhou, R. N. Rajule, J. L. Arnst, A. R. Munkarah, *et al.*, Isatin Derived Spirocyclic Analogues with α -Methylene- γ -butyrolactone as Anticancer Agents: A Structure-Activity Relationship Study, *J. Med. Chem.*, 2016, **59**, 5121.
- 256 N. D. Heindel and J. A. Minatelli, Synthesis and Antibacterial and Anticancer Evaluations of α -Methylene- γ -butyrolactones, *J. Pharm. Sci.*, 1981, **70**, 84.
- 257 A. Grossmann, S. Bartlett, M. Janecek, J. T. Hodgkinson and D. R. Spring, Diversity-Oriented Synthesis of Drug-Like Macrocyclic Scaffolds Using an Orthogonal Organo- and Metal Catalysis Strategy, *Angew. Chem., Int. Ed.*, 2014, **53**, 13093.
- 258 E. D. Styduhar, A. D. Hutters, N. A. Weires and N. K. Garg, Enantiospecific Total Synthesis of N-Methylwelwitindolinone D Isonitrile, *Angew. Chem., Int. Ed.*, 2013, **52**, 12422.
- 259 (a) M. C. Nakhla and J. L. Wood, Total Synthesis of ($\pm$)-Aspergilline A, *J. Am. Chem. Soc.*, 2017, **139**, 18504. For an asymmetric synthesis of a related core structure see: (b) L. Caruana, M. Fochi, M. C. Franchini, S. Ranieri, A. Mazzanti and L. Bernardi, Asymmetric synthesis of 3,4-annulated indoles through an organocatalytic cascade approach, *Chem. Commun.*, 2014, **50**, 445.
- 260 H. Liu, L. Chen, K. Yuan and Y. Jia, A Ten-Step Total Synthesis of Speradine C, *Angew. Chem., Int. Ed.*, 2019, **58**, 6362.
- 261 M. A. Maskeri, M. J. O'Connor, A. A. Jaworski, A. V. Davies and K. A. Scheidt, A Cooperative Hydrogen Bond Donor-Brønsted Acid System for the Enantioselective Synthesis of Tetrahydropyrans, *Angew. Chem., Int. Ed.*, 2018, **57**, 17225.
- 262 T. Wei and D. J. Dixon, Catalytic stereoselective total synthesis of a spiro-oxindole alkaloid and the pentacyclic core of tryptoqualines, *Chem. Commun.*, 2018, **54**, 12860.
- 263 G. Bergonzini and P. Melchiorre, Dioxindole in Asymmetric Catalytic Synthesis: Routes to Enantioenriched 3-Substituted 3-Hydroxyoxindoles and the Preparation of Maremycin A, *Angew. Chem., Int. Ed.*, 2012, **51**, 971.
- 264 (a) M. Silvi, I. Chatterjee, Y. Liu and P. Melchiorre, Controlling the Molecular Topology of Vinylogous Iminium Ions by Logical Substrate Design: Highly Regio- and Stereoselective Aminocatalytic 1,6-Addition to Linear 2,4-Dienals, *Angew. Chem., Int. Ed.*, 2013, **52**, 10780. For a related reaction for cyclopentane synthesis see: (b) X. Tian and P. Melchiorre, Control of Remote Stereochemistry in the Synthesis of Spirocyclic Oxindoles: Vinylogous Organocascade Catalysis, *Angew. Chem., Int. Ed.*, 2013, **52**, 5360.
- 265 C. Zheng, W. Yao, Y. Zhang and C. Ma, Chiral Spirooxindole-Butenolide Synthesis through Asymmetric N-Heterocyclic Carbene-Catalyzed Formal (3 + 2) Annulation of 3-Bromo-enals and Isatins, *Org. Lett.*, 2014, **16**, 5028.
- 266 J. L. Li, B. Sahoo, C. G. Daniliuc and F. Glorius, Conjugate Umpolung of β,β -Disubstituted Enals by Dual Catalysis with an N-Heterocyclic Carbene and a Brønsted Acid: Facile Construction of Contiguous Quaternary Stereocenters, *Angew. Chem., Int. Ed.*, 2014, **53**, 10515.



- 267 J. Cao, S. Dong, D. Jiang, P. Zhu, H. Zhang, R. Li, Z. Li, X. Wang, W. Tang and D. Du, β -Functionalization of Indolin-2-one-Derived Aliphatic Acids for the Divergent Synthesis of Spirooxindole γ -Butyrolactones, *J. Org. Chem.*, 2017, **82**, 4186.
- 268 (a) X. Y. Chen, K. Q. Chen, D. Q. Sun and S. Ye, N-Heterocyclic, carbene-catalyzed oxidative [3 + 2] annulation of dioxindoles and enals: cross coupling of homoenolate and enolate, *Chem. Sci.*, 2017, **8**, 1936; (b) Z. Y. Song, K. Q. Chen, X. Y. Chen and S. Ye, Diastereo- and Enantioselective Synthesis of Spirooxindoles with Contiguous Tetrasubstituted Stereocenters via Catalytic Coupling of Two Tertiary Radicals, *J. Org. Chem.*, 2018, **83**, 2966; (c) For a related report at a similar time see: S. Mukherjee, S. Joseph, A. Bhunia, R. G. Gonnade, S. R. Yetra and A. T. Biju, Enantioselective synthesis of spiro γ -butyrolactones by N-heterocyclic carbene (NHC)-catalyzed formal [3 + 2] annulation of enals with 3-hydroxy oxindoles, *Org. Biomol. Chem.*, 2017, **15**, 2013.
- 269 S. Y. Zhu, H. Zhang, Q. W. Ma, D. Liu and X. P. Hui, Oxidative NHC catalysis: direct activation of β sp³ carbons of saturated acid chlorides, *Chem. Commun.*, 2019, **55**, 298.
- 270 (a) Z. Jin, S. Chen, Y. Wang, P. Zheng, S. Yang and Y. R. Chi, β -Functionalization of Carboxylic Anhydrides with β -Alkyl Substituents through Carbene Organocatalysis, *Angew. Chem., Int. Ed.*, 2014, **53**, 13506; (b) J. Xu, S. Yuan, M. Miao and Z. Chen, 1-Hydroxybenzotriazole-Assisted, N-Heterocyclic Carbene Catalyzed β -Functionalization of Saturated Carboxylic Esters: Access to Spirooxindole Lactones, *J. Org. Chem.*, 2016, **81**, 11454; (c) Y. Gao, Y. Ma, C. Xu, L. Li, T. Yang, G. Sima, Z. Fu and W. Huang, Potassium 2-oxo-3-enates as Effective and Versatile Surrogates for α , β -Unsaturated Aldehydes in NHC-Catalyzed Asymmetric Reactions, *Adv. Synth. Catal.*, 2018, **360**, 479; (d) B. Liu, G. Luo, H. Wang, L. Hao, S. Yang, Z. Jin and Y. R. Chi, Carbene-Catalyzed Direct Functionalization of the β -sp³-Carbon Atoms of α -Chloroaldehydes, *Chem. – Eur. J.*, 2019, **25**, 12719.
- 271 Indeed for many of the previously discussed papers, where protected 3-aminooxindoles were used, this can be replaced with 3-hydroxyoxindole to produce the analogous oxygenated product. See ref. 218, 219 and 230.
- 272 S. Ming, B. L. Zhao and D. M. Du, Chiral squaramide-catalysed enantioselective Michael/cyclization cascade reaction of 3-hydroxyoxindoles with α,β -unsaturated N-acylated succinimides, *Org. Biomol. Chem.*, 2017, **15**, 6205.
- 273 (a) X. Q. Zhu, J. S. Wu and J. W. Xie, Stereoselective construction of Bi-spirooxindole frameworks via a Michael addition/cyclization and an unexpected redox/oxidative coupling/cyclization, *Tetrahedron*, 2016, **72**, 8327; (b) Y. S. Zhu, W. B. Wang, B. B. Yuan, Y. N. Li, Q. L. Wang and Z. W. Bu, A DBU-catalyzed Michael-Pinner-isomerization cascade reaction of 3-hydroxyoxindoles with isatylidene malononitriles: access to highly functionalized bispirooxindoles containing a fully substituted dihydrofuran motif, *Org. Biomol. Chem.*, 2017, **15**, 984; (c) N. Gupta, G. Bhojani, R. Tak, A. Jakhar, N. ul H. Khan, S. Chatterjee and R. I. Kureshy, Highly Diastereoselective Syntheses of Spiro-Oxindole Dihydrofuran Derivatives in Aqueous Media and Their Antibacterial Activity, *ChemistrySelect*, 2017, **2**, 10902.
- 274 M. Balha, B. Mondal and S. C. Pan, Organocatalytic asymmetric synthesis of dihydrofuran-spirooxindoles from benzylidene malononitriles and dioxindoles, *Org. Biomol. Chem.*, 2019, **17**, 6557.
- 275 Z. T. Yang, J. Zhao, W. L. Yang and W. P. Deng, Enantioselective Construction of CF₃-Containing Spirooxindole γ -Lactones via Organocatalytic Asymmetric Michael/Lactonization, *Org. Lett.*, 2019, **21**, 1015.
- 276 For an alternative Michael addition/Cyclisation see: C. K. Tang, Z. Y. Zhou, A. B. Xia, L. Bai, J. Liu, D. Q. Xu and Z. Y. Xu, Combining Organocatalysis and Iodine Catalysis: One-Pot Sequential Catalytic Synthesis of Chiral Spirodihydrobenzofuran Pyrazolones and Spirodihydrobenzofuran Oxindoles, *Org. Lett.*, 2018, **20**, 5840.
- 277 (a) J. W. Ren, L. Zheng, Z. P. Ye, Z. X. Deng, Z. Z. Xie, J. A. Xiao, F. W. Zhu, H. Y. Xiang, X. Q. Chen and H. Yang, Organocatalytic, Enantioselective, Polarity-Matched Ring-Reorganization Domino Sequence Based on the 3-Oxindole Scaffold, *Org. Lett.*, 2019, **21**, 2166. For a related cascade reaction. (b) B. L. Zhao and D. M. Du, Squaramide-Catalyzed Enantioselective Cascade Approach to Bisprirooxindoles with Multiple Stereocenters, *Adv. Synth. Catal.*, 2016, **358**, 3992.
- 278 X. L. Jiang, S. J. Liu, Y. Q. Gu, G. J. Mei and F. Shi, Catalytic Asymmetric [4 + 1] Cyclization of ortho-Quinone Methides with 3-Chlorooxindoles, *Adv. Synth. Catal.*, 2017, **359**, 3341.
- 279 (a) L. Cerisoli, M. Lombardo, C. Trombini and A. Quintavalla, The First Enantioselective Organocatalytic Synthesis of 3-Spiro- α -Alkylidene- γ -Butyrolactone Oxindoles, *Chem. – Eur. J.*, 2016, **22**, 3865. For another enantioselective aldol/cyclisation see: (b) W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu and C. Li, Facile Synthesis of Chiral Spirooxindole-Based Isoelectronic Acids and 5-1H-Pyrrol-2-ones through Cascade Reactions with Bifunctional Organocatalysts, *Chem. – Eur. J.*, 2014, **20**, 8545. For aldol/Michael see: (c) D. Trubitsin, S. Žari, S. Kaabel, M. Kudrjashova, K. Kriis, I. Järving, T. Pehk and T. Kanger, Asymmetric Organocatalytic Cascade Synthesis of Tetrahydro-furanyl Spirooxindoles, *Synthesis*, 2018, **50**, 314.
- 280 (a) H. Chen, H. Liu, S. H. Zhao, S. B. Cheng, X. Y. Xu, W. C. Yuan and X. M. Zhang, Enantioselective Arylation of 3-Carboxamide Oxindoles with Quinone Monoimines and Synthesis of Chiral Spirooxindole-benzofuranones, *Synlett*, 2019, **30**, 1067; (b) J. Li, Y. Liu, C. Li and X. Jia, Syntheses of Spirocyclic Oxindole-Butenolides by Using Three-Component Cycloadditions of Isocyanides,



- Allenates, and Isatins, *Chem. – Eur. J.*, 2011, **17**, 7409;
- (c) Z. Tang, Z. Liu, Y. An, R. Jiang, X. Zhang, C. Li, X. Jia and J. Li, Isocyanide-Based Multicomponent Bicyclization with Substituted Allenate and Isatin: Synthesis of Unusual Spirooxindole Containing [5.5]-Fused Heterocycle, *J. Org. Chem.*, 2016, **81**, 9158; (d) K. Zhang, H. Han, L. Wang, Z. Zhang, Q. Wang, W. Zhang and Z. Bu, An unexpected cascade reaction of 3-hydroxyoxindoles with coumarin-3-carboxylates to construct 2,3-dihydrobenzofuran spirooxindoles, *Chem. Commun.*, 2019, **55**, 13681; (e) H. Bin Yang, Y. Z. Zhao, R. Sang, Y. Wei and M. Shi, Asymmetric Synthesis of Bioindole-Substituted Hexahydrofuro[2,3-b]furans via Hydroquinine Anthraquinone-1,4-diyl Diether-Catalyzed Domino Annulation of Acylidenoxindoles/Isatins, Acylidenoxindoles and Allenates, *Adv. Synth. Catal.*, 2014, **356**, 3799.
- 281 S. De, M. K. Das, A. Roy and A. Bisai, Synthesis of 2-Oxindoles Sharing Vicinal All-Carbon Quaternary Stereocenters via Organocatalytic Aldol Reaction, *J. Org. Chem.*, 2016, **81**, 12258.
- 282 J. A. Sclafani, J. Chen, D. V. Levy, H. Reese, M. Dimitri, P. Mudipalli, M. Christie, C. J. Neville, M. Olsen and R. P. Bakale, The First Asymmetric Pilot-Scale Synthesis of TV-45070, *Org. Process Res. Dev.*, 2017, **21**, 1616.
- 283 Q. L. Wang, L. Peng, F. Y. Wang, M. L. Zhang, L. N. Jia, F. Tian, X. Y. Xu and L. X. Wang, An organocatalytic asymmetric sequential allylic alkylation-cyclization of Morita-Baylis-Hillman carbonates and 3-hydroxyoxindoles, *Chem. Commun.*, 2013, **49**, 9422.
- 284 (a) Y. L. Liu, X. Wang, Y. L. Zhao, F. Zhu, X. P. Zeng, L. Chen, C. H. Wang, X. L. Zhao and J. Zhou, One-Pot Tandem Approach to Spirocyclic Oxindoles Featuring Adjacent Spiro-Stereocenters, *Angew. Chem., Int. Ed.*, 2013, **52**, 13735; (b) P. K. Warghude, A. S. Sabale and R. G. Bhat, Access to highly enantioselective and diastereoselective spirooxindole dihydrofuran fused pyrazolones, *Org. Biomol. Chem.*, 2020, **18**, 1794.
- 285 S. Jayakumar, S. Muthusamy, M. Prakash and V. Kesavan, Enantioselective Synthesis of Spirooxindole α -exo-Methylene- γ -butyrolactones from 3-OBoc-Oxindoles, *Eur. J. Org. Chem.*, 2014, 1893.
- 286 (a) F. Le Hu, Y. Wei and M. Shi, Phosphine-catalyzed asymmetric [4 + 1] annulation of activated α,β -unsaturated ketones with Morita-Baylis-Hillman carbonates: enantioselective synthesis of spirooxindoles containing two adjacent quaternary stereocenters, *Chem. Commun.*, 2014, **50**, 8912. For a related diastereoselective reaction see: (b) R. Zhou, K. Zhang, Y. Chen, Q. Meng, Y. Liu, R. Li and Z. He, $P(NMe_2)_3$ -mediated reductive [1 + 4] annulation of isatins with enones: a facile synthesis of spirooxindole-dihydrofurans, *Chem. Commun.*, 2015, **51**, 14663.
- 287 For a related enantioselective transformation see: (a) N. J. Zhong, F. Wei, Q. Q. Xuan, L. Liu, D. Wang and Y. J. Chen, Highly diastereo- and enantioselective [3 + 2] annulation of isatin-derived Morita-Baylis-Hillman carbonates with trifluoropyruvate catalyzed by tertiary amines, *Chem. Commun.*, 2013, **49**, 11071.
- 288 Z. C. Chen, P. Chen, Z. Chen, Q. Ouyang, H. P. Liang, W. Du and Y. C. Chen, Organocatalytic Enantioselective 1,3-Difunctionalizations of Morita-Baylis-Hillman Carbonates, *Org. Lett.*, 2018, **20**, 6279.
- 289 (a) Y. Murata, M. Takahashi, F. Yagishita, M. Sakamoto, T. Sengoku and H. Yoda, Construction of Spiro-Fused 2-Oxindole/ α -Methylene- γ -Butyrolactone Systems with Extremely High Enantioselectivity via Indium-Catalyzed Amide Allylation of N-Methyl Isatin, *Org. Lett.*, 2013, **15**, 6182. Also see: (b) M. Takahashi, Y. Murata, F. Yagishita, M. Sakamoto, T. Sengoku and H. Yoda, Catalytic Enantioselective Amide Allylation of Isatins and Its Application in the Synthesis of 2-Oxindole Derivatives Spiro-Fused to the α -Methylene- γ -Butyrolactone Functionality, *Chem. – Eur. J.*, 2014, **20**, 11091.
- 290 For a related Pd-catalysed allylation see: S. Jayakumar, N. Kumarswamyreddy, M. Prakash and V. Kesavan, Palladium Catalyzed Asymmetric Allylation of 3-OBoc-Oxindoles: An Efficient Synthesis of 3-Allyl-3-hydroxyoxindoles, *Org. Lett.*, 2015, **17**, 1066.
- 291 H. Zhang, Q. Yao, W. Cao, S. Ge, J. Xu, X. Liu and X. Feng, Catalytic enantioselective ene-type reactions of vinylogous hydrazone: construction of α -methylene- γ -butyrolactone derivatives, *Chem. Commun.*, 2018, **54**, 12511.
- 292 B. M. Trost and K. Hirano, Dinuclear Zinc Catalyzed Asymmetric Spirannulation Reaction: An Umpolung Strategy for Formation of α -Alkylated- α -Hydroxyoxindoles, *Org. Lett.*, 2012, **14**, 2446.
- 293 (a) M. M. Liu, X. C. Yang, Y. Z. Hua, J. B. Chang and M. C. Wang, Synthesis of Chiral Bispirotetrahydrofuran Oxindoles by Cooperative Bimetallic-Catalyzed Asymmetric Cascade Reaction, *Org. Lett.*, 2019, **21**, 2111. Also see: (b) Y. H. Miao, Y. Z. Hua and M. C. Wang, Dinuclear zinc cooperative catalytic three-component reactions for highly enantioselective synthesis of 3,3'-dihydrofuran spirooxindoles, *Org. Biomol. Chem.*, 2019, **17**, 7172.
- 294 Y.-J. Guo, X. Guo, D.-Z. Kong, H. Lu, L. Liu, Y.-Z. Hua and M.-C. Wang, Catalytic Asymmetric Synthesis of Tetrahydrofuran Spirooxindoles via a Dinuclear Zinc Catalyst, *J. Org. Chem.*, 2020, **85**, 4195.
- 295 (a) J. Liu, X. Xu, J. Li, B. Liu, H. Jiang and B. Yin, Palladium-catalyzed dearomatizing 2,5-alkoxyarylation of furan rings: diastereospecific access to spirooxindoles, *Chem. Commun.*, 2016, **52**, 9550; (b) J. Liu, H. Peng, L. Lu, X. Xu, H. Jiang and B. Yin, Diastereospecific and Enantioselective Access to Dispirooxindoles from Furfurylcyclobutanols by Means of a Pd-Catalyzed Arylative Dearomatization/Ring Expansion Cascade, *Org. Lett.*, 2016, **18**, 6440.
- 296 D. F. Li, Y. Gu, J. R. Zhang, K. Liu and L. M. Zhao, Diastereoselective Construction of Spiro-furo[3,2-c]benzopyranoxindoles through a $Cu(OTf)_2/AcOH$ Cooperative Promoted Bicyclization Reaction, *J. Org. Chem.*, 2019, **84**, 879.



- 297 J. L. Nallasivam and T. K. Chakraborty, Titanocene(III)-Mediated 5-exo-trig Radical Cyclization: En Route to Spirooxindole-Based Tetrahydrofuran and Bicyclic Lactone, *J. Org. Chem.*, 2019, **84**, 16124.
- 298 (a) E. L. McInturff, J. Mowat, A. R. Waldeck and M. J. Krische, Ruthenium-Catalyzed Hydrohydroxyalkylation of Acrylates with Diols and α -Hydroxycarbonyl Compounds To Form Spiro- and α -Methylene- γ -butyrolactones, *J. Am. Chem. Soc.*, 2013, **135**, 17230; (b) T. Luong, S. Chen, K. Qu, E. L. McInturff and M. J. Krische, Ruthenium(0)-Catalyzed C-C Coupling of Alkynes and 3-Hydroxy-2-oxindoles: Direct C-H Vinylation of Alcohols, *Org. Lett.*, 2017, **19**, 966.
- 299 C. S. Buxton, D. C. Blakemore and J. F. Bower, Reductive Coupling of Acrylates with Ketones and Ketimines by a Nickel-Catalyzed Transfer-Hydrogenative Strategy, *Angew. Chem., Int. Ed.*, 2017, **56**, 13824.
- 300 B. M. Trost, Z. Jiao and C. I. Hung, Elaborating Complex Heteroaryl-Containing Cycles via Enantioselective Palladium-Catalyzed Cycloadditions, *Angew. Chem., Int. Ed.*, 2019, **58**, 15154.
- 301 S. M. Nicolle, W. Lewis, C. J. Hayes and C. J. Moody, Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Diverted Carbene O-H Insertion Reaction, *Angew. Chem., Int. Ed.*, 2015, **54**, 8485.
- 302 (a) G. Karthik, T. Rajasekaran, B. Sridhar and B. V. Subba Reddy, Highly regio- and diastereoselective three-component reaction of acyclic/cyclic donor-acceptor carbenoids for the synthesis of angularly fused furocoumarins and spirooxindolyfurocoumarins, *Tetrahedron*, 2014, **70**, 8148; (b) B. V. S. Reddy, G. Karthik, T. Rajasekaran and B. Sridhar, Stereoselective Synthesis of Highly Functionalized Dispirooxindoles through [3 + 2] Cycloaddition of Carbonyl Ylides with 3-Arylideneoxindoles, *Eur. J. Org. Chem.*, 2015, 2038; (c) B. V. S. Reddy, E. P. Reddy, B. Sridhar and Y. J. Rao, Rhodium-catalyzed cycloaddition of carbonyl ylides for the synthesis of spiro[furo[2,3-a]xanthene-2,3'-indolin]-2'-one scaffolds, *RSC Adv.*, 2016, **6**, 50497; (d) S. Murarka, C. Golz, C. Strohmman, A. Antonchick and H. Waldmann, Biology-Oriented Synthesis of 3,3-Spiro(2-tetrahydrofuran)oxindoles, *Synthesis*, 2016, **49**, 87; (e) A. C. Hunter, S. C. Schlitzer, J. C. Stevens, B. Almutwalli and I. Sharma, A Convergent Approach to Diverse Spiroethers through Stereoselective Trapping of Rhodium Carbenoids with Gold-Activated Alkynols, *J. Org. Chem.*, 2018, **83**, 2744; (f) N. P. Massaro, J. C. Stevens, A. Chatterji and I. Sharma, Stereoselective Synthesis of Diverse Lactones through a Cascade Reaction of Rhodium Carbenoids with Ketoacids, *Org. Lett.*, 2018, **20**, 7585; (g) G. Xu, S. Tang, Y. Shao and J. Sun, B(C₆F₅)₃-Catalyzed formal (4 + 1)-annulation of ortho-quinone methides with diazoacetates: access to 2,3-dihydrobenzofurans, *Chem. Commun.*, 2019, **55**, 9096–9099; (h) S. Muthusamy, A. Prabu and E. Suresh, Copper-catalyzed synthesis of spiro-indolofurobenzopyrans: tandem reactions of diazoamides and O-propargyl salicylaldehydes, *Org. Biomol. Chem.*, 2019, **17**, 8088.
- 303 L. Y. Mei, Y. Wei, Q. Xu and M. Shi, Diastereo- and Enantioselective Construction of Oxindole-Fused Spirotetrahydrofuran Scaffolds through Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition of Vinyl Cyclopropanes and Isatins, *Organometallics*, 2013, **32**, 3544.
- 304 J. A. Xiao, Y. C. Li, Z. J. Luo, X. L. Cheng, Z. X. Deng, W. Q. Chen, W. Su and H. Yang, Construction of Bispirooxindole Heterocycles via Palladium-Catalyzed Ring-Opening Formal [3 + 2]-Cycloaddition of Spirovinylcyclopropyl Oxindole and 3-Oxindole Derivatives, *J. Org. Chem.*, 2019, **84**, 2297.
- 305 (a) B. M. Sharma, M. Yadav, R. G. Gonnade and P. Kumar, Unified Approach to Fused and Spirocyclic Oxindoles through Lewis-Acid-Promoted Opening of Spiroepoxyoxindoles with Allylsilanes: Application to the Formal Synthesis of ($\pm$)-Physovenine, *Eur. J. Org. Chem.*, 2017, 2603; (b) For a related reaction using Sc(OTf)₃ as catalyst see: S. Hajra, S. Roy and S. Maity, Reversal of Selectivity in C3-Allylation and Formal [3 + 2]-Cycloaddition of Spiro-epoxyoxindole: Unified Synthesis of Spiro-furanooxindole, ($\pm$)-N-Methylcoerulescine, ($\pm$)-Physovenine, and 3a-Allylhexahydropyrrolo[2,3-b]indole, *Org. Lett.*, 2017, **19**, 1998–2001. Also see ref. 63.
- 306 (a) S. Hajra, S. Maity and S. Roy, Regioselective Friedel-Crafts Reaction of Electron-Rich Benzenoid Arenes and Spiroepoxyoxindole at the Spiro-Centre: Efficient Synthesis of Benzofuroindolines and 2H-Spiro[benzofuran]-3,3'-oxindoles, *Adv. Synth. Catal.*, 2016, **358**, 2300. For a related report see: (b) S. Hajra, S. Maity, S. Roy, R. Maity and S. Samanta, Brønsted Acid Promoted Regioselective C-3 Arylation and Heteroarylation of Spiro-epoxyoxindoles for the Construction of All Carbon Quaternary Centres: A Detailed Study, *Eur. J. Org. Chem.*, 2019, 969.
- 307 B. A. Laevens, J. Tao and G. K. Murphy, Iodide-Mediated Synthesis of Spirooxindole Dihydrofurans from Iodonium Ylides and 3-Alkylidene-2-oxindoles, *J. Org. Chem.*, 2017, **82**, 11903.
- 308 H. Wu, Y. P. He, L. Xu, D. Y. Zhang and L. Z. Gong, Asymmetric Organocatalytic Direct C(sp²)-H/C(sp³)-H Oxidative Cross-Coupling by Chiral Iodine Reagents, *Angew. Chem., Int. Ed.*, 2014, **53**, 3466.
- 309 (a) Y. Cao, X. Zhang, G. Lin, D. Zhang-Negrerie and Y. Du, Chiral Aryliodine-Mediated Enantioselective Organocatalytic Spirocyclization: Synthesis of Spirofurooxindoles via Cascade Oxidative C-O and C-C Bond Formation, *Org. Lett.*, 2016, **18**, 5580. For related work by Du see: (b) X. Zhen, X. Wan, W. Zhang, Q. Li, D. Zhang-Negrerie and Y. Du, Synthesis of Spirooxindoles from N-Arylamide Derivatives via Oxidative C(sp²)-C(sp³) Bond Formation Mediated by PhI(OMe)₂ Generated in Situ, *Org. Lett.*, 2019, **21**, 890.
- 310 (a) C. Serradeil-Le Gal, C. Lacour, G. Valette, G. Garcia, L. Foulon, G. Galindo, L. Bankir, B. Pouzet, G. Guillon, C. Barberis, *et al.*, Characterization of SR 121463A, a



- highly potent and selective, orally active vasopressin V2 receptor antagonist, *J. Clin. Invest.*, 1996, **98**, 2729; (b) H. Venkatesan, M. C. Davis, Y. Altas, J. P. Snyder and D. C. Liotta, Total Synthesis of SR 121463 A, a Highly Potent and Selective Vasopressin V₂ Receptor Antagonist, *J. Org. Chem.*, 2001, **66**, 3653.
- 311 J.-J. Liu and Z. Zhang, Spiroindolinone Derivatives, *PCT Int. Appl* WO2008055812A1, 2008.
- 312 Y. Zhang, J. Zhang, H. Xie, T. Yu, H. Luo, Q. Ren, X. Wu, C. Fu, S. Li, Y. Lei and B. Hu, Preparation of Pyrrolidine Derivatives as Hepatitis C Inhibitors for Treating Hepatitis C Virus Infection, *PCT Int. Appl* CN103420991, 2013.
- 313 A. Fensome, W. R. Adams, A. L. Adams, T. J. Berrodin, J. Cohen, C. Huselton, A. Illenberger, J. C. Kern, V. A. Hudak, M. A. Marella, *et al.*, Design, Synthesis, and SAR of New Pyrrole-Oxindole Progesterone Receptor Modulators Leading to 5-(7-Fluoro-3,3-dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile (WAY-255348), *J. Med. Chem.*, 2008, **51**, 1861.
- 314 (a) H. Lin and S. J. Danishefsky, Gelsemine: A Thought-Provoking Target for Total Synthesis, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (b) A. Ghosh and R. G. Carter, Recent Syntheses and Strategies toward Polycyclic Gelsemium Alkaloids, *Angew. Chem., Int. Ed.*, 2019, **58**, 681.
- 315 (a) J. K. Lam, S. B. Joseph and C. D. Vanderwal, A Zincke aldehyde approach to gelsemine, *Tetrahedron Lett.*, 2015, **56**, 3165; (b) X. Chen, S. Duan, C. Tao, H. Zhai and F. G. Qiu, Total synthesis of (+)-gelsemine via an organocatalytic Diels-Alder approach, *Nat. Commun.*, 2015, **6**, 7204.
- 316 R. Samineni, J. Madapa, S. Pabbaraja and G. Mehta, Stitching Oxindoles and Ynones in a Domino Process: Access to Spirooxindoles and Application to a Short Synthesis of Spindomycin B, *Org. Lett.*, 2017, **19**, 6152.
- 317 M. Gicquel, C. Gomez, P. Retailleau, A. Voituriez and A. Marinetti, Synthesis of 3,3'-Spirocyclic Oxindoles via Phosphine Catalyzed [4 + 2] Cyclizations, *Org. Lett.*, 2013, **15**, 4002.
- 318 B. X. Xiao, B. Jiang, X. Song, W. Du and Y. C. Chen, Phosphine-catalysed asymmetric dearomative formal [4 + 2] cycloadditions of 3-benzofuranyl vinyl ketones, *Chem. Commun.*, 2019, **55**, 3097.
- 319 (a) D. B. Ramachary, C. Venkaiah and R. Madhavachary, Asymmetric Synthesis of Druglike Six-Membered Spirooxindoles through an Amino Enyne Catalysis, *Org. Lett.*, 2013, **15**, 3042. For a related reaction using 3-methylene oxindoles to react with malonitriles under Mg catalysis see: (b) H. Mei, L. Lin, B. Shen, X. Liu and X. Feng, Highly enantioselective desymmetrization of prochiral cyclic α,α -dicyanoalkenes via the direct vinylogous Michael/cyclization domino reaction, *Org. Chem. Front.*, 2018, **5**, 2505. For reaction of related malonitrile oxindoles with allenes: (c) R. Chen, X. Fan, Z. Xu and Z. He, Facile Synthesis of Spirooxindole-Cyclohexenes via Phosphine-Catalyzed [4 + 2] Annulation of α -Substituted Allenates, *Chin. J. Chem.*, 2017, **35**, 1469.
- 320 (a) H. Huang, M. Bihani and J. C. G. Zhao, Stereoselective synthesis of spirooxindole derivatives using an organocatalyzed tandem Michael-Michael reaction, *Org. Biomol. Chem.*, 2016, **14**, 1755; (b) Z. Zhou, Q. He, Y. Jiang, Q. Ouyang, W. Du and Y. C. Chen, Double Thiol-Chiral Brønsted Base Catalysis: Asymmetric Cross Rauht-Currier Reaction and Sequential [4 + 2] Annulation for Assembly of Different Activated Olefins, *Org. Lett.*, 2019, **21**, 7184.
- 321 (a) X. L. He, H. R. Zhao, X. Song, B. Jiang, W. Du and Y. C. Chen, Asymmetric Barton-Zard Reaction To Access 3-Pyrrole-Containing Axially Chiral Skeletons, *ACS Catal.*, 2019, **9**, 4374; (b) L. Peng, K. Li, C. Xie, S. Li, D. Xu, W. Qin and H. Yan, Organocatalytic Asymmetric Annulation of ortho-Alkynylanilines: Synthesis of Axially Chiral Naphthyl-C2-indoles, *Angew. Chem., Int. Ed.*, 2019, **58**, 17199.
- 322 (a) X. Zuo, X. L. Liu, J. X. Wang, Y. M. Yao, Y. Y. Zhou, Q. Di Wei, Y. Gong and Y. Zhou, Organocatalytic Reaction of Chromone-Oxindole Synthon: Access to Chromanone-Based Spirocyclohexanoxindoles with Five Adjacent Stereocenters, *J. Org. Chem.*, 2019, **84**, 6679; (b) X. L. Liu, G. Zhou, Y. Gong, Z. Yao, X. Zuo, W. H. Zhang and Y. Zhou, Stereocontrolled Synthesis of Bispirooxindole-Based Hexahydroxanthones with Five Contiguous Stereocenters, *Org. Lett.*, 2019, **21**, 2528; (c) S. Q. Chang, X. Zou, Y. Gong, X. W. He, X. L. Liu and Y. Zhou, Stereocontrolled construction of six vicinal stereogenic centers on a hexahydroxanthone framework through a formal [2 + 1 + 3] annulation, *Chem. Commun.*, 2019, **55**, 14003; (d) X. L. Liu, Q. Di Wei, X. Zuo, S. W. Xu, Z. Yao, J. X. Wang and Y. Zhou, Organocatalytic Michael/Michael Cycloaddition Enabled Asymmetric Construction of Hexahydroxanthones with Skeletal Diversity, *Adv. Synth. Catal.*, 2019, **361**, 2836; (e) X. L. Liu, Y. Gong, S. Chen, X. Zuo, Z. Yao and Y. Zhou, Bifunctional oxindole-chromone 4C building block directed asymmetric synthesis of bispirocyclic hexahydroxanthones featuring five contiguous stereocenters and two side-by-side oxindoles, *Org. Chem. Front.*, 2019, **6**, 1603; (f) M. Zhang, J. X. Wang, S. Q. Chang, X. L. Liu, X. Zuo and Y. Zhou, Highly efficient enantioselective synthesis of bispiro[benzofuran-oxindole/benzofuran-chromanone]s through organocatalytic inter-/intramolecular Michael cycloaddition, *Chin. Chem. Lett.*, 2020, **31**, 381.
- 323 W. Ren, X. Y. Wang, J. J. Li, M. Tian, J. Liu, L. Ouyang and J. H. Wang, Efficient construction of biologically important functionalized polycyclic spiro-fused carbocyclooxindoles via an asymmetric organocatalytic quadruple-cascade reaction, *RSC Adv.*, 2017, **7**, 1863.
- 324 (a) A. K. Ghosh and B. Zhou, Enantioselective synthesis of spiro[cyclohexane-1,3'-indolin]-2'-ones containing multiple stereocenters via organocatalytic Michael/aldol cascade reactions, *Tetrahedron Lett.*, 2013, **54**, 2311; (b) S. Roy, M. Amireddy and K. Chen, Organocatalytic formal [5 + 1] annulation: diastereoselective cascade syn-



- thesis of functionalized six-membered spirocyclic indane-1,3-diones/oxindoles via Michael-aldol reaction, *Tetrahedron*, 2013, **69**, 8751; (c) S. Xu, C. Li, X. Jia and J. Li, AlCl₃-Promoted Selective Michael Addition with Allenolate and Methyleneindolinone: Synthesis of Spirocyclic Oxindole by Using Allenolate as a Four-Carbon Component Building Block, *J. Org. Chem.*, 2014, **79**, 11161; (d) M. Vishwanath, P. Vinayagam, V. P. R. Gajulapalli and V. Kesavan, Asymmetric Organocatalytic Assembly of Oxindoles Fused with Spiro-3,4-dihydropyrans with Three Contiguous Stereocenters Consisting of Vicinal Quaternary Centers, *Asian J. Org. Chem.*, 2016, **5**, 613. For a desymmetrising aldol reaction see: (e) B. B. Sun, Y. F. Zhang, J. Q. Zhang, S. J. Yin, W. T. Fan, H. Y. Li and X. W. Wang, Cinchona Alkaloid Derived Primary Amine Catalyzed Intramolecular Desymmetrizing Aldolization Reaction of Diacetyloxindoles, *Eur. J. Org. Chem.*, 2017, 2871.
- 325 These examples include reactions with more than 2 steps or conjugate additions followed by a different cyclisation mode: (a) B. Zhou, Y. Yang, J. Shi, Z. Luo and Y. Li, Synthesis of Six-Membered Spirocyclic Oxindoles with Five Consecutive Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence, *J. Org. Chem.*, 2013, **78**, 2897; (b) Z. Zhou, X. Feng, X. Yin and Y. C. Chen, Direct Remote Asymmetric Bisvinylogous 1,4-Additions of Cyclic 2,5-Dienones to Nitroalkenes, *Org. Lett.*, 2014, **16**, 2370; (c) R. Zhou, Q. Wu, M. Guo, W. Huang, X. He, L. Yang, F. Peng, G. He and B. Han, Organocatalytic cascade reaction for the asymmetric synthesis of novel chroman-fused spirooxindoles that potentially inhibit cancer cell proliferation, *Chem. Commun.*, 2015, **51**, 13113; (d) Q. S. Sun, H. Lin, X. Sun and X. W. Sun, Highly efficient synthesis of enantio-enriched fully-substituted spirocyclohexane oxindoles via a Michael-Michael-aldol cascade reaction, *Tetrahedron Lett.*, 2016, **57**, 5673. Radical pathway: (e) H. R. Wu, L. Cheng, D. L. Kong, H. Y. Huang, C. L. Gu, L. Liu, D. Wang and C. J. Li, FeCl₃-Mediated Radical Tandem Reactions of 3-Benzyl-2-oxindoles with Styrene Derivatives for the Stereoselective Synthesis of Spirocyclohexene Oxindoles, *Org. Lett.*, 2016, **18**, 1382.
- 326 B. Wang, X. H. Wang, W. Huang, J. Zhou, H. P. Zhu, C. Peng and B. Han, Protecting Group-Directed Diastereodivergent Synthesis of Chiral Tetrahydronaphthalene-Fused Spirooxindoles via Bifunctional Tertiary Amine Catalysis, *J. Org. Chem.*, 2019, **84**, 10349.
- 327 (a) Y. Liu, M. Nappi, E. Arceo, S. Vera and P. Melchiorre, Asymmetric Catalysis of Diels-Alder Reactions with in Situ Generated Heterocyclic ortho-Quinodimethanes, *J. Am. Chem. Soc.*, 2011, **133**, 15212; (b) B. Tan, G. Hernández-Torres and C. F. Barbas, Highly Efficient Hydrogen-Bonding Catalysis of the Diels-Alder Reaction of 3-Vinylindoles and Methyleneindolinones Provides Carbazolespirooxindole Skeletons, *J. Am. Chem. Soc.*, 2011, **133**, 12354.
- 328 Hydrogen bonding catalysis: (a) L. J. Huang, J. Weng, S. Wang and G. Lu, Organocatalytic Diels-Alder Reaction of 2-Vinylindoles with Methyleneindolinones: An Efficient Approach to Functionalized Carbazolespirooxindoles, *Adv. Synth. Catal.*, 2015, **357**, 993; (b) J. W. Ren, J. Wang, J. A. Xiao, J. Li, H. Y. Xiang, X. Q. Chen and H. Yang, L-Pyroglutamic, Sulphonamide as Hydrogen-Bonding Organocatalyst: Enantioselective Diels-Alder Cyclization to Construct Carbazolespirooxindoles, *J. Org. Chem.*, 2017, **82**, 6441. TfOH catalysed domino reactions: (c) R. Y. Yang, J. Sun, Y. Tao, Q. Sun and C. G. Yan, TfOH-Catalyzed One-Pot Domino Reaction for Diastereoselective Synthesis of Polysubstituted Tetrahydrospiro[carbazole-1,3'-indoline]s, *J. Org. Chem.*, 2017, **82**, 13277; (d) R. Y. Yang, J. Sun, Q. Sun and C. G. Yan, Selective Synthesis of 3-(9H-Carbazol-2-yl)indolin-2-ones and Spiro[tetrahydrocarbazole-3,3'-oxindoles] via a HOTf Catalyzed Three-Component Reaction, *J. Org. Chem.*, 2018, **83**, 5909; (e) J. Guo, X. Bai, Q. Wang and Z. Bu, Diastereoselective Construction of Indole-Bridged Chroman Spirooxindoles through a TfOH-Catalyzed Michael Addition-Inspired Cascade Reaction, *J. Org. Chem.*, 2018, **83**, 3679. Ag catalysed aminoenyne formation: (f) P. Sharma, N. P. Kumar, N. H. Krishna, D. Prasanna, B. Sridhar and N. Shankaraiah, Silver(I)-catalysed domino alkyne-annulation/Diels-Alder reaction: a mild synthetic approach to tetrahydrospiro[carbazole-4,3'-indoline] scaffolds, *Org. Chem. Front.*, 2016, **3**, 1503. Iminium ion catalysis: (g) Z. H. You, Y. H. Chen, Y. Tang and Y. K. Liu, Organocatalytic Asymmetric Synthesis of Spiro-Bridged and Spiro-Fused Heterocyclic Compounds Containing Chromane, Indole, and Oxindole Moieties, *Org. Lett.*, 2018, **20**, 6682. Cu mediated 3-component reaction: (h) S.-C. Zhan, J. Sun, R.-Z. Liu and C.-G. Yan, Diastereoselective construction of carbazole-based spirooxindoles via the Levy three-component reaction, *Org. Biomol. Chem.*, 2020, **18**, 163.
- 329 H. Zheng, P. He, Y. Liu, Y. Zhang, X. Liu, L. Lin and X. Feng, Efficient synthesis of carbazolespirooxindole skeletons via asymmetric Diels-Alder reaction of 3-vinylindoles and methyleneindolinones, *Chem. Commun.*, 2014, **50**, 8794.
- 330 Y. Wang, M. S. Tu, L. Yin, M. Sun and F. Shi, Brønsted Acid Catalyzed Asymmetric Diels-Alder Reactions: Stereoselective Construction of Spiro[tetrahydrocarbazole-3,3'-oxindole] Framework, *J. Org. Chem.*, 2015, **80**, 3223.
- 331 H. Miyamoto, T. Hirano, Y. Okawa, A. Nakazaki and S. Kobayashi, Stereoselective synthesis of spirocyclic oxindoles based on a one-pot Ullmann coupling/Claissen rearrangement and its application to the synthesis of a hexahydropyrrolo[2,3-b]indole alkaloid, *Tetrahedron*, 2013, **69**, 9481.
- 332 G. Li, T. Liang, L. Wojtas and J. C. Antilla, An Asymmetric Diels-Alder Reaction Catalyzed by Chiral Phosphate Magnesium Complexes: Highly Enantioselective Synthesis of Chiral Spirooxindoles, *Angew. Chem., Int. Ed.*, 2013, **52**, 4628.



- 333 (a) J. Zheng, L. Lin, K. Fu, H. Zheng, X. Liu and X. Feng, Synthesis of Optically Pure Spiro[cyclohexane-oxindoline] Derivatives via Catalytic Asymmetric Diels-Alder Reaction of Brassard-Type Diene with Methyleneindolines, *J. Org. Chem.*, 2015, **80**, 8836. Also see: (b) Y. F. Zhang, S. J. Yin, M. Zhao, J. Q. Zhang, H. Y. Li and X. W. Wang, Dinuclear zinc-catalyzed desymmetric intramolecular aldolization: an enantioselective construction of spiro[cyclohexanone-oxindole] derivatives, *RSC Adv.*, 2016, **6**, 30683.
- 334 For a related diastereoselective reaction mediated by AcOH see: R. Y. Yang, J. Sun and C. G. Yan, HOAc-Mediated Domino Diels-Alder Reaction for Synthesis of Spiro[cyclohexane-1,3'-indolines] in Ionic Liquid [Bmim] Br, *ACS Omega*, 2018, **3**, 5406.
- 335 (a) S. Muthusamy and V. Kesavan, Asymmetric Cycloaddition Reactions of Oxindole α -Keto Esters via Cascade Dienamine-Enamine and Trienamine Strategies, *Eur. J. Org. Chem.*, 2019, 4046. For a similar reaction of 2,4-dienals see: (b) A. S. Marques, J. Marrot, I. Chataigner, V. Coeffard, G. Vincent and X. Moreau, In Situ Generation of Cyclopentadienol Intermediates from 2,4-Dienals. Application to the Synthesis of Spirooxindoles via a Domino Polycyclization, *Org. Lett.*, 2018, **20**, 792.
- 336 H. Zheng, Y. Wang, C. Xu, Q. Xiong, L. Lin and X. Feng, Diversified Cycloisomerization/Diels-Alder Reactions of 1,6-Enynes through Bimetallic Relay Asymmetric Catalysis, *Angew. Chem., Int. Ed.*, 2019, **58**, 5327.
- 337 Y. Luo, H. Zhang, S. Wang, Y. Zhou, S. Dong and X. Feng, Asymmetric Catalytic Diverse Ring Opening/Cycloadditions of Cyclobutenones with (E)-Alkenyloxindoles and (E)-Dioxypyrrolidines, *Org. Lett.*, 2020, **22**, 2645.
- 338 L. J. Huang, J. Weng, S. Wang and G. Lu, Organocatalytic Diels-Alder Reaction of 2-Vinylindoles with Methyleneindolinones: An Efficient Approach to Functionalized Carbazolespirooxindoles, *Adv. Synth. Catal.*, 2015, **357**, 993.
- 339 (a) B. K. Min, D. Y. Seo, J. Y. Ryu, J. Lee and J. N. Kim, Synthesis of Spirocyclohexadienyl-2-Oxindoles by 6π -Electrocyclization of Trienes Derived from Wittig Reaction of Morita-Baylis-Hillman Carbonates and α,β -Unsaturated Aldehydes, *Bull. Korean Chem. Soc.*, 2018, **39**, 115. For related reaction to bispirooxindoles: (b) B. K. Min, S. Lee, H. J. Roh, J. Y. Ryu, J. Lee and J. N. Kim, Synthesis of dispirocyclohexadiene bisoxindole from Morita-Baylis-Hillman carbonate of isatin, *Tetrahedron Lett.*, 2017, **58**, 3251.
- 340 (a) J. R. Huang, M. Sohail, T. Taniguchi, K. Monde and F. Tanaka, Formal (4 + 1) Cycloaddition and Enantioselective Michael-Henry Cascade Reactions To Synthesize Spiro[4,5]decanes and Spirooxindole Polycycles, *Angew. Chem., Int. Ed.*, 2017, **56**, 5853. For work on related oxygenated heterocycles see: (b) M. Sohail and F. Tanaka, Dynamic stereoselective annulation via aldol-oxa-cyclization cascade reaction to afford spirooxindole pyran polycycles, *Commun. Chem.*, 2019, **2**, 73.
- 341 K. H. Kim, H. R. Moon, J. Lee and J. N. Kim, Palladium-Catalyzed Construction of Spirooxindoles by Arylative Cyclization of 3-(γ,δ -Disubstituted)allylidene-2-Oxindoles, *Adv. Synth. Catal.*, 2015, **357**, 701. Also see ref. 81.
- 342 (a) H. Yoon, A. Lossouarn, F. Landau and M. Lautens, Pd-Catalyzed Spirocyclization via C-H Activation and Benzyne Insertion, *Org. Lett.*, 2016, **18**, 6324; (b) M. Pérez-Gómez and J. A. García-López, Trapping σ -Alkyl-Palladium(II) Intermediates with Arynes Encompassing Intramolecular C-H Activation: Spirobiaryls through Pd-Catalyzed Cascade Reactions, *Angew. Chem., Int. Ed.*, 2016, **55**, 14389.
- 343 (a) H. Yoon, M. Röhlz, F. Landau and M. Lautens, Palladium-Catalyzed Spirocyclization through C-H Activation and Regioselective Alkyne Insertion, *Angew. Chem., Int. Ed.*, 2017, **56**, 10920; (b) I. Franzoni, H. Yoon, J.-A. García-López, A. I. Poblador-Bahamonde and M. Lautens, Exploring the mechanism of the Pd-catalyzed spirocyclization reaction: a combined DFT and experimental study, *Chem. Sci.*, 2018, **9**, 1496. For a review see: (c) A. D. Marchese, E. M. Larin, B. Mirabi and M. Lautens, Metal-Catalyzed Approaches toward the Oxindole Core, *Acc. Chem. Res.*, 2020, **53**, 1605.
- 344 X. Luo, Y. Xu, G. Xiao, W. Liu, C. Qian, G. Deng, J. Song, Y. Liang and C. Yang, Palladium-Catalyzed Tandem Reaction of Three Aryl Iodides Involving Triple C-H Activation, *Org. Lett.*, 2018, **20**, 2997.
- 345 D. Arunprasath, B. D. Bala and G. Sekar, Stereoselective Construction of α -Tetralone-Fused Spirooxindoles via Pd-Catalyzed Domino Carbene Migratory Insertion/Conjugate Addition Sequence, *Org. Lett.*, 2017, **19**, 5280.
- 346 D.-Y. Zhang, L. Xu, H. Wu and L.-Z. Gong, Chiral Iodine-Catalyzed Dearomatizative Spirocyclization for the Enantioselective Construction of an All-Carbon Stereogenic Center, *Chem. – Eur. J.*, 2015, **21**, 10314.
- 347 (a) A. V. Chate, S. P. Kamdi, A. N. Bhagat, C. K. Jadhav, A. Nipte, A. P. Sarkate, S. V. Tiwari and C. H. Gill, Design, Synthesis and SAR Study of Novel Spiro [Pyrimido[5,4-b]Quinoline-10,5'-Pyrrolo[2,3-d]Pyrimidine] Derivatives as Promising Anticancer Agents, *J. Heterocycl. Chem.*, 2018, **55**, 2297; (b) J. Li, N. Wu, Y. Tian, J. Zhang and S. Wu, Aminopyridyl/Pyrazinyl Spiro[indoline-3,4'-piperidine]-2-ones As Highly Selective and Efficacious c-Met/ALK Inhibitors, *ACS Med. Chem. Lett.*, 2013, **4**, 806; (c) F. Shirai, A. Mizutani, Y. Yashiroda, T. Tsumura, Y. Kano, Y. Muramatsu, T. Chikada, H. Yuki, H. Niwa, S. Sato, *et al.*, Design and Discovery of an Orally Efficacious Spiroindolinone-Based Tankyrase Inhibitor for the Treatment of Colon Cancer, *J. Med. Chem.*, 2020, **63**, 4183.
- 348 F. Shirai, T. Tsumura, Y. Yashiroda, H. Yuki, H. Niwa, S. Sato, T. Chikada, Y. Koda, K. Washizuka, N. Yoshimoto, *et al.*, Discovery of Novel Spiroindoline Derivatives as Selective Tankyrase Inhibitors, *J. Med. Chem.*, 2019, **62**, 3407.
- 349 H. Richter, A. L. Satz, M. Bedoucha, B. Buettelmann, A. C. Petersen, A. Harmeier, R. Hermosilla,



- R. Hochstrasser, D. Burger, B. Gsell, *et al.*, DNA-Encoded Library-Derived DDR1 Inhibitor Prevents Fibrosis and Renal Function Loss in a Genetic Mouse Model of Alport Syndrome, *ACS Chem. Biol.*, 2019, **14**, 37.
- 350 J. Xu, X. Xie, N. Ye, J. Zou, H. Chen, M. A. White, P.-Y. Shi and J. Zhou, Design, Synthesis, and Biological Evaluation of Substituted 4,6-Dihydrospiro[[1,2,3]triazolo[4,5-b]pyridine-7,3'-indoline]-2',5(3H)-dione Analogues as Potent NS4B Inhibitors for the Treatment of Dengue Virus Infection, *J. Med. Chem.*, 2019, **62**, 7941.
- 351 (a) G. C. Bignan, K. Battista, P. J. Connolly, M. J. Orsini, J. Liu, S. A. Middleton and A. B. Reitz, Preparation of 3-spirocyclic indolin-2-ones as ligands for the ORL-1 receptor, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5022; (b) S. Ansorge, U. Bank, K. Noordhoff, M. Täger and F. Striggow, Novel Alanyl-Amino Peptidase Inhibitors for Functionally Influencing Different Cells and Treating Immunological, Inflammatory, Neuronal, and Other Diseases, *PCT Int. Appl* WO2005037257A2, 2005.
- 352 E. Hayashi and S. Yamada, Pharmacological studies on surugatoxin, the toxic principle from Japanese ivory mollusc (*Babylonia japonica*), *Br. J. Pharmacol.*, 1975, **53**, 207.
- 353 See ref. 16 and (a) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, *et al.*, Spiroindolones, a Potent Compound Class for the Treatment of Malaria, *Science*, 2010, **329**, 1175; (b) N. J. White, S. Pukrittayakamee, A. P. Phyo, R. Rueangweeraayut, F. Nosten, P. Jittamala, A. Jeeyapant, J. P. Jain, G. Lefèvre, R. Li, *et al.*, Spiroindolone KAE609 for Falciparum and Vivax Malaria, *N. Engl. J. Med.*, 2014, **371**, 403; (c) H. Turner, Spiroindolone NITD609 is a novel antimalarial drug that targets the P-type ATPase PfATP4, *Future Med. Chem.*, 2016, **8**, 227; (d) T. D. Ashton, S. M. Devine, J. J. Möhrle, B. Laleu, J. N. Burrows, S. A. Charman, D. J. Creek and B. E. Sleebs, The Development Process for Discovery and Clinical Advancement of Modern Antimalarials, *J. Med. Chem.*, 2019, **62**, 10526.
- 354 H. Takada, N. Kumagai and M. Shibasaki, Stereoselective Total Synthesis of KAE609 via Direct Catalytic Asymmetric Alkynylation to Ketimine, *Org. Lett.*, 2015, **17**, 4762.
- 355 H. Zheng, X. Liu, C. Xu, Y. Xia, L. Lin and X. Feng, Regio- and Enantioselective Aza-Diels-Alder Reactions of 3-Vinylindoles: A Concise Synthesis of the Antimalarial Spiroindolone NITD609, *Angew. Chem., Int. Ed.*, 2015, **54**, 10958.
- 356 For piperazines see: (a) K. Ramakumar, T. Maji, J. J. Partridge and J. A. Tunge, Synthesis of Spirooxindoles via the tert-Amino Effect, *Org. Lett.*, 2017, **19**, 4014; (b) L.-L. Wang, T. Jiang, P.-H. Li, R.-J. Sun and Z. Zuo, Asymmetric Syntheses of Spirooxindole-dihydroquinazolinones by Cyclization Reactions between N-substituted Anthranilamides and Isatins, *Adv. Synth. Catal.*, 2018, **360**, 4832; (c) R. Ye and C. G. Yan, Construction of Spiro[indoline-3,3'-pyridazines] and Spiro[indene-2,3'-pyridazines] via TEMPO-Mediated Oxidative Aza-Diels-Alder Reactions, *Eur. J. Org. Chem.*, 2019, 5882. For morpholines see: (d) M. Montesinos-Magraner, C. Vila, R. Cantón, G. Blay, I. Fernández, M. C. Muñoz and J. R. Pedro, Organocatalytic Asymmetric Addition of Naphthols and Electron-Rich Phenols to Isatin-Derived Ketimines: Highly Enantioselective Construction of Tetrasubstituted Stereocenters, *Angew. Chem., Int. Ed.*, 2015, **54**, 6320; (e) P. W. Xu, C. Chen, J. K. Liu, Y. T. Song, F. Zhou, J. Yan and J. Zhou, One-Pot Sequential [3 + 3] Dipolar Cycloaddition of Aldehyde or Ketone and Hydroxylamine with Spirocyclopropyl Oxindole, *J. Org. Chem.*, 2018, **83**, 12763; (f) S. Hajra, A. Hazra and S. K. Abu Saleh, One-Pot Synthesis of Enantiopure Spiro[3,4-dihydrobenzo[b],[1,4]oxazine-2,3'-oxindole] via Regio- and Stereoselective Tandem Ring Opening/Cyclization of Spiroaziridine Oxindoles with Bromophenols, *J. Org. Chem.*, 2019, **84**, 10412. Urea: (g) M. Stocchi, G. Lesma, F. Meneghetti, G. Rainoldi, A. Sacchetti and A. Silvani, Organocatalytic Asymmetric Biginelli-like Reaction Involving Isatin, *J. Org. Chem.*, 2016, **81**, 1877. Carbamate: (h) W. Guo, L. Li, Q. Ding, X. Lin, X. Liu, K. Wang, Y. Liu, H. Fan and C. Li, Synthesis of Chiral Trispirocyclic Oxindoles via Organic-Base/Au(I)-Catalyzed Sequential Reactions, *ACS Catal.*, 2018, **8**, 10180. Other: (i) G. Zhu, W. Sun, C. Wu, G. Li, L. Hong and R. Wang, Base-Catalyzed Diastereoselective [3 + 3] Annulation of 3-Isothiocyanatooxindoles and Azomethine Imines, *Org. Lett.*, 2013, **15**, 4988.
- 357 X. N. Zhang, G. Q. Chen, X. Dong, Y. Wei and M. Shi, Phosphine-Catalyzed Asymmetric [4 + 2] Annulation of Vinyl Ketones with Oxindole-Derived α,β -Unsaturated Imines: Enantioselective Syntheses of 2',3'-Dihydro-1'H-spiro[indoline-3,4'-pyridin]-2-ones, *Adv. Synth. Catal.*, 2013, **355**, 3351.
- 358 B. V. S. Reddy, M. Swain, S. M. Reddy, J. S. Yadav and B. Sridhar, Gold-Catalyzed 5-endo-dig Cyclization of 2-[(2-Aminophenyl)ethynyl]phenylamine with Ketones for the Synthesis of Spiroindolone and Indolo[3,2-c]quinolone Scaffolds, *Eur. J. Org. Chem.*, 2014, 3313.
- 359 S. Jayakumar, K. Louven, C. Strohmman and K. Kumar, A Tunable and Enantioselective Hetero-Diels-Alder Reaction Provides Access to Distinct Piperidinoyl Spirooxindoles, *Angew. Chem., Int. Ed.*, 2017, **56**, 15945.
- 360 (a) W. Cao, X. Liu, J. Guo, L. Lin and X. Feng, Asymmetric Tandem 1,5-Hydride Shift/Ring Closure for the Synthesis of Chiral Spirooxindole Tetrahydroquinolines, *Chem. – Eur. J.*, 2015, **21**, 1632; (b) Z. Mao, F. Mo and X. Lin, Diastereo- and Enantioselective Assembly of Spirooxindole Tetrahydroquinoline Skeletons through Asymmetric Binary Acid Catalyzed Hydride Transfer-Cyclization, *Synlett*, 2016, **27**, 546; (c) S. S. Li, S. Zhu, C. Chen, K. Duan, Q. Liu and J. Xiao, Hydride Transfer Involved Redox-Neutral Cascade Cyclizations for Construction of Spirocyclic Bisoxindoles Featuring a [3,4]-Fused Oxindole Moiety, *Org. Lett.*, 2019, **21**, 1058.
- 361 G. J. Mei, D. Li, G. X. Zhou, Q. Shi, Z. Cao and F. Shi, A catalytic asymmetric construction of a tetrahydroquino-



- line-based spirooxindole framework via a diastereo- and enantioselective decarboxylative [4 + 2] cycloaddition, *Chem. Commun.*, 2017, **53**, 10030.
- 362 L. Hao, C. Chuen, R. Ganguly and Y. Chi, NHC-Catalyzed Ester Activation: Access to Sterically Congested Spirocyclic Oxindoles via Reaction of α -Aryl Esters and Unsaturated Imines, *Synlett*, 2013, **24**, 1197.
- 363 D. Xie, L. Yang, Y. Lin, Z. Zhang, D. Chen, X. Zeng and G. Zhong, Rapid Access to Spirocyclic Oxindoles: Application of Asymmetric N-Heterocyclic Carbene-Catalyzed [3 + 3] Cycloaddition of Imines to Oxindole-Derived Enals, *Org. Lett.*, 2015, **17**, 2318.
- 364 W. Q. Jia, H. M. Zhang, C. L. Zhang, Z. H. Gao and S. Ye, N-Heterocyclic, carbene-catalyzed [4 + 2] annulation of α,β -unsaturated carboxylic acids: enantioselective synthesis of dihydropyridinones and spirocyclic oxindolodihydropyridinones, *Org. Chem. Front.*, 2016, **3**, 77.
- 365 J. Xu, S. Yuan and M. Miao, N-Heterocyclic, Carbene Catalyzed [4 + 2] Annulation Reactions with in Situ Generated Heterocyclic ortho-Quinodimethanes, *Org. Lett.*, 2016, **18**, 3822.
- 366 C. He, Z. Li, J. Xu and H. Ren, Asymmetric Synthesis of Spirocyclic Oxindole δ -Lactams via NHC-Catalyzed Formal [2 + 4] Annulation of Aliphatic Aldehydes with Oxindole-Derived α,β -Unsaturated Ketimines, *J. Org. Chem.*, 2019, **84**, 12177.
- 367 (a) Q. Liu, X. Y. Chen, S. Li, K. Rissanen and D. Enders, N-Heterocyclic, Carbene Catalyzed Asymmetric Synthesis of Pentacyclic Spirooxindoles via [3 + 3] Annulations of Isatin-Derived Enals and Cyclic N-Sulfonyl Ketimines, *Adv. Synth. Catal.*, 2019, **361**, 1991. For a further example see: (b) H. Lu, C. Y. Tan, H. X. Zhang, J. L. Zhang, J. Y. Liu, H. Y. Li and P. F. Xu, Participation of β -Ketothioamides in N-Heterocyclic Carbene-Catalyzed [3 + 3] Spiroannulation: Asymmetric Synthesis of Functionalized Spiro-piperidinone Derivatives, *J. Org. Chem.*, 2018, **83**, 15245.
- 368 F. Shi, G.-J. Xing, R.-Y. Zhu, W. Tan and S. Tu, A Catalytic Asymmetric Isatin-Involved Povarov Reaction: Diastereo- and Enantioselective Construction of Spiro[indolin-3,2'-quinoline] Scaffold, *Org. Lett.*, 2013, **15**, 128.
- 369 For other reports of the use of the Povarov reaction to spiro-piperidines see: (a) H. Gao, J. Sun and C. G. Yan, Povarov Reaction of β -Enamino Esters and Isatin-3-imines for Diastereoselective Synthesis of Spiro[indoline-3,2'-quinolines], *Synthesis*, 2014, **46**, 489; (b) G. Bianchini, P. Ribelles, D. Becerra, M. T. Ramos and J. C. Menéndez, Efficient synthesis of 2-acylquinolines based on an aza-vinyllogous Povarov reaction, *Org. Chem. Front.*, 2016, **3**, 412.
- 370 (a) H. H. Zhang, X. X. Sun, J. Liang, Y. M. Wang, C. C. Zhao and F. Shi, Catalytic asymmetric Povarov reaction of isatin-derived 2-azadienes with 3-vinylindoles, *Org. Biomol. Chem.*, 2014, **12**, 9539. Also see: (b) Z. Mao, F. Mo and X. Lin, Diastereo- and Enantioselective Assembly of Spirooxindole Tetrahydroquinoline Skeletons through Asymmetric Binary Acid Catalyzed Hydride Transfer-Cyclization, *Synlett*, 2016, **27**, 546.
- 371 H. Mao, A. Lin, Y. Tang, Y. Shi, H. Hu, Y. Cheng and C. Zhu, Organocatalytic oxa/aza-Michael-Michael Cascade Strategy for the Construction of Spiro [Chroman/Tetrahydroquinoline-3,3'-oxindole] Scaffolds, *Org. Lett.*, 2013, **15**, 4062.
- 372 (a) Y. You, B. D. Cui, M. Q. Zhou, J. Zuo, J. Q. Zhao, X. Y. Xu, X. M. Zhang and W. C. Yuan, Organocatalytic Asymmetric Michael/Friedel-Crafts Cascade Reaction of 3-Pyrrolyl-oxindoles and α,β -Unsaturated Aldehydes for the Construction of Chiral Spiro[5,6-dihydropyrido[1,2-a]pyrrole-3,3'-oxindoles], *J. Org. Chem.*, 2015, **80**, 5951. Also see: (b) W. T. Fan, N. K. Li, L. Xu, C. Qiao and X. W. Wang, Organo-Catalyzed Asymmetric Michael-Hemiketalization-Oxa-Pictet-Spengler Cyclization for Bridged and Spiro Heterocyclic Skeletons: Oxocarbenium Ion as a Key Intermediate, *Org. Lett.*, 2017, **19**, 6626; (c) Z. Gao, J. Zhang, H. Yang and G. Jiang, Brønsted Acid-Promoted Friedel-Crafts Alkylation/Cyclization of (7-Hydroxynaphthalenyl) pyrrole or (2-Hydroxyphenyl)pyrroles with Isatins for the Construction of Pyrrolospirooxindole Derivatives, *J. Org. Chem.*, 2018, **83**, 11407; (d) N. K. Li, W. T. Fan, J. Q. Zhang, B. B. Sun, J. B. Chen and X. W. Wang, Diastereodivergent synthesis of bispirooxindoles via asymmetric Friedel-Crafts/aldol cascade reaction: co-catalyst effects on diastereoselective outcomes, *Chem. Commun.*, 2018, **54**, 2260.
- 373 (a) W. Yang and D.-M. Du, Cinchona-based squaramide-catalysed cascade aza-Michael-Michael addition: enantioselective construction of functionalized spirooxindole tetrahydroquinolines, *Chem. Commun.*, 2013, **49**, 8842; (b) Y. M. Huang, C. W. Zheng and G. Zhao, Organocatalyzed aza-Michael-Michael cascade reactions to construct spirooxindole tetrahydroquinolines with all-carbon chiral centers, *RSC Adv.*, 2013, **3**, 16999; (c) Y. Tan, E. L. Feng, Q. S. Sun, H. Lin, X. Sun, G. Q. Lin and X. W. Sun, Enantioselective synthesis of spirooxindole benzoquinolizines via organo-catalyzed cascade reactions, *Org. Biomol. Chem.*, 2017, **15**, 778; (d) W. Dai, H. Lu, X. Li, F. Shi and S. J. Tu, Diastereo- and Enantioselective Construction of a Bispirooxindole Scaffold Containing a Tetrahydro- β -carboline Moiety through an Organocatalytic Asymmetric Cascade Reaction, *Chem. – Eur. J.*, 2014, **20**, 11382; (e) Y. Liu, J. Xue, Z. Sun, D. Liu, Y. Xing and Y. Li, Substituent-Controlled Selective Synthesis of Spirooxindoles and Oxazolyloxindoles via Two Tandem Reactions, *Asian J. Org. Chem.*, 2016, **5**, 43; (f) Q. Zhao, C. Peng, H. Huang, S. J. Liu, Y. J. Zhong, W. Huang, G. He and B. Han, Asymmetric synthesis of tetrahydroisoquinoline-fused spirooxindoles as Ras-GTP inhibitors that inhibit colon adenocarcinoma cell proliferation and invasion, *Chem. Commun.*, 2018, **54**, 8359.
- 374 M. C. Yang, C. Peng, H. Huang, L. Yang, X. H. He, W. Huang, H. L. Cui, G. He and B. Han, Organocatalytic Asymmetric Synthesis of Spiro-oxindole Piperidine Derivatives That Reduce Cancer Cell Proliferation by Inhibiting MDM2-p53 Interaction, *Org. Lett.*, 2017, **19**, 6752.



- 375 (a) Y. Liao, M. Bai, S. Yu, M. Zhang, F. Hu, X. Xu, W. Yuan and X. Zhang, Construction of Novel Tetrahydro- β -carboline-1-thione Spirooxindoles by Brønsted Acid Mediated Formal [3 + 3] Cyclization of 3-Indolylmethanols with 3-Isothiocyanto Oxindoles, *J. Heterocycl. Chem.*, 2017, **54**, 1311; (b) S. Kawamura, K. Dosei, E. Valverde, K. Ushida and M. Sodeoka, N-Heterocycle-Forming, Amino/Carboperfluoroalkylations of Aminoalkenes by Using Perfluoro Acid Anhydrides: Mechanistic Studies and Applications Directed Toward Perfluoroalkylated Compound Libraries, *J. Org. Chem.*, 2017, **82**, 12539; (c) L. Qi, H. Hou, F. Ling, L. Fang, W. Luo and W. Zhong, Cinchona Alkaloid Thiourea Catalyzed Asymmetric Synthesis and Anticancer Activity Evaluation of Tetrahydro- β -spirooxindoles, *Heterocycles*, 2018, **96**, 1119; (d) G. Zhan, M. L. Shi, W. J. Lin, Q. Ouyang, W. Du and Y. C. Chen, Direct Asymmetric Aza-Vinyllogous-Type Michael Additions of Nitrones from Isatins to Nitroalkenes, *Chem. – Eur. J.*, 2017, **23**, 6286.
- 376 For examples see: (a) S. J. Kalita, B. Das and D. C. Deka, A Quick, Simple and Clean Synthesis of Spiro(indoline-3,4'-pyrazolo[4', 3':5,6]pyrido[2, 3-d]pyrimidines) in Water through a Novel One-Pot Multicomponent Reaction, *ChemistrySelect*, 2017, **2**, 5701; (b) A. Mondal, B. Naskar, S. Goswami, C. Prodhan, K. Chaudhuri and C. Mukhopadhyay, I₂ catalyzed access of spiro[indoline-3,4'-pyridine] appended amine dyad: new ON-OFF chemosensors for Cu²⁺ and imaging in living cells, *Org. Biomol. Chem.*, 2018, **16**, 302; (c) M. Esmaeilpour, A. R. Sardarian and H. Firouzabadi, Theophylline Supported on Modified Silica-Coated Magnetite Nanoparticles as a Novel, Efficient, Reusable Catalyst in Green One-Pot Synthesis of Spirooxindoles and Phenazines, *ChemistrySelect*, 2018, **3**, 9236; (d) Q. Niu, J. Xi, L. Li, L. Li, C. Pan, M. Lan and L. Rong, Isatins 3-C annulation vs ring-opening: Two different pathways for synthesis of spiro compounds via multicomponent reactions, *Tetrahedron Lett.*, 2019, **60**, 151181.
- 377 (a) Q. N. Zhu, Y. C. Zhang, M. M. Xu, X. X. Sun, X. Yang and F. Shi, Enantioselective Construction of Tetrahydroquinolin-5-one-Based Spirooxindole Scaffold via an Organocatalytic Asymmetric Multicomponent [3 + 3] Cyclization, *J. Org. Chem.*, 2016, **81**, 7898; (b) P. Zhou, B. Hu, L. Lu, R. Huang and F. Yu, One-Pot Synthesis of Functionalised 4-Spiro-1,4-Dihydropyridines Via [1 + 2 + 1 + 2]-Cyclisation, *J. Chem. Res.*, 2017, **41**, 513.
- 378 Y. H. Wang, J. S. Tian, P. W. Tan, Q. Cao, X. X. Zhang, Z. Y. Cao, F. Zhou, X. Wang and J. Zhou, Regiodivergent Intramolecular Nucleophilic Addition of Ketimines for the Diverse Synthesis of Azacycles, *Angew. Chem., Int. Ed.*, 2020, **59**, 1634.
- 379 Y. Bin Shen, L. X. Wang, Y. M. Sun, F. Y. Dong, L. Yu, Q. Liu and J. Xiao, Hexafluoroisopropanol-Mediated Redox-Neutral α -C(sp³)-H Functionalization of Cyclic Amines via Hydride Transfer, *J. Org. Chem.*, 2020, **85**, 1915.
- 380 M. Holmquist, G. Blay, M. C. Muñoz and J. R. Pedro, Aza-Henry Reaction of Isatin Ketimines with Methyl 4-Nitrobutyrate en Route to Spiro[piperidine-3,3'-oxindoles], *Adv. Synth. Catal.*, 2015, **357**, 3857.
- 381 (a) Y. Zhu, Y. Li, Q. Meng and X. Li, An organocatalytic enantioselective vinyllogous Mannich reaction of α,α -dicyanoolefins with isatin N-Boc ketimines, *Org. Chem. Front.*, 2016, **3**, 709; (b) S. Nakamura, K. Matsuzaka, T. Hatanaka and Y. Funahashi, Enantioselective Vinyllogous Mannich Reaction of Acyclic Vinylketene Silyl Acetals with Ketimines Using Chiral Bis(imidazoline)-Cu(II) Catalysts, *Org. Lett.*, 2020, **22**, 2868. For a phase transfer catalysed version see: (c) C. Cheng, X. Lu, L. Ge, J. Chen, W. Cao, X. Wu and G. Zhao, Effective asymmetric vinyllogous Mannich reaction of isatin imines with α,α -dicyanoolefins in the presence of a simple chiral amide phosphonium bifunctional phase transfer catalyst, *Org. Chem. Front.*, 2017, **4**, 101.
- 382 Z. Chang, C. Ye, J. Fu, P. Chigumbu, X. Zeng, Y. Wang, C. Jiang and X. Han, Enantioselective Synthesis of Oxindole-Derived α -Aryl- β -Amino Acid Derivatives and δ -Lactams with Homophthalic Anhydrides, *Adv. Synth. Catal.*, 2019, **361**, 5516.
- 383 K. R. Senwar, P. Sharma, T. S. Reddy, M. K. Jeengar, V. L. Nayak, V. G. M. Naidu, A. Kamal and N. Shankaraiah, Spirooxindole-derived morpholine-fused-1,2,3-triazoles: Design, synthesis, cytotoxicity and apoptosis inducing studies, *Eur. J. Med. Chem.*, 2015, **102**, 413.
- 384 G. Schwartz, M. C. Witschel, M. Rottmann, U. Leartsakulpanich, P. Chitnumsub, A. Jaruwat, W. Amornwatcharapong, W. Ittarat, A. Schäfer, R. A. Aponte, *et al.*, Potent Inhibitors of Plasmodial Serine Hydroxymethyltransferase (SHMT) Featuring a Spirocyclic Scaffold, *ChemMedChem*, 2018, **13**, 931.
- 385 (a) P. R. Eastwood, J. Gonzalez Rodriguez and V. Giulio Matassa, New Substituted Indolin-2-one. Derivatives and Their Use as P39 Mitogen-Activated Kinase-Inhibitors, *PCT Int. Appl* WO2009132774A1, 2009; (b) P. Eastwood, J. González, E. Gómez, F. Caturla, N. Aguilar, M. Mir, J. Aiguadé, V. Matassa, C. Balagué, A. Orellana, *et al.*, Indolin-2-one p38 α inhibitors III: Bioisosteric amide replacement, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 6253.
- 386 S. J. Han, F. Vogt, S. Krishnan, J. A. May, M. Gatti, S. C. Virgil and B. M. Stoltz, A Diastereodivergent Synthetic Strategy for the Syntheses of Communesin F and Perophoramidine, *Org. Lett.*, 2014, **16**, 3316.
- 387 J. Z. Huang, C. L. Zhang, Y. F. Zhu, L. L. Li, D. F. Chen, Z. Y. Han and L. Z. Gong, Organocatalytic Highly Enantioselective Substitution of 3-(1-Tosylalkyl)indoles with Oxindoles Enables the First Total Synthesis of (+)-Trigolutes B, *Chem. – Eur. J.*, 2015, **21**, 8389.
- 388 For related total synthesis: B. N. Reddy and C. V. Ramana, A concise approach for central core of trigolutes: Total synthesis of trigolute B and 3-epi-trigolute B and analogues, *Tetrahedron*, 2017, **73**, 888.
- 389 S. Zhao, J. B. Lin, Y. Y. Zhao, Y. M. Liang and P. F. Xu, Hydrogen-Bond-Directed Formal [5 + 1] Annulations of



- Oxindoles with Ester-Linked Bisenones: Facile Access to Chiral Spirooxindole δ -Lactones, *Org. Lett.*, 2014, **16**, 1802.
- 390 (a) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, Organocatalytic Domino Oxa-Michael/1,6-Addition Reactions: Asymmetric Synthesis of Chromans Bearing Oxindole Scaffolds, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104. For a recent diastereoselective oxa-Michael reaction see: (b) M. Pasha, M. Sohail and F. Tanaka, Intramolecular Oxa-Michael Reactions of Aldols Generated from Enones and Isatins to Afford Spirooxindole Tetrahydropyrans, *Heterocycles*, 2020, **101**, 339.
- 391 (a) L. Zhu, Q. Chen, D. Shen, W. Zhang, C. Shen, X. Zeng and G. Zhong, Enantioselective Construction of Spirocyclic Oxindole Derivatives with Multiple Stereocenters via an Organocatalytic Michael/Aldol/Hemiacetalization Cascade Reaction, *Org. Lett.*, 2016, **18**, 2387. Also see: (b) N. Kumarswamyreddy and V. Kesavan, Enantioselective Synthesis of Dihydrospiro[indoline-3,4'-pyrano[2,3-c]pyrazole] Derivatives via Michael/Hemiketalization Reaction, *Org. Lett.*, 2016, **18**, 1354; (c) L. Qiao, Z. W. Duan, X. N. Wu, D. H. Li, Q. Q. Gu and Y. K. Liu, Organocatalytic Diversity-Oriented Asymmetric Synthesis of Structurally and Stereochemically Complex Heterocycles, *Org. Lett.*, 2018, **20**, 1630.
- 392 (a) J.-L. Han and C.-H. Chang, An asymmetric assembly of spirooxindole dihydropyranones through a direct enantioselective organocatalytic vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles with isatins, *Chem. Commun.*, 2016, **52**, 2322; (b) J. L. Han, Y. Da Tsai and C. H. Chang, Asymmetric Synthesis of Spirooxindole δ -Lactones with Vicinal Tertiary and Quaternary Stereocenters via Regio-, Diastereo-, and Enantioselective Organocatalytic Vinylogous Aldol-cyclization Cascade Reaction, *Adv. Synth. Catal.*, 2017, **359**, 4043.
- 393 J. L. Hu, F. Sha, Q. Li and X. Y. Wu, Highly enantioselective Michael/cyclization tandem reaction between dimedone and isatylidene malononitriles, *Tetrahedron*, 2018, **74**, 7148.
- 394 For a further enantioselective example of a related scaffold: (a) S. Konda, S. Jakkampudi, H. D. Arman and J. C. G. Zhao, Enantioselective synthesis of spiro[4H-pyran-3,3'-oxindole] derivatives catalyzed by cinchona alkaloid thioureas: Significant water effects on the enantioselectivity, *Synth. Commun.*, 2019, **49**, 2971. For racemic synthesis of related scaffolds see selected examples: (b) M. Zhang, W. Yang, M. Qian, T. Zhao, L. Yang and C. Zhu, Iodine-promoted three-component reaction for the synthesis of spirooxindoles, *Tetrahedron*, 2018, **74**, 955; (c) A. S. Hussien, A. P. Pandey and A. Sharma, Mechanochemical- (Hand-Grinding-) Assisted Domino Synthesis of Fused Pyran-Spirooxindoles under Solvent- and Catalyst-Free Condition, *ChemistrySelect*, 2018, **3**, 11505; (d) D. Y. Seo, S. Lee, B. K. Min and J. N. Kim, Synthesis of Spirooxindoles Bearing Benzopyrano[2,3-b]indole Moiety by NBS-Mediated Oxidative Coupling Reaction, *Bull. Korean Chem. Soc.*, 2018, **39**, 1011. Also see ref. 371.
- 395 (a) M. Liu, X. Zhang, X. Huang, G. Dhawan, J. Evans, M. Kaur, J. P. Jasinski and W. Zhang, Recyclable Organocatalyst for One-Pot Asymmetric Synthesis of Dihydrofuranone and Tetrahydropyranone Spirooxindoles, *Eur. J. Org. Chem.*, 2019, 150; (b) Z. H. Wang, X. Y. Zhang, C. W. Lei, J. Q. Zhao, Y. You and W. C. Yuan, Highly enantioselective sequential vinylogous aldol reaction/transesterification of methyl-substituted olefinic butyrolactones with isatins for the construction of chiral spirocyclic oxindole-dihydropyranones, *Chem. Commun.*, 2019, **55**, 9327.
- 396 (a) H. L. Cui and F. Tanaka, Catalytic Enantioselective Formal Hetero-Diels-Alder Reactions of Enones with Isatins to Give Spirooxindole Tetrahydropyranones, *Chem. – Eur. J.*, 2013, **19**, 6213; (b) D. B. Ramachary, M. Shiva Prasad, S. Vijaya Laxmi and R. Madhavachary, Asymmetric synthesis of drug-like spiro[chroman-3,3'-indolin]-2'-ones through amination-catalysis, *Org. Biomol. Chem.*, 2014, **12**, 574; (c) M. Chennapuram, I. A. Owolabi, C. Seki, Y. Okuyama, E. Kwon, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, New Hybrid-type Squaramide-Fused Amino Alcohol Organocatalyst for Enantioselective Domino Michael Addition/Cyclization Reaction of Oxindolines with Cyclic 1,3-Diketones, *ACS Omega*, 2018, **3**, 11718.
- 397 (a) Y. Bin Shen, S. S. Li, X. Liu, L. Yu, Q. Liu and J. Xiao, Dearomative [4 + 2] Cycloaddition of Oxindole-Embedded ortho-Quinone Methides with 2,5-Dialkylfurans, *Adv. Synth. Catal.*, 2019, **361**, 1453; (b) Y. Bin Shen, S. S. Li, X. Liu, L. Yu, Y. M. Sun, Q. Liu and J. Xiao, Formal [4 + 2] Annulation of Oxindole-Embedded ortho-Quinone Methides with 1,3-Dicarbonyls: Synthesis of Spiro [Chromen-4,3'-Oxindole] Scaffolds, *J. Org. Chem.*, 2019, **84**, 3990.
- 398 H. Shi, L. Wang, S. S. Li, Y. Liu and L. Xu, Divergent syntheses of spirooxindoles from oxindole-embedded four-membered synthon via cycloaddition reactions, *Org. Chem. Front.*, 2020, **7**, 747.
- 399 (a) Y. Jiang, S. W. Yu, Y. Yang, Y. Le Liu, X. Y. Xu, X. M. Zhang and W. C. Yuan, Synthesis of polycyclic spirooxindoles via an asymmetric catalytic one-pot stepwise Aldol/chloroetherification/aromatization procedure, *Org. Biomol. Chem.*, 2018, **16**, 6647; (b) M. Luo, X. Zhu, R. Liu, S. Yu and W. Wei, FeCl₃-Promoted Annulation of 2-Haloindoles: Switchable Synthesis of Spirooxindole-chromeno[2,3-b]indoles and Spirooxindole-chromeno[3,2-b]indoles, *J. Org. Chem.*, 2020, **85**, 3638.
- 400 (a) J. Peng, G. Y. Ran, W. Du and Y. C. Chen, Divergent Cyclization Reactions of Morita-Baylis-Hillman Carbonates of 2-Cyclohexenone and Isatylidene Malononitriles, *Org. Lett.*, 2015, **17**, 4490; (b) A. Yadav, J. Banerjee, S. K. Arupula, S. M. Mobin and S. Samanta, Lewis-Base-Catalyzed Domino Reaction of Morita-Baylis-Hillman Carbonates of Isatins with Enolizable Cyclic



- Carbonyl Compounds: Stereoselective Access to Spirooxindole-Pyrans, *Asian J. Org. Chem.*, 2018, **7**, 1595.
- 401 (a) Y. Que, T. Li, C. Yu, X. S. Wang and C. Yao, Enantioselective Assembly of Spirocyclic Oxindole-dihydropyranones through NHC-Catalyzed Cascade Reaction of Isatins with N-Hydroxybenzotriazole Esters of α,β -Unsaturated Carboxylic Acid, *J. Org. Chem.*, 2015, **80**, 3289. Also see: (b) J. T. Cheng, X. Y. Chen, Z. H. Gao and S. Ye, N-Heterocyclic Carbene Catalyzed Generation and [4 + 2] Annulation of Unsubstituted Dienolate - Enantioselective Synthesis of Spirocyclic Oxindolodihydropyranones, *Eur. J. Org. Chem.*, 2015, 1047.
- 402 W. Zhang, J. Xu, J. Cao, C. Fang, J. Zhu, T. Lu and D. Du, N-heterocyclic carbene-mediated formal [3 + 3] annulation of isatin-derived α , β -unsaturated acids: Access to functionalized 3,4'-spirooxindole δ -lactones, *Tetrahedron*, 2017, **73**, 3249.
- 403 J.-B. Lin, X.-N. Cheng, X.-D. Tian, G.-Q. Xu, Y.-C. Luo and P.-F. Xu, A C_1 -symmetric N-heterocyclic carbene catalysed oxidative spiroannulation of isatin-derived enals: highly enantioselective synthesis of spirooxindole δ -lactones, *RSC Adv.*, 2018, **8**, 15444.
- 404 Z. J. Zhang, L. Zhang, R. L. Geng, J. Song, X. H. Chen and L. Z. Gong, N-Heterocyclic, Carbene/Copper Cooperative Catalysis for the Asymmetric Synthesis of Spirooxindoles, *Angew. Chem., Int. Ed.*, 2019, **58**, 12190.
- 405 J. Zheng, L. Lin, K. Fu, Y. Zhang, X. Liu and X. Feng, *Chem. – Eur. J.*, 2014, **20**, 14493–14498.
- 406 J. Wang, Q. Zhang, Y. Li, X. Liu, X. Li and J.-P. Cheng, $Bi(OAc)_3$ /chiral phosphoric acid catalyzed enantioselective allylation of isatins, *Chem. Commun.*, 2020, **56**, 261.
- 407 R. Sato, T. Tosaka, H. Masu and T. Arai, Catalytic Asymmetric Synthesis of Chiral Bis(indolyl)methanes Using a Ts-Pyridine-Nickel Complex, *J. Org. Chem.*, 2019, **84**, 14248.
- 408 B. V. Subba Reddy, V. Swathi, M. Swain, M. P. Bhadra, B. Sridhar, D. Satyanarayana and B. Jagadeesh, Stereoselective Synthesis of Spiro[tetrahydropyran-3,3'-oxindole] Derivatives Employing Prins Cascade Strategy, *Org. Lett.*, 2014, **16**, 6267.
- 409 S. Jia, Y. Lei, L. Song, A. G. Krishna Reddy, D. Xing and W. Hu, Diastereoselective Intramolecular Aldol-Type Trapping of Zwitterionic Intermediates by Ketones for the Synthesis of Spiro[chroman-4,3'-oxindole] Derivatives, *Adv. Synth. Catal.*, 2017, **359**, 58.
- 410 N. Probst, G. Grelier, N. E. Ghermani, V. Gandon, M. Alami and S. Messaoudi, Intramolecular Pd-Catalyzed Anomeric $C(sp^3)$ -H Activation of Glycosyl Carboxamides, *Org. Lett.*, 2017, **19**, 5038.
- 411 S. R. Kandimalla and G. Sabitha, Diversity-Oriented Synthesis of Oxacyclic Spirooxindole Derivatives through Ring-Closing Enyne Metathesis and Intramolecular Pauson-Khand (2 + 2 + 1) Cyclization of Oxindole Enynes, *Adv. Synth. Catal.*, 2017, **359**, 3444.
- 412 See ref. 314b and (a) J. Qu, L. Fang, X. D. Ren, Y. Liu, S. S. Yu, L. Li, X. Q. Bao, D. Zhang, Y. Li and S. G. Ma, Bisindole Alkaloids with Neural Anti-inflammatory Activity from *Gelsemium elegans*, *J. Nat. Prod.*, 2013, **76**, 2203; (b) W. Zhang, W. Xu, G. Y. Wang, X. Y. Gong, N. P. Li, L. Wang and W. C. Ye, Gelsekoudines A and B: Two Pairs of Atropisomeric Bisindole Alkaloids from the Roots of *Gelsemium elegans*, *Org. Lett.*, 2017, **19**, 5194; (c) N. P. Li, M. Liu, X. J. Huang, X. Y. Gong, W. Zhang, M. J. Cheng, W. C. Ye, L. Wang and A.-E. Gelsecorydines, Five Gelsedine-Corynanthe-Type Bisindole Alkaloids from the Fruits of *Gelsemium elegans*, *J. Org. Chem.*, 2018, **83**, 5707.
- 413 (a) O.-G. Berge, A. Claesson and B.-M. Swahn, New Compounds, *PCT Int. Appl* WO2001005790A1, 2001; (b) J.-J. Liu, J. W. Tilley and Z. Zhang, 3,3-Spiroindolinone Derivatives, *PCT Int. Appl* WO2008141917A1, 2008.
- 414 S. Pellegrino, M. Ruscica, P. Magni, G. Vistoli and M. L. Gelmi, Antiproliferative activity on human prostate carcinoma cell lines of new peptidomimetics containing the spiroazepinoindolinone scaffold, *Bioorg. Med. Chem.*, 2013, **21**, 5470.
- 415 (a) Y. Liu, Z. Sun, S. Li, K. Xiang, Y. Zhang and Y. Li, $Mg(ClO_4)_2$ -promoted [4 + 3] cycloaddition of oxindole derivatives with conjugated dienes: concise synthesis of spirocycloheptane oxindole derivatives, *RSC Adv.*, 2016, **6**, 26954; (b) Z. J. Jia, G. Shan, C. G. Daniliuc, A. P. Antonchick and H. Waldmann, Enantioselective Synthesis of the Spirotropanyl Oxindole Scaffold through Bimetallic Relay Catalysis, *Angew. Chem., Int. Ed.*, 2018, **57**, 14493; (c) M. Balha and S. C. Pan, Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton, *J. Org. Chem.*, 2018, **83**, 14703; (d) B. Hu, X. Zhang, Y. Mo, J. Li, L. Lin, X. Liu and X. Feng, Catalytic Asymmetric Tandem Cycloisomerization/[5 + 2] Cycloaddition Reaction of N-Aryl Nitron Alkynes with Methyleneindolinones, *Org. Lett.*, 2020, **22**, 1034.
- 416 (a) S. Diethelm and E. M. Carreira, Total Synthesis of ($\pm$)-Gelsemoxonine, *J. Am. Chem. Soc.*, 2013, **135**, 8500; (b) S. Diethelm and E. M. Carreira, Total Synthesis of Gelsemoxonine through a Spirocyclopropane Isoxazolidine Ring Contraction, *J. Am. Chem. Soc.*, 2015, **137**, 6084.
- 417 E. T. Newcomb, P. C. Knutson, B. A. Pedersen and E. M. Ferreira, Total Synthesis of Gelsenicine via a Catalyzed Cycloisomerization Strategy, *J. Am. Chem. Soc.*, 2016, **138**, 108.
- 418 (a) T. Harada, J. Shimokawa and T. Fukuyama, Unified Total Synthesis of Five Gelsedine-Type Alkaloids: (–)-Gelsenicine, (–)-Gelsedine, (–)-Gelsedilam, (–)-14-Hydroxygelsenicine, and (–)-14,15-Dihydroxygelsenicine, *Org. Lett.*, 2016, **18**, 4622; (b) P. Wang, Y. Gao and D. Ma, Divergent Entry to Gelsedine-Type Alkaloids: Total Syntheses of (–)-Gelsedilam, (–)-Gelsenicine, (–)-Gelsedine, and (–)-Gelsemoxonine, *J. Am. Chem. Soc.*, 2018, **140**, 11608.
- 419 A. Saito, N. Kogure, M. Kitajima and H. Takayama, Total Synthesis of (–)-14-Hydroxygelsenicine and Six



- Biogenetically Related Gelsemium Alkaloids, *Org. Lett.*, 2019, **21**, 7134.
- 420 (a) L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen and D. Enders, Asymmetric Synthesis of Spirobenzazepinones with Atroposelectivity and Spiro-1,2-Diazepinones by NHC-Catalyzed [3 + 4] Annulation Reactions, *Angew. Chem., Int. Ed.*, 2016, **55**, 11110. For a mechanistic study see: (b) Y. Li and Z. Zhang, Mechanisms and Stereoselectivities of NHC-Catalyzed [3 + 4] Cycloaddition Reaction between Isatin-Derived Enal and N-(ortho-Chloromethyl)aryl Amide, *Eur. J. Org. Chem.*, 2019, 2989.
- 421 W. Li, H. Yuan, Z. Liu, Z. Zhang, Y. Cheng and P. Li, NHC-Catalyzed Enantioselective [4 + 3] Cycloaddition of Ortho-Hydroxyphenyl Substituted Para-Quinone Methides with Isatin-Derived Enals, *Adv. Synth. Catal.*, 2018, **360**, 2460.
- 422 Q. Liu, S. Li, X. Y. Chen, K. Rissanen and D. Enders, Asymmetric Synthesis of Spiro-oxindole- ϵ -lactones through N-Heterocyclic Carbene Catalysis, *Org. Lett.*, 2018, **20**, 3622.
- 423 Z.-H. Gao, K.-Q. Chen, Y. Zhang, L.-M. Kong, Y. Li and S. Ye, Enantioselective N-Heterocyclic Carbene-Catalyzed Synthesis of Spirocyclic Oxindole-benzofuroazepinones, *J. Org. Chem.*, 2018, **83**, 15225.
- 424 D. Liu, Z. Hu, Y. Zhang, M. Gong, Z. Fu and W. Huang, Access to Enantioenriched Spiro- ϵ -Lactam Oxindoles by an N-Heterocyclic Carbene-Catalyzed [4 + 3] Annulation of Flexible Oxotryptamines with Enals, *Chem. – Eur. J.*, 2019, **25**, 11223.
- 425 G. Zhan, M.-L. Shi, Q. He, W. Du and Y.-C. Chen, [4 + 3] Cycloadditions with Bromo-Substituted Morita-Baylis-Hillman Adducts of Isatins and N-(ortho-Chloromethyl) aryl Amides, *Org. Lett.*, 2015, **17**, 4750.
- 426 J. Y. Liu, H. Lu, C. G. Li, Y. M. Liang and P. F. Xu, Lewis Base and Brønsted Base Dual-Catalyzed Formal [4 + 3] Cyclo-addition Reaction: Synthesis of Aza-Spirocycloheptane Oxindole, *Synlett*, 2016, **27**, 1287.
- 427 J.-Y. Du, Y.-H. Ma, F.-X. Meng, R.-R. Zhang, R.-N. Wang, H.-L. Shi, Q. Wang, Y.-X. Fan, H.-L. Huang, J.-C. Cui, *et al.*, Lewis Base-Catalyzed [4 + 3] Annulation of ortho-Quinone Methides and MBH Carbonates: Synthesis of Functionalized Benzo[b]oxepines Bearing Oxindole Scaffolds, *Org. Lett.*, 2019, **21**, 465.
- 428 Z. Chen, Z. Chen, Z. Yang, L. Guo, W. Du and Y. Chen, Cooperative Tertiary Amine/Chiral Iridium Complex Catalyzed Asymmetric [4 + 3] and [3 + 3] Annulation Reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 15021.
- 429 F. Zhou, G. J. Cheng, W. Yang, Y. Long, S. Zhang, Y. D. Wu, X. Zhang and Q. Cai, Enantioselective Formation of Cyano-Bearing All-Carbon Quaternary Stereocenters: Desymmetrization by Copper-Catalyzed N-Arylation, *Angew. Chem., Int. Ed.*, 2014, **53**, 9555.
- 430 K. L. Ivanov, A. A. Kravtsova, E. A. Kirillova, M. Y. Melnikov and E. M. Budynina, Domino Michael/aza-Wittig reaction in the diastereoselective construction of spiro[azepane-4,3'-oxindoles], *Tetrahedron Lett.*, 2019, **60**, 1952.
- 431 W. Ren, Q.-M. Zuo, Y.-N. Niu and S.-D. Yang, Palladium-NHC-Catalyzed Allylic Alkylation of Pronucleophiles with Alkynes, *Org. Lett.*, 2019, **21**, 7956.
- 432 (a) B. Niu, X. Y. Wu, Y. Wei and M. Shi, Palladium-Catalyzed Diastereoselective Formal [5 + 3] Cycloaddition for the Construction of Spirooxindoles Fused with an Eight-Membered Ring, *Org. Lett.*, 2019, **21**, 4859; (b) H. Zhao, L. Wang, J. Guo, W. Ding, X. Song, H. Wu, Z. Tang, X. Fan and X. Bi, Formal [5 + 3] Cycloaddition of Vinylethylene Carbonates with Isatin-Based α -(Trifluoromethyl)imines for Diastereoselective Synthesis of Medium-Heterocycle-Fused Spirooxindoles, *Adv. Synth. Catal.*, 2019, **361**, 4761–4771; (c) H. Zhao, L. Wang, J. Guo, W. Ding, J. Du and N. Feng, Eight-membered nitrogen-oxygen heterocyclic spiro indolone compound and preparation method thereof, *PCT Int. Appl* CN108864147A, 2018.

