New development in the enantioselective synthesis of spiro compounds

Aishun Ding,[§a] Marta Meazza,[§b] Hao Guo,*[a] Jung Woon Yang*[c] and Ramon Rios*[b,c]

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The enantioselective synthesis of spirocycles has been long pursued by organic chemists. Despite their unique 3D properties and presence in several natural products, the difficulty in their enantioselective synthesis makes them underrepresented in pharmaceutical libraries. Since the first pioneering reports of the enantioselective construction of spirosilanes by Tamao *et al*., significant effort has been devoted towards the development of new promising asymmetric methodologies. Remarkably, with the advent of organocatalysis, particularly over six years, the reported methodologies for the synthesis of spirocycles have increased exponentially. The aim of this review is to summarize the lastest trends and developments in the enantioselective synthesis of spirocompounds during these last six years.

1. Introduction

One of the goals of synthetic organic chemists is the complete stereo-defined synthesis of highly complex 3D structures. Arguably, the most important challenge is the regio- and stereo-controlled generation of spiro compounds. Spiro compounds,[1] formally known as bicyclic organic compounds, comprise rings connected through just one atom that present several unique characteristics, such as 3D structural properties, related to their inherent rigidity. Notably, these compounds display a broad range of biological activities.

Nowadays, spiro compounds are attracting increasing attention as scaffolds in modern drug discovery. The intrinsic complexity and more importantly, rigidity of these scaffolds offer several advantages to drug discovery programs. Moreover, the latter characteristic could be used for a more efficient design of the 3D orientation of the pharmacophore to maximize H-bonding, hydrophobic, and π-stacking interactions. This benefits both the recognition between the drug and its target and the physico-chemical properties of the drug, including its solubility and lipophilicity.

Spiro compounds are present in a plethora of natural products such as the angiotensin antagonist irbersetan (**1**), analgesic morphine (**2**), β-vetivone (**3**), the antibiotic monensin (**4**), (-)-acorenone B (**5**), opioid receptor agonist oxycodone (**6**), Shizuka-acordienol (**7**), rosmadial (**8**), (-)-cannabispirenone A (**9**), trigolute B (**10**) used in Thai folk medicine, marine alkaloid (+)-discorhabdin A (**11**), and alkaloid citrinalin A (**12**). Taking advantage of their rigidity and extremely precise 3D structure, spiro compounds have emerged as one of the most attractive ligand and catalyst motifs in asymmetric synthesis as well as catalysis. Mainly, these scaffolds are derived from spinol (**13**) and show excellent stereochemical recognition. Some examples, such as spirobis(oxazoline) (**14**), spinol-derived phosphoric acid (**15**), and the diphosphine spirOP (**16**), are illustrated in Figure 1.

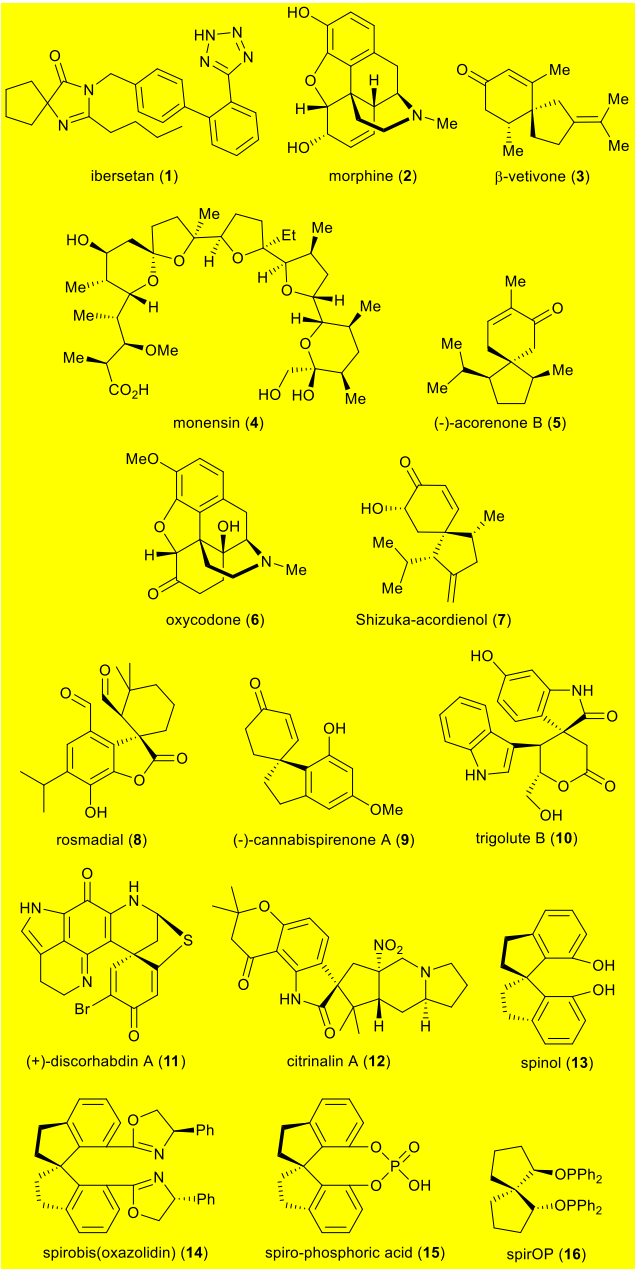


Figure 1: Examples of compounds containing a spirocyclic ring

The challenges associated with the synthesis of spiro compounds are long to enumerate. Group compatibility is one of the major issues associated with the synthesis of spiro compounds. However, from the stereoselective perspective, the presence of the quaternary and generally chiral spiro atom is probably the most important issue. Notably, similar to allenes, the spiro atom in these compounds can present both central and axial chirality. The rigidity of the spirocycle allows the formation of two enantiomers, despite the absence of an asymmetric centre.

The discovery of spirocycles can be traced back to the pioneering works of Von Baeyer in the late 1890s.[2] Von Bayer proposed the name spirocyclane for bicyclic hydrocarbons having two rings with a common carbon atom (spiro carbon atom). Since then, numerous attempts have been made to synthesize spirocycles. The most important strategies are summarized in Figure 2 and include intermolecular double substitutions (a), metal-promoted cyclizations (b), intramolecular substitution (c), cycloadditions (d), radical cyclizations (e), and intramolecular arrangements (f).

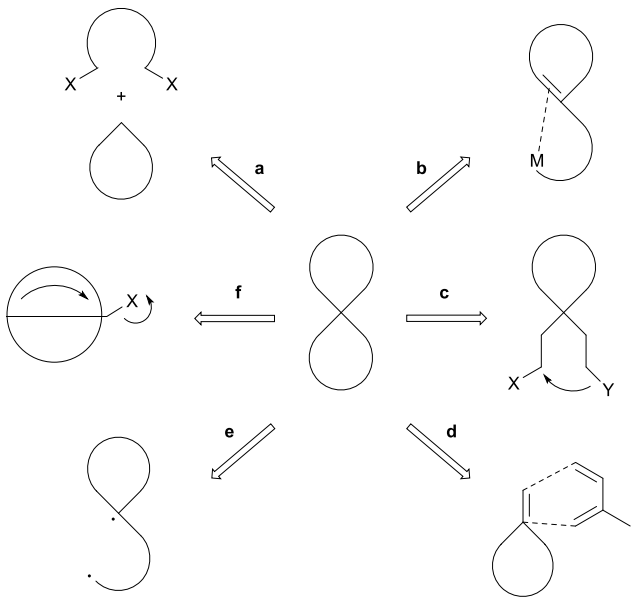


Figure 2: Common strategies for the synthesis of spirocycles: (a) alkylation methods, (b) metal-catalysed methods, (c) ring-closure methods, (d) cycloaddition strategies, (e) radical strategies, and (f) rearrangement strategies.

While spiro compounds are gaining increasing attention in the drug discovery field, they are still underrepresented in screening libraries and suffer from low diversity.[3] The relatively low occurrence of spiro motifs in modern drug discovery is not the result of intrinsic adverse physico-chemical properties, but rather reflects the need for new strategies for their efficient synthesis and derivatization. Moreover, 3D/sp^3-rich scaffolds provide more vectors for functionalization compared to common flat/aromatic scaffolds, overrepresented in many fragment libraries. Several issues arise for the synthesis of spirocycles, including functional group compatibility and the addition of functional functionality in the newly formed ring system for further synthetic manipulation. These issues, together with the previously cited necessity to control the newly formed stereogenic centre and the difficulties of the synthesis of quaternary centres, have attracted the interests of synthetic chemists. Thus, a plethora of enantioselective methodologies has been developed to circumvent these problems.

In this review, we will focus on the new methodologies reported in the last five years, updating our previous tutorial review.[1]

In the first part of the review, we will present the enantioselective syntheses of spirocycles using organometallic catalysts. This section is divided according to the metal employed in the synthetic reaction rather than in the strategy employed. Metals have been reported as catalysts for the synthesis of spiro compounds, achieving high levels of stereoselectivity due to the development of new chiral ligands. Several reviews related to the synthesis of spiro compounds by organometallic methodologies have been reported during this period. For example, in catalytic asymmetric dearomatization, several reviews devoted to this topic, including methodologies for the synthesis of spiro compounds,[4] have been published. Thus, this review is not comprehensive in organometallic methodologies but highlights the most important advances in this area.

The second part of this review is devoted to enantioselective organocatalytic methodologies for the synthesis of spirocycles. This part is organized according to the nature of the synthesized spirocyclic ring. In this selection, we first disclose the different methodologies reported for the synthesis of spirooxindoles. These comprise several organocatalytic methodologies that have been recently developed, including [3+2] cycloadditions, alkylations, and ring closing reactions. Next, we cover other spirocycles such as benzofuranones and pyrazolones.

Finally, we focus on synergistic methodologies for the synthesis of spiro compounds. Despite this field being relatively new, several powerful strategies for the synthesis of spiro compounds have been reported.[5]

2. Organometallic Approaches

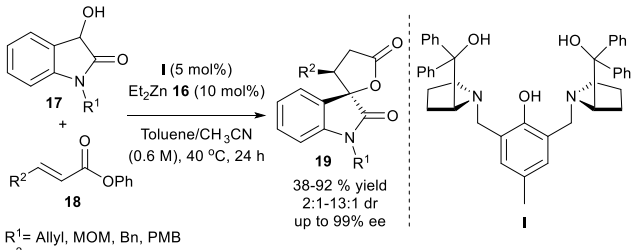
For many years organometallic chemistry has been the preferred approach for the development of enantioselective methodologies. Transition metals such as Zn, Rh, Pd, and so forth have demonstrated unique properties that allow the development of new bond forming reactions. Moreover, their effectiveness has greatly increased with the development of new chiral ligands. In this section, we focus on the enantioselective methodologies for the synthesis of spiro compounds developed over the past few years. A major diversity in the spiro structures and a higher control in stereoselectivity have been achieved from the methodologies developed in the last five years over earlier methods. The development of new chiral ligands has resulted in more active and selective processes as well as the development of new metal-catalysed reactions; for example, the application of Zn

combined with the Trost or *N*-oxide ligands and the use of iridium and cobalt metals.

The synthesis of spiro compounds has greatly benefitted from their use in medicinal chemistry as the intense quest for new oxindole scaffolds with rigid sructures has increased the interest to develop new strategies for the synthesis of spiro-oxindoles.

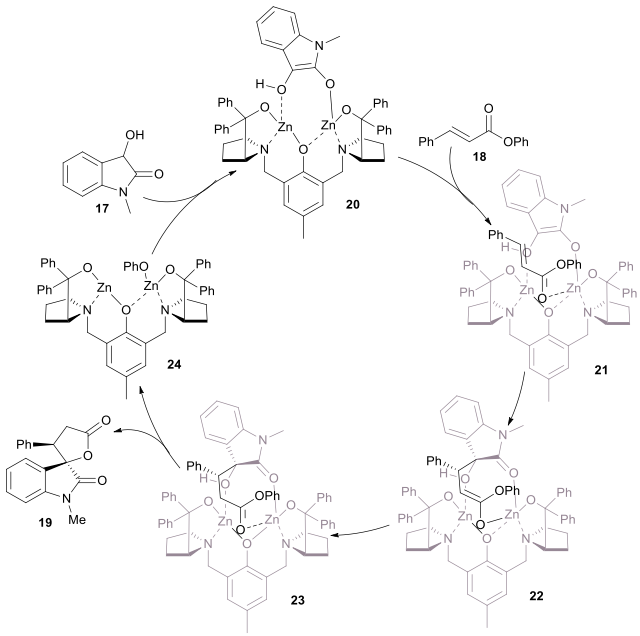
2.1 Zinc-catalysed methodologies

3,3-Disubstituted oxindoles are a recurrent structural motif present in several natural products. Trost *et al*. reported the enantioselective addition of 3-hydroxyoxindoles **17**, as isatinic anion equivalent, to electrophiles via the formal umpolung strategy to afford spirocyclic oxindoles **19**.[6] The reaction relies on the dinuclear zinc-ProPhenol-calalysed asymmetric tandem Michael addition of **17** to α,β-unsaturated esters **18** followed by a transesterification process to afford the spirocyclic δ-lactones **19** in generally high yields (38-92%), moderate diastereoselectivities (2:1-13:1 d.r.), and high enantioselectivities (up to 99% ee; Scheme 1).



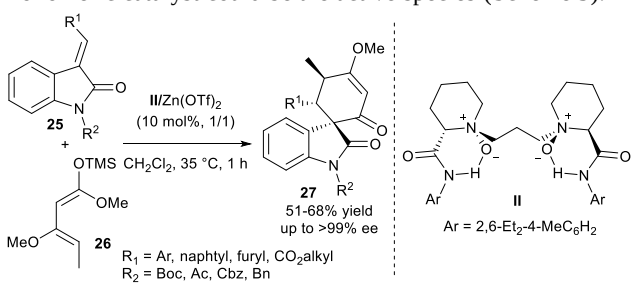
Scheme 1: Reaction reported by Trost

The proposed mechanism of the high diastereo- and enantioselective formal [3+2] cycloaddition is described in Scheme 2: 3-hydroxyoxindole is deprotonated by an ethylzinc species to produce **20** that coordinates cinnamate **18** to the less-hindered zinc atom to form **21**. Next, nucleophilic addition leads to **22** followed by tautomerization to complex **23**. After cyclization, **23** releases spirocyclic oxindole **19** and restores the zinc phenoxide catalyst **24** (Scheme 2).



Scheme 2: Mechanism for the spirocyclization reported by Trost

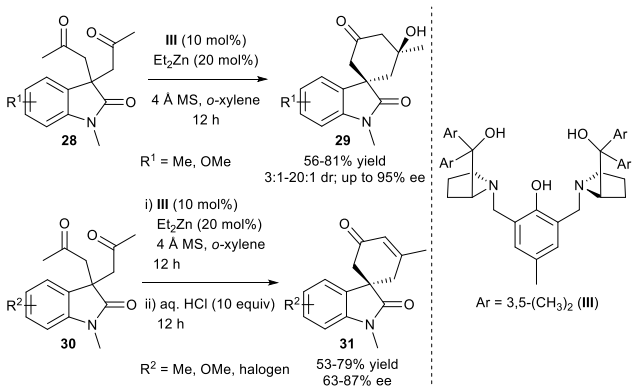
Another zinc-catalyzed synthesis of 3,3-disubstituted spirooxindoles was reported by Feng *et al*. This comprised the asymmetric Diels-Alder reaction of methyleneidolinones **25** and dienes **26** (Brassard's type).[7] The catalytic system is based on $Zn(OTf)_2$ and L-PiEt$_2$-Me (**II**) as ligand, affording the final spiro compounds (**27**) in moderate yields (58-68%) and excellent enantioselectivities (98-99% ee). Various substituents on the *N*-Boc-protected indolinones are tolerated, such as substituted phenyl, naphthyl, furyl, and alkylesters. Moreover, the presence of electron-donating group (EDG) in the phenyl moiety afforded better results over electron-withdrawing group (EWG). For *N*-substitution, Boc, Ac, and Cbz groups were allowed but no reaction was observed with Bn. This indicates that both carbonyl groups present in the indolinone exhibit bidentate coordination with the Zn catalyst. Moreover, a linear effect between the enantiomeric excess of the ligand and the product was observed, indicating that the monomeric catalyst could be the active species (Scheme 3).



Scheme 3: Spirocyclization reported by Feng

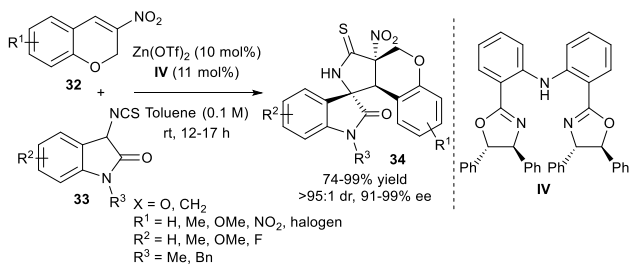
The synthesis of spiro[cyclohexanone-oxindole] compounds, reported by Wang *et al*., starts from diketone oxindole **28** with Trost's dinuclear zinc catalyst.[8] The asymmetric intramolecular

aldol reaction (4 Å molecular sieves and the best dinuclear zinc catalysts results $ZnEt_2$/**III)** affords spiro(cyclohexanone-oxindole) **29** in reasonable yields (55-81%) with moderate to good enantioselectivities (63-95% ee). The outcome of the reaction is strictly dependent on the temperature and catalyst loading. The best conditions were observed when 10 mol% **III** and 20 mol% $ZnEt_2$ were employed as catalyst. The reaction leads to the formation of an inseparable mixture of aldol and dehydration compounds. Thus, the authors investigated the possibility to attain only the dehydrated products **31** by an acidic treatment of the reaction mixture generated in the first step (Scheme 4).



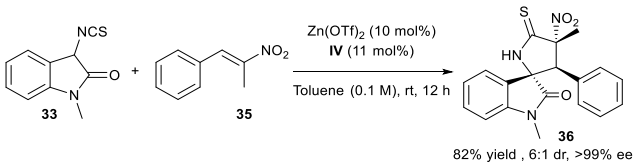
Scheme 4: Spirocyclization reported by Wang

Xiao and Chen *et al*. described an asymmetric Michael addition/cyclization cascade reaction of 3-nitro-2*H*-chromenes (**32**) with 3-isocyanato oxindoles **33** catalysed by chiral Zn(II) under mild conditions.[9] The reaction is highly stereoselective leading to functionalized polycyclic spirooxindoles (**34**) in 72-99% yields, >95:5 d.r., and >99% ee. The optimized reaction conditions employ 10 mol % $Zn(OTf)_2$ and 11 mol% **IV** in toluene at room temperature (Scheme 5). Various substituents on the 3-isocyanato oxindole moiety and on the 3-nitro-2*H*-chromene are well tolerated.



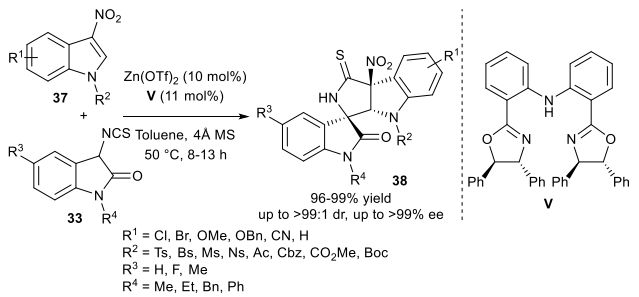
Scheme 5: Cascade reaction reported by Xiao and Chen

Acyclic nitrostyrenes were also successfully employed; however, to gain good results, the nitroalkene was substituted at the carbon atom bearing the nitro group. Thus, β-methyl-β-nitrostyrene afforded the product in 82% yield, 3:1 d.r., and 99% ee, compared to the 29% yield, 3:1 d.r., and 4% ee observed when simple β-nitrostyrene was used (Scheme 6).



Scheme 6: Cascade reaction reported by Xiao and Chen

Yuan and Xu *et al.* reported a similar cascade reaction involving 3-isocyanato oxindoles **33** and 3-nitroindoles **37**. The asymmetric Michael/cyclization cascade reaction was catalysed by $Zn(OTf)_2$/diphenylamine-linked bis(oxazoline) **V** and afforded the products (**38**) in 95−99% yield, >99:1 d.r., and up to >99% ee with good functional group tolerance (Scheme 7).[10] The optimized conditions involve 10 mol% $Zn(OTf)_2$ and 11 mol% ligand **V**. A broad range of substituents on the phenyl ring of 3-nitroindole as well as several types of substituents at the *N*1 position of 3-nitroindole were well tolerated. The proposed transition state involves the Zn(II) Lewis acid activation of the 3-nitroindoles, while the NH group in the catalyst acts as a Lewis base coordinating to the 3-isocyanato oxindoles.

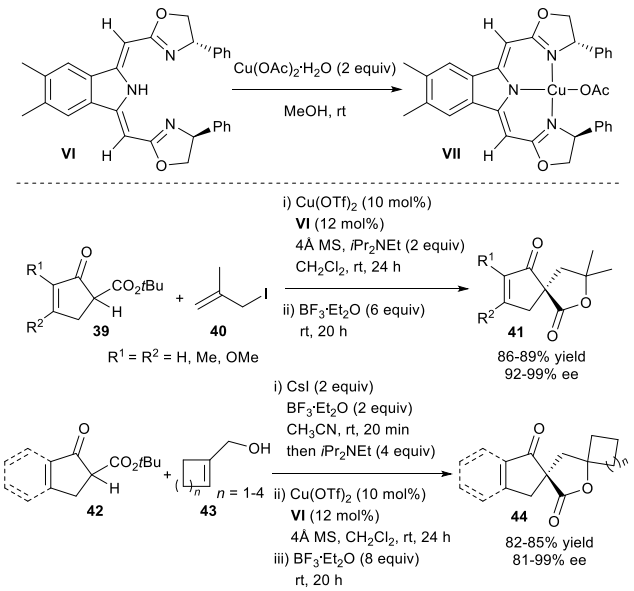


Scheme 7: Spirocyclization reported by Yuan and Xu

2.2 Copper-catalysed methodologies

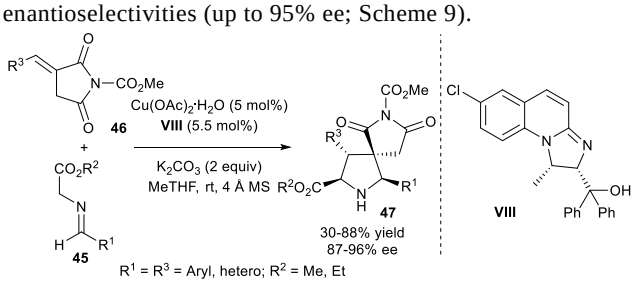
Gade *et al.* reported the enantioselective synthesis of spirolactones and bi-spirolactones catalysed by a Cu(II) complex with chiral pincer ligands, boxmi (**VI**). The procedure is based on the stereoselective alkylation of cyclic β-ketoesters (**39**) with benzylic and allylic iodides (40).[11] The iodides prepared in situ from the corresponding alcohols via CsI and $BF_3{\cdot}Et_2O$ in CH_3CN after quenching with DIPEA, were reacted with the β-ketoesters. The Cu complex promotes the enantioselective alkylation and lactonization of the allylic derivatives. Optimum alkylation results (>90% yield and up to 99% ee) were observed with the bulky *tert*-butyl β-ketoesters. The reaction works with indanones and cyclopentanones but fails with six-membered rings and acyclic ketoesters. When the allylic moiety is part of a cycle, a bi-spirolactone was produced. In these cases, the reaction works better with cyclopentanones with respect to indanones. A reasonable mechanism for the Cu(II) catalysed alkylation has been proposed where the cyclization is promoted by $BF_3{\cdot}Et_2O$ and the Cu(II) complex. In the absence of the Cu(II) complex, only a trace amount of

spirolactone was detected (Scheme 8).



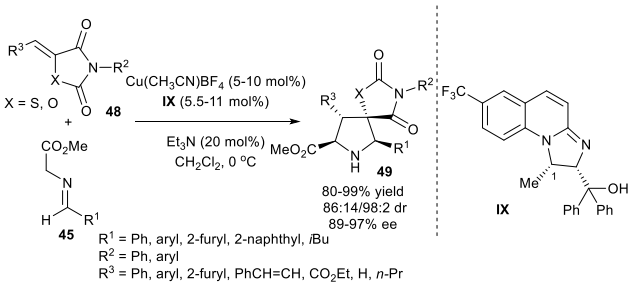
Scheme 8: Spirocyclizations reported by Gade

Deng and Yu *et al*. employed a 1,3-dipolar cycloaddition of azomethine ylides to contruct spiropyrrolidine derivatives.[12] The reaction of azomethine ylides **45** with α-alkylidene succinimides **46** catalysed by $Cu(OAc)_2$/*N,O*-ligand systems leads to *endo*-dispiropyrrolidines **47** in good yields and >20:1 d.r., and up to 97% ee. The reaction requires the presence of an electron-withdrawing group such as CO_2Me and Cbz on the succinimide nitrogen. Among the chiral *N,O*-ligands tested, **VIII** affored the best yields. The methyl substituent in position 1 of the ligand is necessary to gain high enantioselectivity. The reaction works well with azomethine ylides **45** derived from glycine esters in which the subtituents on the aromatic group R^1 can be indifferently neutral, electron-donating or -withdrawing, heteroarylic, and even sterically hindered. α-Alkylidene succinimides **46** tollerate both electron-rich and electron-deficient substituents in several positions of the aryl ring. With the more reactive terminal α-alkylidene succinimides, the reaction requires the chiral *N,O*-ligand/$Cu(CH_3CN)_4BF_4$ complex. Moreover, the $Cu(OAc)_2$/*N,O*-ligand **VIII** catalytic system can be applied to the cycloaddition of azomethine ylides with 2-oxoindolin-3-ylidenes to afford *exo*-dispiropyrrolidines **47** in excellent yields (88-99%), excellent diastereoselectivities (99:1 d.r.), and high enantioselectivities (up to 95% ee; Scheme 9).



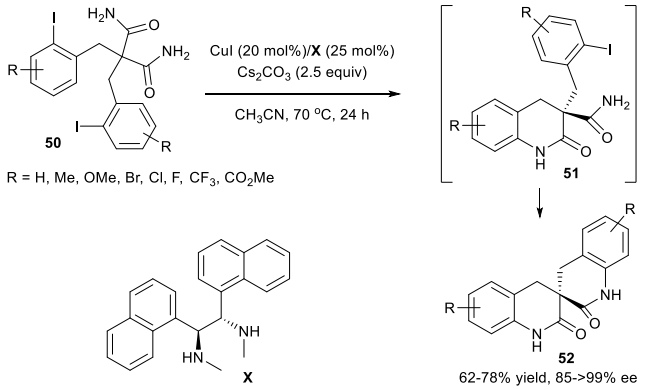
Scheme 9: Spirocyclization reported by Deng and Yu

Deng and Yu *et al*. applied this procedure to the synthesis of spirocyclic pyrrolidine-thia(oxa)zolidinediones.[13] The *exo*-pyrrolidine-thiazolidinedione bearing heteroquaternary stereocentres, were produced via the 1,3-dipolar cycloaddition of azomethine ylides **45** with 5-alkylidene thiazolidine-2,4-diones **48** in excellent yields (up to 99%), high diastereoselectivity (up to 99:1) and enantioselectivity up to 98%. Once again, the presence of the methyl substituent in position 1 of the ligand is essential to achieve high yields and enantioselectivities. In the azomethine ylides **45** derived from glycine esters, neutral, heteroaryl, and electron-donating and electron-withdrawing substituents on the aromatic group R^1 are well tolerated and gave the corresponding products in excellent yields (88-99%) and stereoselectivities (86:14-99:1 d.r. and 89-97% ee). The reaction also worked well when R^1 was an alkyl with ligand **IX** at room temperature. Excellent results (80-99% yields, 87:13-99:1 d.r., and 87-97% ee) observed with thiazolidine-2,4-diones **48** (X = S), which were insensitive to the presence of different type of substituents on the phenyl rings (R^2 and R^3). Thiazolidine-2,4-diones bearing an alkyl substituent on either R^2 or R^3 reacted very well. The reaction was also applied to 5-alkylidene oxazolidine-2,4-diones **48** (X = O), using ligand **IX** to produce *exo*-spirocyclic pyrrolidine-oxazolidinedione **49** (X = O) in good yields (88-92%), high diastereoselectivities (80:20-98:2 d.r.), and high enantioselectivities (92-97% ee; Scheme 10).



Scheme 10: Spirocyclization reported by Deng and Yu

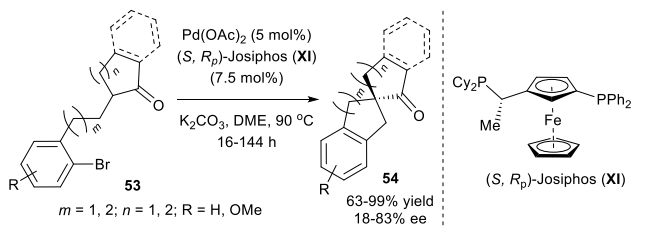
Cai *et al*. studied the enantioselective synthesis of spirobilactams *via* Cu-catalysed intramolecular double *N*-arylation and phase separation.[14] The reactions of 2,2-bis(2-iodobenzyl)-malonamides **50** were performed in CH_3CN at 70 °C with $CsCO_3$ as a base in the presence of CuI and a chiral ligand (**X**); this ligand produced the best yields and enantioselectivities. In the model reaction the lactam was reduced to benzospirodiamine to allow better HPLC measurement. With the except of the CF_3-substituted product, an increase in ee was observed in the *in situ* precipitation of the racemate. At the end of the reaction, the addition of more solvent allows the dissolution of the enantiopure product precipitated together with the racemate. The products (**52**) were obtained from the filtrate in the yields range 65-78% and up to 99% ee. Different substituents on the phenyl ring are well tolerated. The enantioselectivity arises from the first desymmetric cyclization (Scheme 11).



Scheme 11: Spirocyclization reported by Cai

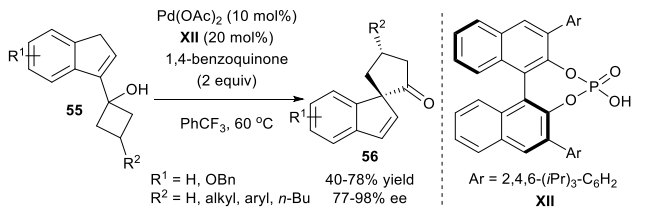
2.3 Palladium-catalysed methodologies

Takisawa and Sasai *et al*. reported the synthesis of spirocyclic ketones **54** based on the intramolecular α-arylation of α-substituted cyclic ketones **53**.[15] The reaction is catalysed by Pd complexes and the Josiphos (**XI**) ligand, rendering the final compounds in excellent yields (63-99%) and moderate enantioselectivities (12-83% ee; Scheme 12). The enantioselectivity of the reaction is highly dependent on the spirobicycle ring formed; spiro[4,4]nonanes afforded higher enantioselectivities than spiro[5,5] and spiro[4,6] alkanones. Another important limitation of this methodology is the need of an *ortho*-OMe substituent in the bromo-phenyl ring.



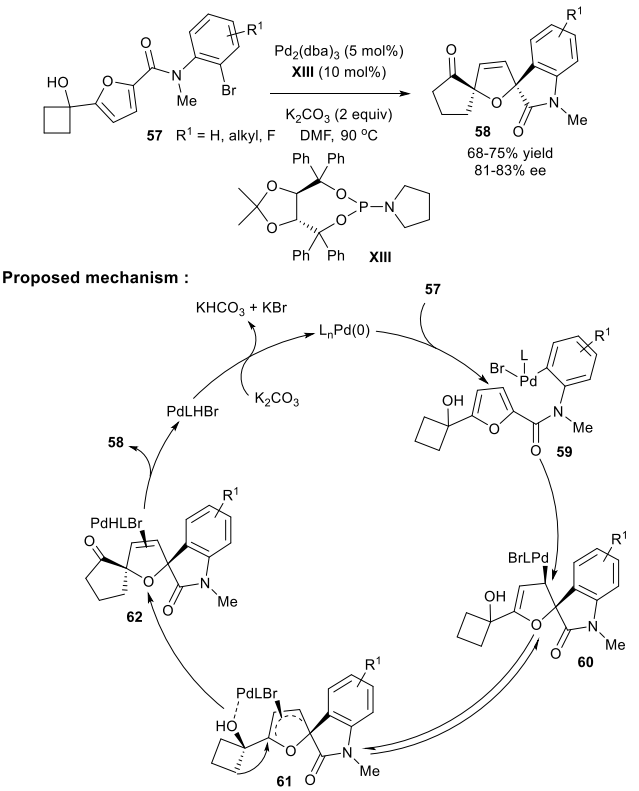
Scheme 12: Spirocyclization reported by Takisawa and Sasai

A migratory ring expansion was reported by Rainey *et al*. for the synthesis of spirocyclic rings.[16] Cyclobutanols **55** bearing an indene ring at the α-position reacted with Pd(II) /phosphoric acid (**XII**) complexes as catalysts, through an enantioselective allylic CH activation with concomitant semipinacol ring expansion, for the construction of spiroindanones **56** in moderate yields (40-78%) and good enatioselectivities (77-98% ee; Scheme 13).



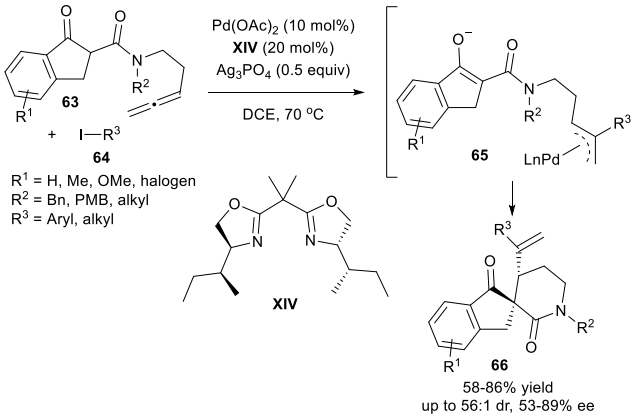
Scheme 13: Ring expansion reported by Rainey

Yin *et al*. reported the synthesis of dispirooxindoles from furfurylcyclobutanols **57**. The reaction occurs through an arylative dearomatization/ring expansion cascade catalysed by Pd(0).[17] First, the oxidative addition of palladium **59** takes place on the bromo aryl, followed by addition to the furan (Heck type addition, **60**). The process proceeds via isomerization to the spiro allylic palladium intermediate and coordination to the hydroxyl group form intermediate **61**. This undergoes a 1,2-alkyl shift and releases palladium to form spirofuran **58** (Scheme 14). The choice of ligand is crucial to attain good enantioselectivities: phosphoramidite **XIII** derived from TADDOL renders the final products in good yields (70-75%) and enantioselectivities (81-83% ee) and only one diastereomer. Only five chiral examples with limited scope have been reported (Scheme 14).



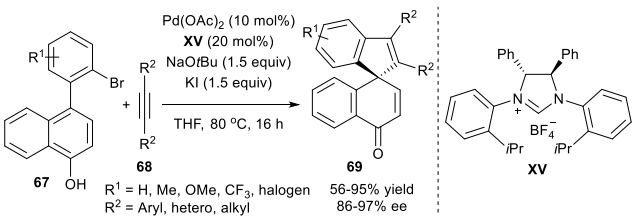
Scheme 14: Synthesis of dispirooxindoles reported by Yin

Dixon *et al*. reported a Pd-catalyzed carbocyclization cascade for the synthesis of heavily decorated spirolactams.[18] Mediated by silver phosphate, allene-linked ketoamides **63** react with aryl or vinyl iodides **64** to form the allyl intermediate **65**, which undergoes intramolecular alkyation to from the ketoamide. The final spirolactams **66** were generated in good yields (61-82%), excellent diastereoselectivities (up to 42:1 d.r.), and good enantioselectivities (65-89% ee) with good group compatibility (Scheme 15).



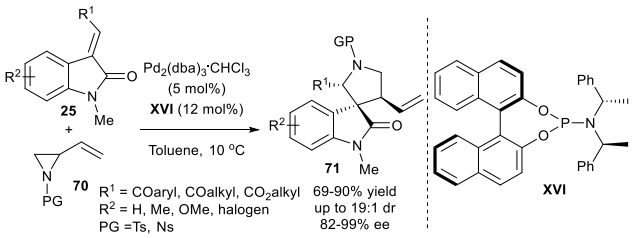
Scheme 15: Spirocyclization reported by Dixon

Luan *et al*. reported a palladium-catalyzed dynamic kinetic asymmetric transformation of a racemic biaryl, showing an axial-to-central chirality transfer.[19] Conformationally labile biaryls bearing an *ortho*-bromo substituent (**67**), undergo and enantioselective reaction with chiral Pd(0) complexes. When the NHC ligand **XV** is employed, the palladium complex discriminates between the two chiral conformations of the biaryl. Next, coordination of the alkyne **68** and subsequent cycloaddition leads to the formation of spirocompound **69** in good yields (up to 95%) and excellent enantioselectivities (up to 97% ee; Scheme 16).



Scheme 16: Spirocyclization reported by Luan

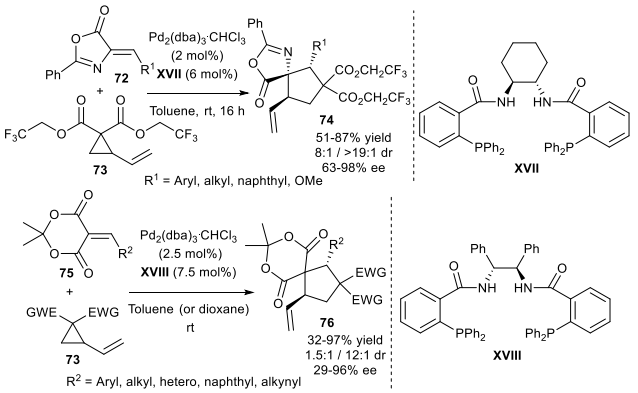
A Pd-catalysed [3+2] cycloaddition between vinyl aziridines **70** and alkylidene oxindoles **25** was reported by Lu *et al*.[20] The reaction starts with the complexation of Pd to the vinylaziridine, opening the aziridine and forming the 1,3-dipole. It then, proceeds with a Michael addition to methylenindoline. This is followed by intramolecular asymmetric allylic alkylation to furnish the 3,3'-pyrrolidonyl spirooxindole and regenerate the Pd(0) catalyst. Phosphoramidate **XVI** is used as ligand, achieving the final compounds **71** in good yields (69-90%), good to excellent diastereoselectivities (up to 19:1 d.r.), and excellent enantioselectivities (82-99% ee). Limitations of the present methodology include the use of Ts-protected aziridines and the requirement of electron-withdrawing substituents at the alkylidene position of the oxindole (Scheme 17).



Scheme 17: Spirocyclization reported by Lu

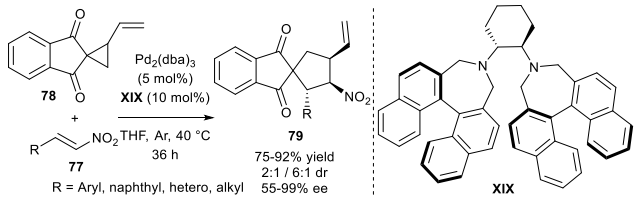
A similar reaction was reported by Shi, Xu and Wei *et al*. where the vinyl cyclopropanes react with isatins.[21] The use of chiral imidazoline-phosphine ligands is crucial to attain excellent yields (up to 98%) and stereoselectivities (up to 94:6 d.r. and 96% ee). Shi *et al*. reported a novel cycloaddition between vinyl cyclopropanes and diazo oxindoles.[22] The reaction is efficiently catalysed by Pd(0) complexes, using chiral imidazoline-phosphines as the ligand. The reaction affords the corresponding oxindole-fused spiropyrazoline in good yields and enantioselectivities. Moreover, they designed a one-pot cascade reaction adding maleimides. The maleimide reacts with the formed dipole to furnish the final multicyclic products, bearing four stereocentres in good yields and stereoselectivities.

Trost *et al*. reported a formal [3+2] cycloaddition between arylidene oxazolones **72** and vinyl cyclopropanes (**73**).[23] The reaction was catalysed by $Pd_2(dba)_3$, using the chiral phosphine ligand **XVII**. Interestingly, a key aspect to attaining good reactivity was the type of substituent present in the malonate moiety of the vinyl cyclopropane. The authors proposed that the use of trifluoroethylester increases the half-life of the intermediate dipole, without losing the reactivity. The reaction afforded the spiro oxazolone derivatives **74** in good yields and excellent stereoselectivities (Scheme 18, top). The same research group later expanded the scope of the reaction using alkylidene Meldrum's acid (**75**).[24] DPPBA biphosphine ligands (**XVIII**) were employed to achieve the final spiro cyclopentanes **76** in good yields and excellent stereoselectivities (Scheme 18, bottom). Zhao *et al*. reported the synthesis of spirocycles based on this approach using *para*-quinonemethides and vinyl epoxides or vinyl cyclopropanes with excellent results.[25]



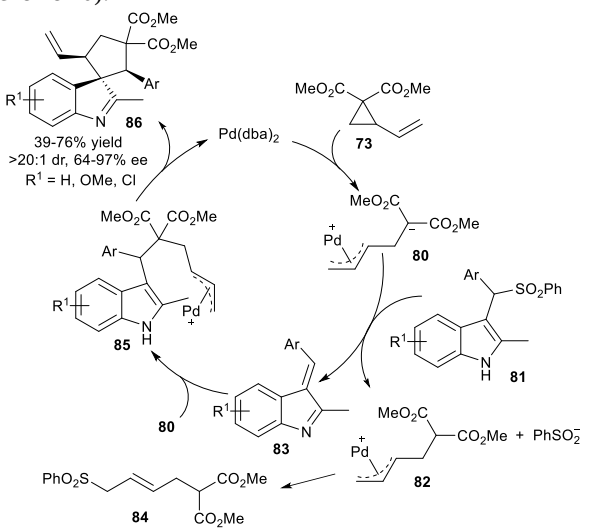
Scheme 18: Spirocyclizations reported by Trost

Nitrostyrenes **77** react with vinyl cyclopropanes **78** derived from 1,3-indanone under Pd(0) catalysis, using the diamine ligand **XIX** to produce spiro compounds **79** in good yields (75-90%) and moderate to good diastereoselectivities (1.2:1 to 14:1 d.r.), and excellent enantioselectivities (92-99% ee; Scheme 19).[26]



Scheme 19: Spirocyclization reported by Liu

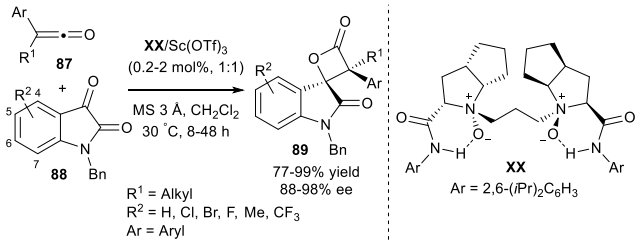
A cycloaddition of vinyl cyclopropanes with arenesulfonyl indoles catalysed by palladium complexess was described by Liu and He *et al*. in 2015.[27] Arenesulfonyl indoles **81** react with the zwitterion (**80**) formed via the ring opening of the vinyl cyclopropane **73** by Pd. Next, the conjugate addition of the malonate and the subsequent Pd-catalysed intramolecular allylation, afforded the spiroindolines **86** in good yields (up to 74%) and stereoselectivities (up to 97% ee; total diastereoselectivity), using phosphoramidite **XVI** as the ligand (Scheme 20).



Scheme 20: Spirocyclization reported by Liu and He

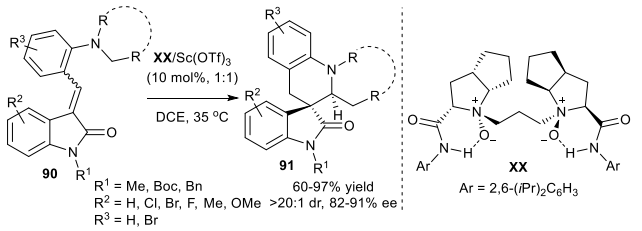
2.4 Scandium-catalysed methodologies

Feng *et al.* reported a highly diastereo- and enantioselective [2+2] cycloaddition reaction of disubstituted ketenes **87** with isatins **88**, catalysed by a chiral *N*,*N*'-dioxide **XX**-Sc(OTf)$_3$ complex in the presence of molecular sieves, to produce β-lactones **89** in very high yields.[28] The substituents on the ketene moiety have little effect on the stereoselectivity, while the subtituents on the isatins exhibits a more pronounced effect on both the reactivity and enantioselectivity. For example, EWG in positions 5 and 6 decrease the performance of the cycloaddition and require higher catalyst loading over isatin-substituted in position 7 (Scheme 21).



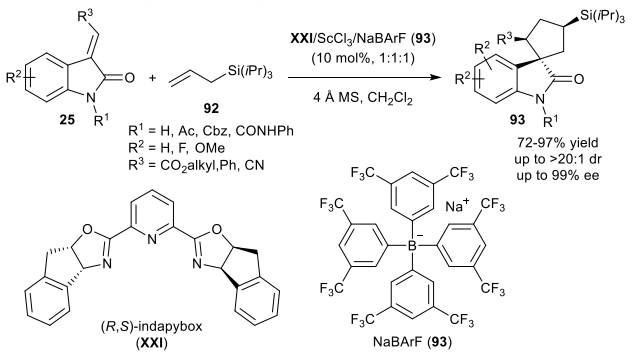
Scheme 21: [2+2] cycloaddition reported by Feng

In a subsequent study, Feng's group studied the asymmetric synthesis of chiral spirooxindole tetrahydroquinolines **91** *via* a tandem 1,5-hydride shift and ring closure. The chiral *N*,*N*'-dioxide **XX**-Sc(OTf)$_3$ complex promoted the reaction with up to 97% yields and >20:1 diastereoselectivities.[29] Notably, partial self disproportionation of enantiomers (SDE) occurs during silica column purification of the products (Scheme 22).



Scheme 22: Spirocyclization reported by Feng

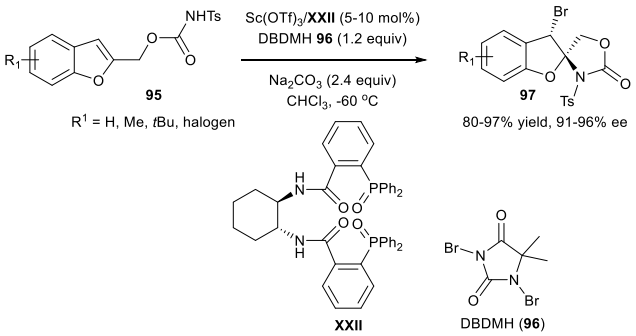
Franz *et al.* describe the first enantioselective [3+2] carboannulation of alkylidene oxindoles **25** with allylsilanes **92** catalysed by a scandium(III)/(*R*,*S*)-indaPybox **XXI** complex with sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF, **93**) to improve the stereoselectivity. The reaction allows access to spirocyclopentanes **94** with up to three stereocenters (Scheme 23).[30]



Scheme 23: Spirocyclization reported by Franz

The bromoaminocyclization of benzofuranylmethyl *N*-tosylcarbamates **95** afforded spiro benzofuran oxazolidinones **97** in high yield and good enetioselectivity.[31] The reaction was accomplished with a Sc(OTf)$_3$-chiral phosphine **XXII** catalytic system in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **96**) as the bromine source and Na_2CO_3 additive at -60 °C for 48 h. The bromo substituent allows the transformation of **97** into other functionalized spiro benzofuran oxazolidinones

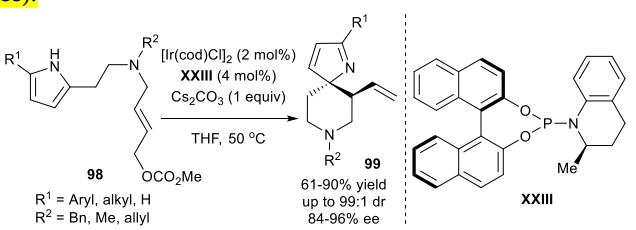
(Scheme 24).



Scheme 24: Spirocyclization reported by Shi

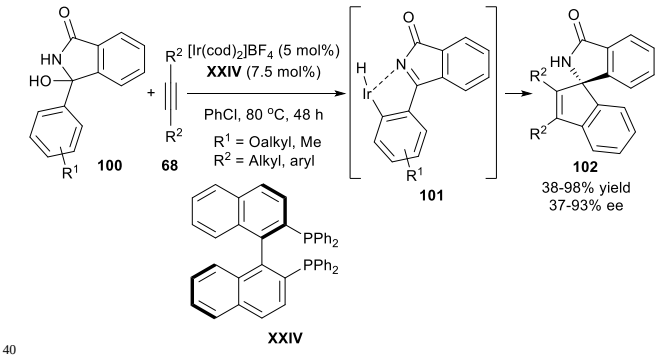
2.5 Iridium-catalysed methodologies

You *et al*. developed a catalytic asymmetric dearomatization (CADA) of pyrroles through an Ir-catalysed allylic substitution.[32] The reaction comprised allylic carbonate tethered pyrroles or indoles (**98**)[33] in the presence of $[Ir(cod)Cl]_2$ and phosphoramidite **XXIII** as the ligand. The spiro compounds **99** were attained in good yields with up to >99:1 d.r. and 96% ee. [6,5] Spirorings were synthesised with limited group scope. Subsequently, this research group reported the synthesis of [5,5] spiro with excellent results (Scheme 25).[34] Recently the same research group expanded the scope of this reaction by making use of the desymmetrization of diindoles. The reaction rendered the final products in yields (99%) and excellent stereoselectivities (>95:5 d.r. and 99% ee).[35]



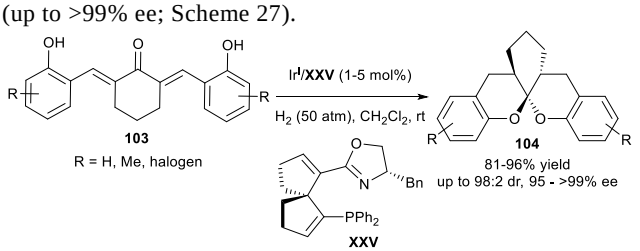
Scheme 25: Spirocyclization reported by You

An Ir-catalysed [3+2] annnulation between aromatic ketimines with alkynes *via* C-H activation have been used for the synthesis of spiro compounds (**102**).[36] In this method, the ketimine were generated *in situ* from **100** by dehydration. Cyclic *N*-acyl ketimines were first reacted with the internal alkynes through C-H activation of the cyclic aromatic ketimine. This was followed by alkyne insertion and annulation with the imine to form the spiroaminoindenes in good yields (up to 94%) and enantioselectivities (up to 92% ee) when (*R*)-BINAP **XXIV** was used as ligand. Surprisingly, the addition of carboxylic acid as additive resulted in an inversion of enantioselectivity with similar results (Scheme 26). A similar reaction was reported by the same group in 2013, using dienes and chiral dienes as iridium ligands with excellent results.[37]



Scheme 26: Spirocyclization reported by Nishimura

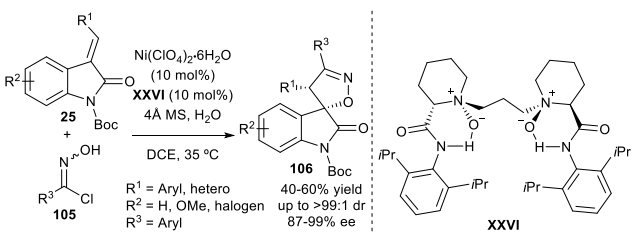
Ding and Wang *et al*. reported an Ir-catalysed dihydrogenation of bis(2-hydroxyarylidene)ketones **103**. After hydrogenation a spiroketalization occurs to form the spiro compounds **104**.[38] A key aspect to this reaction is the use of the SpinPhox ligand **XXV** to achieve excellent yields (81-96%), diastereoselectivities (up to 98:2 d.r.), and enantioselectivities (up to >99% ee; Scheme 27).



Scheme 27: Spirocyclization reported by Ding and Wang

2.6 Nickel-catalysed methodologies

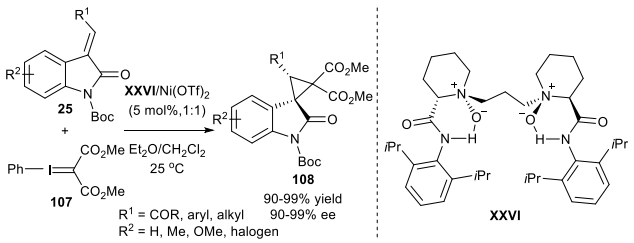
An asymmetric 1,3-dipolar cycloaddition between 3-arylidene oxindoles **25** and nitrile oxides catalysed by *N*,*N*'-dioxide **XXVI**-nickel complexes was also reported.[39] Nitrile oxide was generated from *N*-hydroximoyl chloride **105** by treatment with molecular sieves. This was followed by 1,3-dipolar cycloaddition with 3-arylidene oxindole takes place, catalysed by a Ni complex, to generate spirooxindole **106** in moderate yields (40-60%) with excellent diastereoselecivities (up to >99:1 d.r.) and enantioselecivities (87-99% ee) and good group compatibility (Scheme 28).



Scheme 28: Spirocyclization reported by Feng

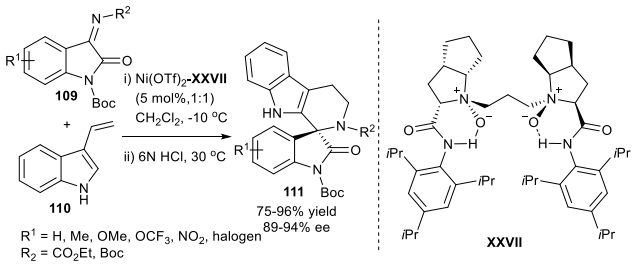
Feng and Liu *et al*. also reported a nickel-catalysed

cyclopropanation of 3-alkenyl-oxindoles **25** with phenyliodonium ylides **107**.[40] The reaction starts with the thermal decomposition of the phenyliodonium ylide malonate under mild conditions, to form the free singlet carbene. Next, the carbene reacts with the 3-alkylidene oxindole catalyzed by an *N*,*N*'-dioxide **XXVI**-nickel complex, to form the spirocyclopropanes **108** in good yields (82-99%) and excellent stereoselectivities (complete diastereoselectivity and up to 99% ee; Scheme 29). The same research group reported a thia-Michael/aldol cascade reaction between alkylidene benzoxazoles and 1,4-dithiane-2,5-diol using the same catalytic system.[41] The reaction furnished the corresponding spirooxindoles in good yields (50-95%), excellent diastereoselectivities (up to <19:1 d.r.) and excellent and enantioselectivities (91-98% ee) with reasonable group compatibility.



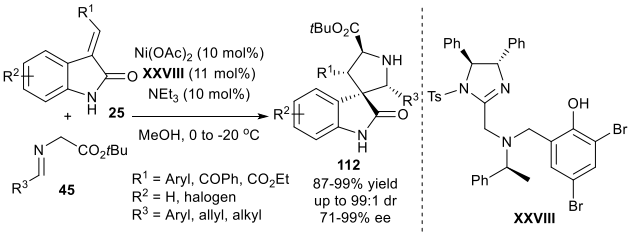
Scheme 29: Spirocyclization reported by Feng and Liu

Simultaneously, Feng and Liu *et al*. also developed a nickel-catalysed Aza-Diels-Alder reaction between 3-vinylindolines **110** and isatin-derived ketimines **109**.[42] The choice of ligand was crucial to achieve high enantioselectivities with *N*,*N*'-dioxide **XXVII** as the ligand. The reaction generated the corresponding *exo*-spirooxindoles **111**, due the π-π interactions between the two indoline rings, in good yields (75-95%) and excellent enantioselectivites (89-94% ee) with moderate substrate scope. The authors demonstrated the applicability of this methodology using it as a key step for the synthesis of NITD609, an antimalarial drug (Scheme 30).



Scheme 30: Spirocyclization reported by Feng and Liu

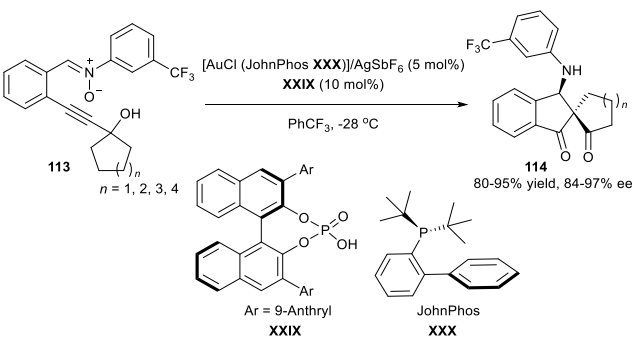
Arai *et al*. reported a [3+2] cycloaddition between 3-arylidene oxindoles **25** and iminoesters **45**, catalysed by chiral Ni complexes.[43] The reaction generates the spirooxindoles **112** in excellent yields (87-99%), diastereoselectivities (up to 99:1 d.r.) and enantioselectivities (up to >99% ee; Scheme 31). The same research group reported the synthesis of a spiro compound based on a Michael/aldol cascade reaction catalysed by Ni complexes.[44] Thus, 3-alkylidene oxindoles react with thiosalicylaldehyde *via* a thio-Michae/aldol sequence to generate a thiochromanyl-spirooxindole with three contiguous stereogenic centers with excellent yields (73-99%) and stereoselectivities (up to 98:2 d.r. and up to 94% ee) when using bis(imidazoline)pyridine ligands.



Scheme 31: Spirocyclization reported by Arai

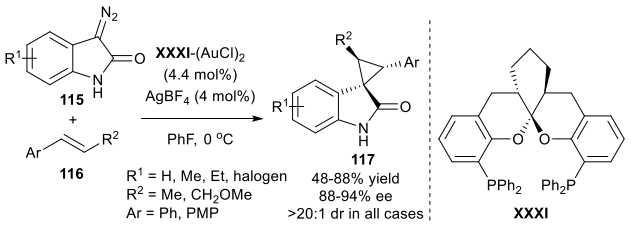
2.7 Gold-catalysed methodologies

The synthesis of spirocyclic ketones catalysed by Au complexes combined with chiral Brønsted acids was reported by Zhang *et al*.[45] This method is based on an asymmetric redox-pinacol-Mannich cascade raction. Aryl nitrones **113** react with Au complexes to deliver an intermediate that proceeds to a pinacol rearrangement and intramolecular Mannich reaction, catalysed by the chiral Brønsted acid **XXIX**. The reaction proceeds to form the spirocyclic diketone **114** in good yields (65-93%) and good to excellent enatioselectivities (90-99% ee; Scheme 32).



Scheme 32: Spirocyclization reported by Zhang

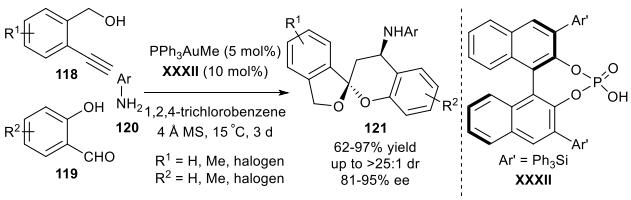
A chiral cyclopropanation between diazooxindoles **115** and olefins **116**, catalysed by Au complexes with spiroketalbiphosphine **XXXI**, produced the final spirocyclopropanes **117** in moderate to good yields (48-88%) and good enantioselectivities (88-94% ee), and complete diastereoselectivities.[46] The reaction presents a broad substrate scope including *cis*- and *trans*-disubstituted alkenes (Scheme 32).



Scheme 32: Cyclopropanation reported by Zhou

A catalytic dearomatization cascade reaction was developed by Bandini *et al*. Indoles decorated with a propargylic alcohol reacted under gold catalysis to furnish polycyclic spiroindolines with high stereoselectivity when diphosphine ligands such as xylylBINAP were employed.[47]

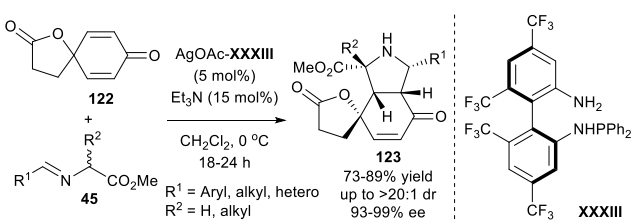
A catalytic three-component reaction for the synthesis of spiroacetals was reported by Gong *et al*.[48] Alkynol **118** reacts with Au (III) and undergoes a cyclization reaction to afford an aromatic enol ether intermediate. This intermediate then participates in a formal [4+2] cyclization comprising an asymmetric Mannich-type reaction with salicylimines generated *in situ* under Brønsted acid catalysis. The subsequent acetalization generates the spiroketal **121** in good to excellent yields (62-97%) and diastereoselectivities (up to >25:1 d.r.) and good enatioselecivties (81-95%; Scheme 33).



Scheme 33: Spiroketalization reported by Gong

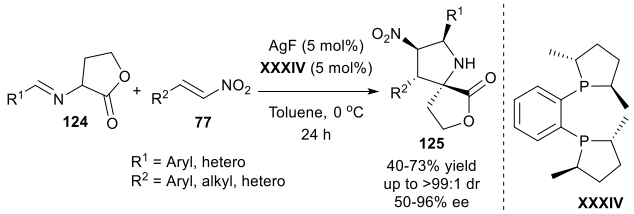
2.8 Silver-catalysed methodologies

An asymmetric desymmetrization of spiro cyclohexadiene lactones was reported by Wang *et al*. in 2013.[49] Meso-spiro cyclohexadiene lactones **122** reacts with iminoesters **45** *via* 1,3-dipolar cycloaddition catalysed by Ag complexes. The chiral spirolactone-pyrrolidines **123** were afforded in good yields (73-89%), excellent enantioselectivities (93-99% ee), and complete diastereoselectivities when TF-BiphamPhos **XXXIII** was used as ligand. The scope of the reaction is excellent, affording similar results when nonsubstituted and substituted aminoesters were employed (Scheme 34).



Scheme 34: Desymmetrization reported by Wang

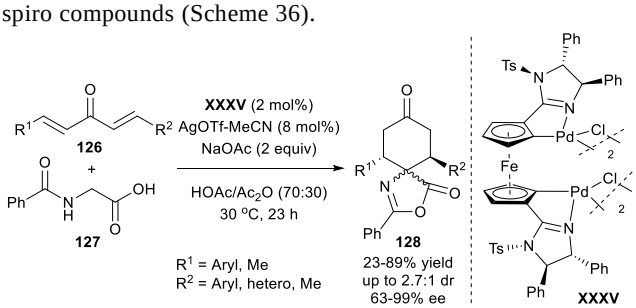
Cossío and Sansano *et al*. reported a [3+2] cycloaddition between α-amino γ-lactones as azomethine ylide precursors **124**, and nitroalkenes **77**, as dipolarophiles, for the formation of spiropyrrolidines **125**; Ag complexes were used as the catalysts.[50] Diphosphine ligand, such as Me-DuPhos (**XXXIV**), afforded the best results in terms of yield and stereoselectivity. The reaction renders the spirocyclic compounds in moderate yields (40-73%), excellent diastereoselectivities (up to 99:1 d.r.) and good enantioselectivities (50-96% ee) with poor functional group scope. Interestingly, the authors performed DFT calculations to confirm the proposed transition state and to determine the stereochemical pathway of the reaction (Scheme 35).



Scheme 35: Spirocyclization reported by Cossío and Sansano

In 2015, Taylor and Unsworth developed a catalytic dearomatization (CADA) of aromatic ynones catalysed by silver. The silver salt activates the triple bond for nucleophilic attack by the indole, thereby leading to the spiro compound. The reaction achieves good yields (62->99%) and moderate enantioselectivities (40-72% ee) using chiral phosphoric acids as the ligands.[51]

Peters *et al*. reported a cascade reaction consisting of an *'in situ'* fomation of azlactones from *N*-benzoylglycine **127**, followed by a double Michael addition with divinylketones **126** catalysed by the bispalladacycles **XXXV**.[52] The reaction renders the final products **128** in moderate to good yields (52-89%), with good to excellent *trans*/*cis* ratios (up to >99:1), moderate diastereoselectivities towards the *trans*-isomer (up to 2.7:1 d.r.), and good enatioselectivities (63-99% ee). Despite the poor reaction scope, the interest of the reaction lies in the possbility to synthesize quaternary cyclic aminoacids from the spiro compounds (Scheme 36).

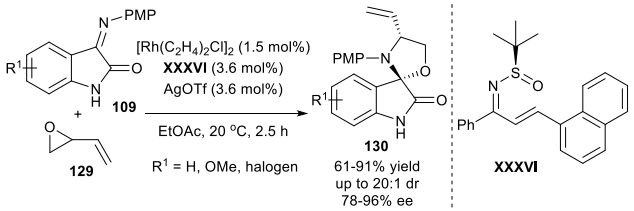


Scheme 36: Spirocyclization reported by Peters

2.9 Rhodium-catalyzed methodologies

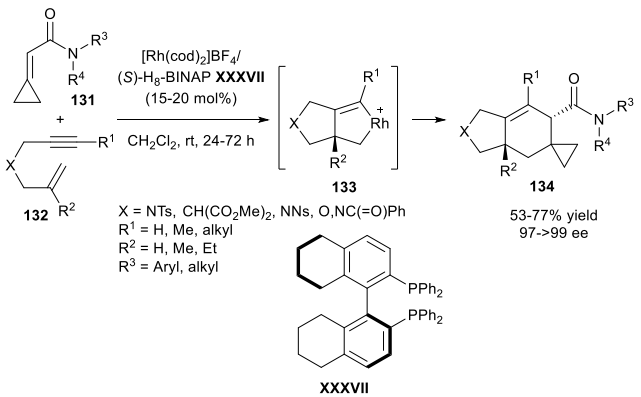
A [3+2] cycloaddition between vinylepoxides **129** and isatine imines **109** was reported by Du *et al*.[53] The key to the success

of this reaction is the use of easily accessible chiral sulphur/alkene ligand **XXXVI**. The spiro oxindoles **130** were attained in good yields (61-90%), diasteroselectivities (up to 20:1 d.r.) and enantioselectivities (78-96% ee; Scheme 37).



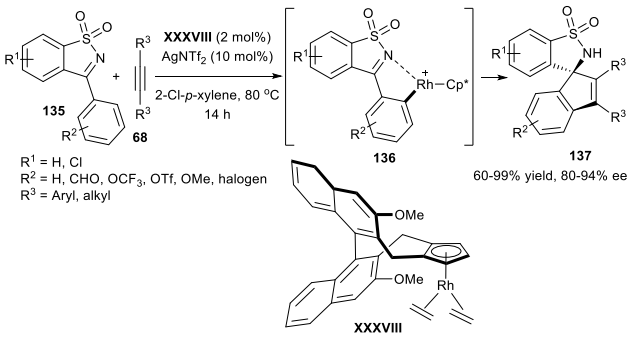
Scheme 37: Spirocyclization reported by Du

Tanaka *et al*. reported the Rh-catalysed [2+2+2] cycloaddition of 1,6-enynes **132** with cyclopropylideneacetamides **131** to generate spirocyclohexenes **134** with excellent results (up to 77% yield and >99% ee) when H_8-BINAP (**XXXVII**) was employed as the ligand.[54,55] The reaction starts with the generation of rhodacyclopentane **133**, followed by the insertion of the alkene to generate the rhodacycle. Finally, reductive elimination renders the spiro compound (**134**, Scheme 38).



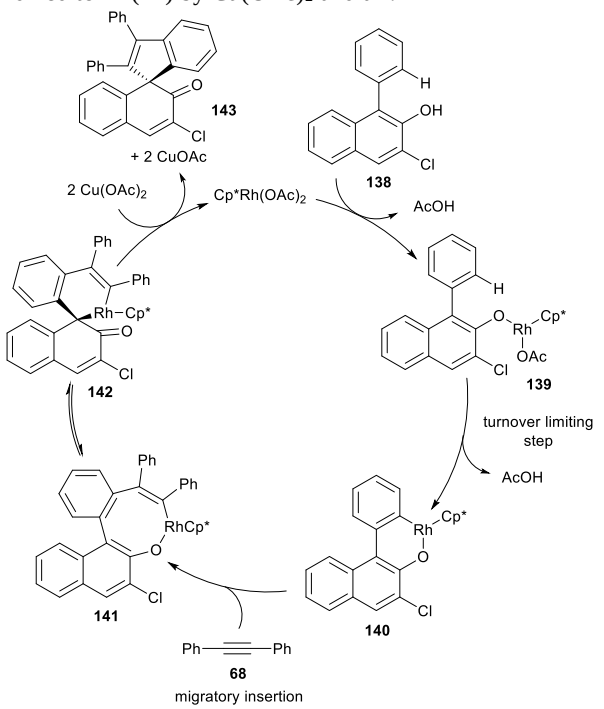
Scheme 38: [2+2+2] Spirocyclization reported by Tanaka

Cramer *et al*. reported a cycloaddition of alkynes **68** and cyclic sulfonimines **135** catalyzed by Rh complexes.[56] The reaction starts with the C-H activation of the cyclic sulfonimine directed by the *N*-sulfonyl imino group, obtaining rhodacycle **136**. This intermediate undergoes alkyne migratory insertion followed by addition to a C=N bond to generate spiro compound **137**. The reaction employs cyclopentadienyl ligands **XXXVIII** to achieve good to excellent yields (60-99%) and enantioselectivities (up to 94% ee; Scheme 39).



Scheme 39: Spirocyclization reported by Cramer

You *et al.* reported a Rh-catalysed C-H functionalization reaction for the asymmetric dearomatization of naphthols leading to the formation of the spirocompounds.[57] Thus, 1-aryl-2-naphthols **138** react with the internal alkynes **68** in the presence of a Rh catalyst and a $Cu(OAc)_2$/air oxidant to form the spirocyclic enones **143** in modeate to good yields (33-98%) and excellent enantioselectivities (up to 94% ee; Scheme 40). The proposed mechanism comprises C-H bond activation between 2-naphthol and Rh to generate the rhodacycle **140**. The rhodacycle undergoes alkyne coordination and migratory insertion to form the eight-membered rhodacycle **141**, which could be in equilibrium with **142**. This is followed by reductive elimination and the release of the Rh(I) species that is finally oxidized to Rh(III) by $Cu(OAc)_2$ and air.

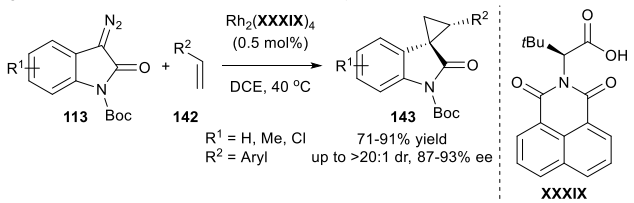


Scheme 40: Proposed mechanism for asymmetric dearomatization by You

The enantioselective synthesis of spiroindenes, catalysed by Rh complexes, was reported by Lam *et al.* in 2015.[58] In this procedure, 4-hydroxy-3-aryl-pyran-2-one derivatives react with the internal alkynes, catalysed by chiral cyclopentadienyl

Rh species, to generate the corresponding spiroindenes in good yields (65-94%) and good to excellent enantioselectivities (81-97% ee).

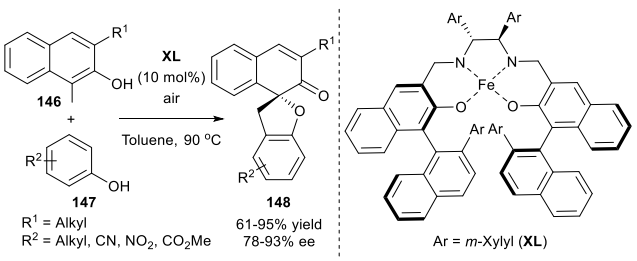
A Rh-catalyzed cyclopropanation was reported by Xu and Qiu *et al*. in 2016.[59] In this reaction, *N*-Boc diazooxindoles **113** react with alkenes (**142**), catalysed by chiral dirhodium carboxylate complexes, to produce spirooxindolic cyclopropane derivatives **143** in good to high yields (71-97%), with good to excellent diastereoselectivities and enantioselectivities (up to 20:1 d.r. and up to 93% ee). The scope of the reaction is broad, allowing the use of aryl, alkyl, cyclic, and disubstituted olefines (Scheme 41.



Scheme 41: Spirocyclization reported by Xu and Qiu

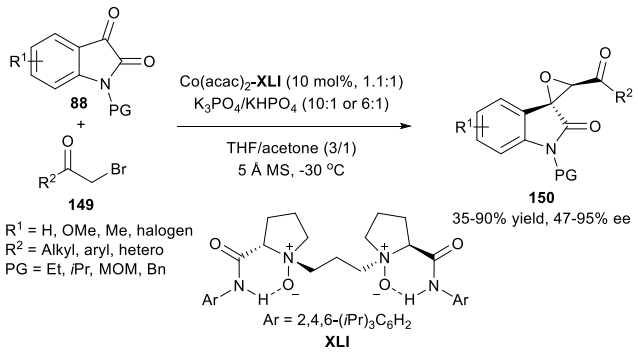
2.10 Other metals

In 2014, Katsuki *et al*. reported an iron-catalysed asymmetric tandem spiro cyclization, using dioxygen as the hydrogen acceptor.[60] The reaction starts with the formation of the *ortho*-quinone methide through the aerobic oxidation of *ortho*-methyl naphthols **146**, catalysed by iron. This is followed by the Michael addition of phenol **147** followed by nucleophilic dearomatization to furnish the spiro compound. A chiral Fe(salen) complex **XL** was used to achieve good enantioselectivities with reasonable functional group scope (Scheme 42).



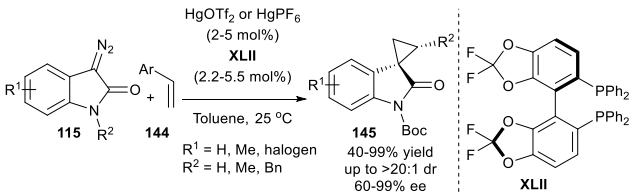
Scheme 42: Spirocyclization reported by Katsuki

Feng *et al*. employed the Darzens reaction, catalysed by Co complexes, for the synthesis of spirooxindoles.[61] Thus, *N*-protected isatins **88** reacted with α-bromoketones **149** *via* a Michael-intramolecular *O*-alkylation cascade to furnish the spirooxindoles epoxides **150** in good yields (up to 95%) and excellent stereoselectivities (up to 99:1 d.r. and up to 99% ee), with good functional group tolerance. The use of Feng's ligand (bis-proline derivative *N*-oxide, **XLI**) was the key to achieve high enantioselectivities (Scheme 43).



Scheme 43: Spirocyclization reported by Feng

Zhou *et al*. reported the synthesis of spirooxindoles catalysed by Hg complexes.[62] Diazooxindoles **115** react with alkenes **144** to form spirocyclopropane **145**. The Hg complex acts as a soft Lewis acid, decomposing the diazooxindole to generate the active species for the cyclopropanation reaction with a series of different alkenes. The choice of ligand is crucial for the stereoselectivity of the reaction. Chiral diphosphine **XLII** derived from biphenyl was the best option. The reaction presents a reasonable substrate scope and renders the final cyclopropanes in good to excellent yields (40-99%) and enantioselectivities (60-99% ee; Scheme 44).



Scheme 44: Spirocyclopropanation reported by Zhou

3. Organocatalytic Approaches

The pioneering works of List[63] and MacMillan[64] on enamine and iminium catalysis in 2000 saw the renaissance of organocatalysis. Since then, organocatalysis has become the third pillar in asymmetric catalysis, complementing the organometallic and enzymatic catalysis for the assembly of chiral compounds. The easy stereoprediction, functional group tolerance, and green approach that avoids the use of metals make organocatalytic methodologies an excellent approach for the synthesis of spirocompounds. In this review, we present a detailed overview of the organocatalytic syntheses of spiro compounds. This section is divided according to the nature of the heterocycle.

3.1 Organocatalytic methodologies for the synthesis of spirooxindoles

The spirooxindoles formation has become one of the biggest goals in organic synthesis. Spirocyclic indoles that contain varied spiro rings fused at the C3 atom represent privileged 3D

scaffolds that are part of several pharmaceutical and natural products. Their prevalence in privileged structures has attracted a notable synthetic methodology interest. This has allowed the creation of libraries containing spirooxindoles that have been used to pursue new candidates for drug discovery. This synergistic effect has magnified the efforts of organic chemists to synthesize well-defined spirooxindoles. This has led to increased group compatibility and easy stereoprediction in organocatalysis together with the development of a vast wave of new methodologies for the synthesis of spirooxindole compounds.

Herein, we have divided the synthesis of oxindoles based on the nature of the starting oxindole: 3-mono-substituted oxindoles **151**, conjugated oxindoles **25**, and isatine **88** (Figure 3).

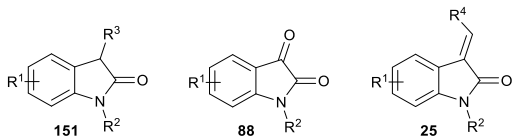
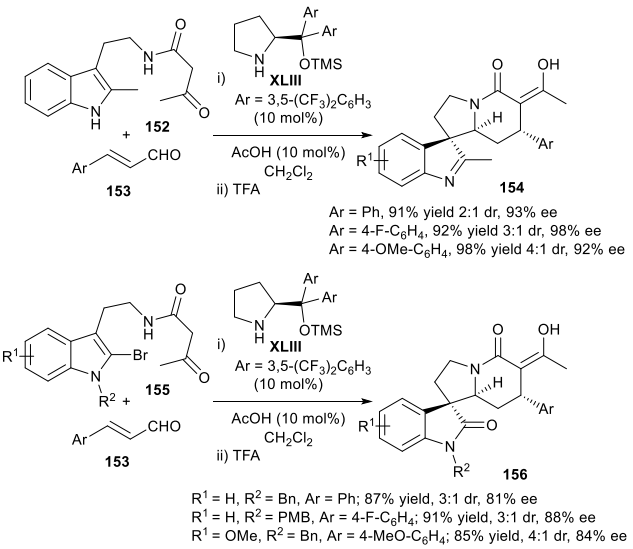


Figure 3: Starting oxindoles

3.1.1 Methodologies with 3-monosubstituted oxindoles

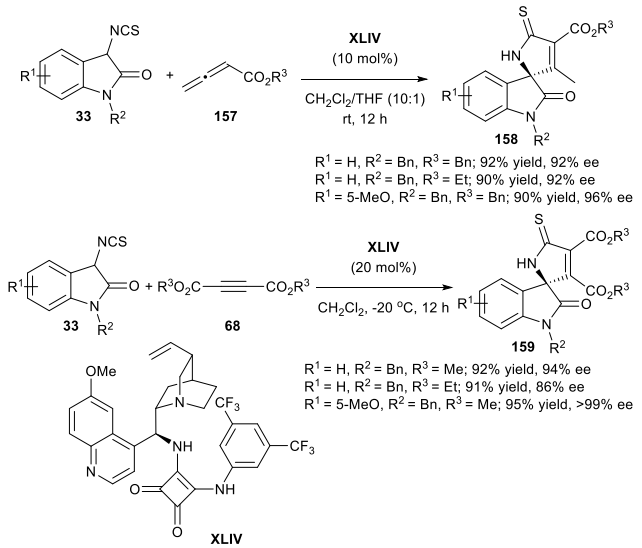
Wu, Cao, and Zhao *et al*. reported the use of 3-substituted indolines bearing an amidomalonate moiety (**152**, **155**) for the synthesis of polycyclic oxindoles.[65] Compound **152** reacts with enals **153** as follows: first malonate anion undergoes a Michael addition with α,β-unsaturated iminium ion, which was generated by reacting enal and Jørgensen-Hayashi catalyst (**XLIII**). The highly functionalized spirotetracyclic indolenines **154** was produced *via* the intramolecular hemiacetal formation between the aldehyde and the amide moiety, subsequent dehydration, and Mannich addition of the oxindole in good yields (69-98%), moderate diastereoselectivities (2:1-4:1 d.r.), and good enantioselectivities (88-99% ee). Moreover, when 2-bromo indolines **155** were employed, the spirooxindoles **156** formed, after hydrolysis, in excellent yields (81-95%), moderate diastereoslectivities (2:1-6:1 d.r.), and good enantioselectivities (77-94% ee; Scheme 45).



Scheme 45: Spirocyclization reported by Zhao, Cao, and Wu

One of the most common approaches for the synthesis of spiro compounds is the use of 3-isothiocyanato oxindoles **33**. In 2013, Shi and Xu *et al*. reported their reaction with allenes **157** and alkynes **68** to render spirooxindoles **158** and **159**, respectively.[66] The reaction comprise a formal [3+2] cycloaddition, catalysed by a bifunctional (hydrogen bonding/tertiary amine) squaramide derivative from cinchona alkaloids **XLIV**. The hydrogen bonding motif in the squaramide activates the allene or alkyne bearing a conjugate ester group, while the tertiary amine abstracts one proton from the oxindole. Subsequently, an intermolecular Michael addition/cyclization takes place followed by migration of the double bond to produce the final product with good group tolerance, yields, and enantioselectivities. Moreover, on increasing the equivalents of the allene/alkyne conjugated ester, an additional thio-Michael reaction takes place without loss of stereoselectivity (Scheme 46). Soon after, the same research group reported a similar synthesis of spirooxindoles using azodicarboxylates as counterpart in the cycloaddition with 3-isothiocyanato oxindoles.[67] The reaction is catalyzed by $(DHQD)_2PHAL$, to produce the spirooxindoles in good yields (90-99%) and enatioselectivities (85-98% ee).

Wang's group and Chowdhury and Ghosh's groups independently reported a similar reaction using 3-isothiocyanato oxindoles and benzylidene oxindoles or benzylidene malonates.[68,69] A bifunctional tertiary amine/thiourea catalyst promoted the reaction, affording the spiro compounds in excellent yields (86-99%) and stereoselectivities (>20:1 d.r. and up to 97% ee). Soon after, Wang *et al*. reported the same approach using unsaturated pyrazolones with excellent results (up to >20:1 d.r. and up to 99% ee).[70]

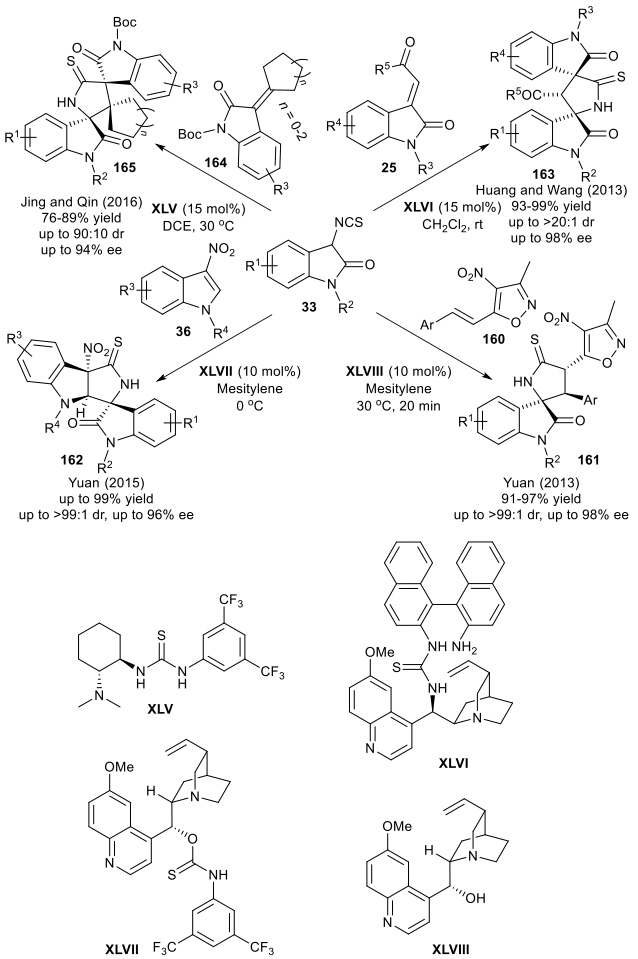


Scheme 46: Spirocyclization reported by Shi and Xu

A similar approach was reported by Yuan *et al*. using 3-methyl-4-nitro-5-alkenyl-isoxazoles **160** as the counterpart of the 3-isothiocyanato oxindoles **33**.[71] The formal [3+2] cycloaddition catalysed by quinine **XLVIII**, achieves excellent yields (91-97%) and stereoselectivities (up to 99:1 d.r. and up to 98% ee; Scheme 47 bottom right). In 2015, the same group expanded the scope of the reaction using 3-nitroindoles **36** for the [3+2] cycloaddition.[72] The reaction is catalysed by a tertiary amine/thiocarbamate catalyst **XLVII**. The mechanism comprises the initial Michael addition of the oxindole to the 3-nitroindole, followed by intramolecular alkylation of the just formed enolate with the isothiocyanate to form the five-membered ring. The reaction shows good group compatibility and renders the final spiro compounds **162** in excellent yields and moderate to good stereoselectivities (99-0% d.r. and 36-95% ee). A crucial factor for the stereoselectivity is the *N*-substituent of the oxindole (Scheme 47 bottom left).

Almost simultaneously, Huang and Wang *et al*. reported the construction of bispirooxindoles by reacting 3-isothiocyanato oxindoles **33** with alkylidene oxindoles **25**.[73] Following a similar mechanism pathway to the last examples, the reaction is efficiently catalysed by a multifunctional catalyst, namely a thiourea derived from cinchona alkaloids **XLVI** (Scheme 47 top right). The reaction afforded bispirooxindoles **163** in excellent yields (95-99%) and stereoselectivities (up to >20:1 d.r. and up to 99% ee). Later on, Jing and Qin *et al*. reported a similar reaction using cyclic methyleneidolinones **164** catalysed by a bifunctional thiourea/tertiary amine catalyst **XLV**, derived from cinchona alkaloids.[74] The reaction affords the tris-spirooxindoles **165** in good yields (71-86%) and stereoselectivities (up 90:10 d.r. and 94% ee; Scheme 47 top left).

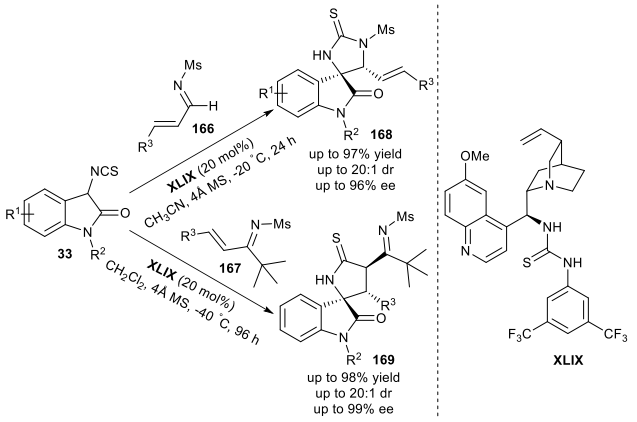
Mukherjee *et al.* reported three different reactions based on 3-isothiocyanato oxindoles. The first comprised a cascade reaction with nitroolefins, catalysed by bifunctional tertiaryamine/thiourea catalyst. This reaction produced the spiro compounds in excellent yields and stereoselectivities.[75] A similar approach reported by Xie *et al*. employs 3-nitro-2*H*-chromene derivatives to afford moderate results.[76] The second approach comprises a cascade reaction with exocyclic enones, catalysed by chiral squaramides, to produce excellent results.[77] The third approach is the reaction with α-ketophosphonates, catalysed by bifunctional thiourea/tertiary amine catalysts, to afford excellent results (up to 91% yield, 20:1 d.r., and 99% ee).[78] A similar reaction comprising the Michael/cyclization cascade reaction of 3-isocyanato oxindoles and chalcones catalysed by chiral squaramides was reported by Du *et al*. This reaction afforded the final products in excellent yields (up to 99%) and stereoselectivities (up to >99:1 d.r. and >99% ee).[79] Zhao and Du *et al*. applied the same strategy, using as the alkene unsaturated barbiturates[80] and maleimides[81], with good results, respectively.



Scheme 47: Spirocyclizations using 3-isothiocyanato oxindoles

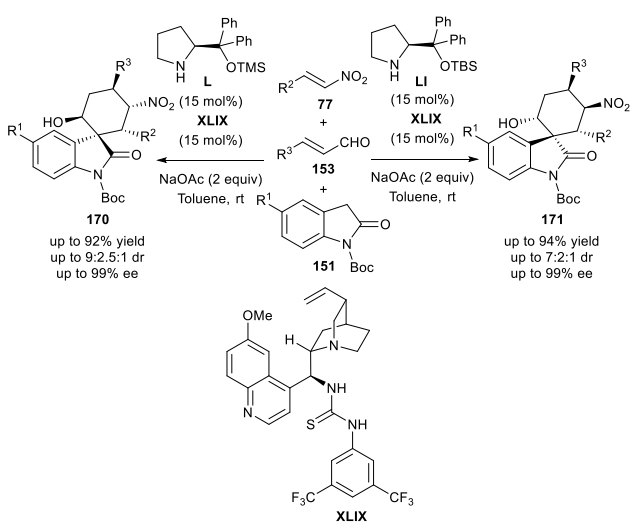
A [3+2] cycloaddition of 3-isothiocyanato oxindoles **33** and unsaturated imines was reported by Shi *et al*.[82] The authors modulated the regiochemistry by tailoring the starting unsaturated imines: terminal imines **166** led to a 1,2-addition, while 1-*tert*-butyl imines **167** led to a 1,4-addition. Moreover, the authors used dibenzylidene imines to perform a [3+2], [4+2] cascade cycloaddition, leading to multicyclic spirooxindoles **168** and **169**. All the reactions were catalysed

by the bifunctional hydrogen bond/tertiary amine catalyst **XLIX**, affording the spirooxindoles in good yields and stereoselectivities (Scheme 48). Subsequently, the same research group expanded the scope of the latter multicascade reaction using dibenzylidene ketones with good results.[83]



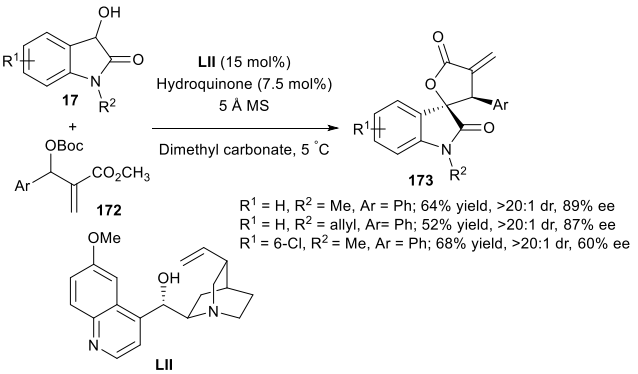
Scheme 48: Spirocyclization reported by Shi

Li and Zhou *et al*. reported an organocascade reaction between oxindoles **151**, enals **153**, and nitrostyrenes **77** that rendered spirocyclohexanones (**170** and **171**) in good yields (90-45%) and stereoselectivities (up to 8:2:1 d.r. and up to >99% ee).[84] The reaction comprises a Michael-Michael-aldol sequence in the presence of two different catalysts (secondary amine catalysts **L** or **LI** and a bifunctional thiourea/tertiary amine catalyst **XLIX**). The reaction tolerates aromatic and aliphatic enals as well as aromatic and aliphatic nitroalkenes; however, a decrease in diastereoselectivity and yield was observed when aliphatic starting materials were employed. The only limitation seems to be the nature of the protecting group of the oxindole as only *N*-Boc-protected oxindoles produced the final product. Remarkably, the nature of the secondary amine catalysts determines the diastereomer obtained (Scheme 49).



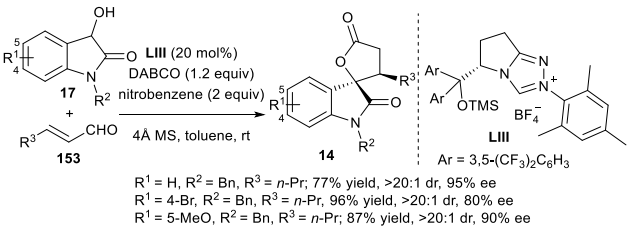
Scheme 49: Spirocyclization reported by Li and Zhou

3-Hydroxy oxindoles **17** have been extensively used in the synthesis of spiro oxindoles. For example, they were reacted with MBH (Morita-Baylis-Hillman) carbonates (**172**)[85] via an S_N2'-ester formation cascade reaction to generate α-methylene-γ-butyrolactone **173** bearing a spiro oxindole.[86] The reaction is catalysed by quinidine **LII**, activating the MBH carbonate. This undergoes an addition from the 3-hydroxy oxindole through a S_N2'-S_N2' process. Subsequently, a lactonization furnishes the spirooxindole derivative with contiguous quaternary and tertiary stereocenters in moderate yields (27-64%) and good enantioselectivities (84-89% ee; Scheme 50). Kesavan reported this reaction, using Boc-protected 3-hydroxy oxindoles, to produce the same products; this provided higher yields and a broader substrate scope.[87]



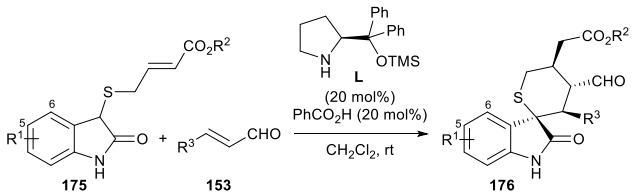
Scheme 50: Spirocyclization reported by Wang

3-Hydroxy oxindoles **17** reacted with enals **153** under NHC catalysis to render the corresponding oxindole-γ-lactones **174** in good yields (67-95%) and high stereoselectivities (6:1->20:1 d.r., 80-99% ee).[88] Ye and Sun *et al*. proposed the oxidative cross coupling of homoenolates and enolates *via* single electron transfer as the key step of the reaction (Scheme 51).



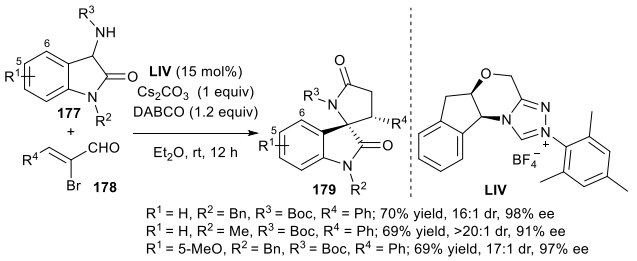
Scheme 51: Spirocyclization reported by Ye and Sun

3-Thioesteroxindole derivatives **175** bearing a Michael acceptor moiety react with enals **153** under secondary amine catalysis to furnish spiro-tetrahydrothioyran oxindoles **176** in good yields (55-74%) and excellent stereoselectivities (up to >30:1 d.r. and 99% ee), through a Michael-Michael cascade reaction.[89] The final products exhibit good antitumor activity, *in vitro*, as p53-MDM2 inhibitors (Scheme 52).



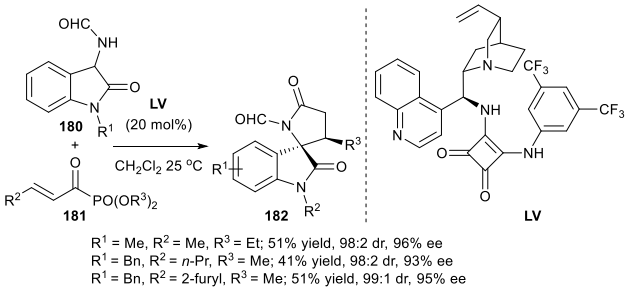
Scheme 52: Spirocyclization reported by Sheng

3-Aminooxindoles **177** were reacted with 2-bromo enals **178** under NHC catalysis (**LIV**) to afford spirooxindoles **179**. The reported mechanism starts with the addition of a NHC catalyst to enal which, after elimination of the bromide, leads to the formation of α,β-unsaturated acyl azolium. This intermediate subsequently undergoes a Michael addition with 3-aminooxindole, followed by intramolecular lactamization. Du and Lu. reported only four enantioselective examples with moderate yields (51-80%) and high stereoselectivities (>95:1 d.r. and 86-95% ee).[90] Later on, Ye and Sun *et al*. reported a full study of the same reaction (Scheme 53).[91]



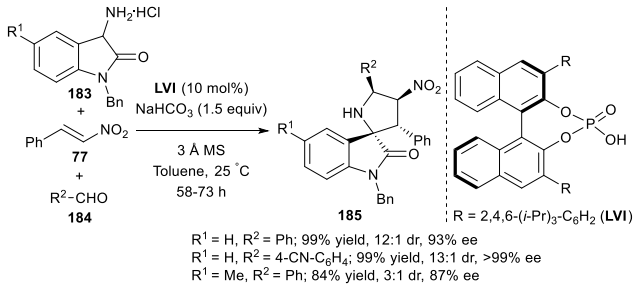
Scheme 53: Spirocyclization reported by Ye and Sun

Yuan and Xu *et al*. reported the reaction between 3-hydroxy oxindoles or 3-amino oxindoles **180** with α,β-unsaturated acylphosphonates **181** for the construction of spirocyclic oxindole-γ-lactones/lactams **182**.[92] The reaction was efficiently catalyzed by a bifunctional tertiary amine/squaramide catalyst **LV**. The mechanism comprises an initial Michael reaction, followed by the intramolecular cyclization of the acyl phosphonate intermediate to afford the spirooxindoles in excellent yields (up to 95%) and stereoselectivities (up to >99:1 d.r. and 95% ee; Scheme 54).



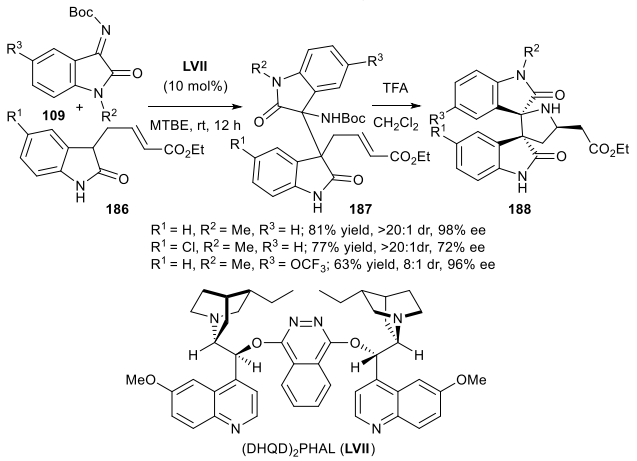
Scheme 54: Spirocyclization reported by Yuan and Xu

Another approach with 3-amino oxindoles for the synthesis of spirooxindoles, was developed by Wang *et al*.[93] In a multicascade fashion, 3-amino oxindoles **183** react with aromatic aldehydes **184** to form the imine which, after the addition of the base, forms the 1,3-dipole. Subsequently, a [3+2] cycloaddition with nitrostyrenes **77**, catalysed by chiral phosphoric acid **LVI**, furnished the spirooxindoles **185** in good yields (78-99%), moderate to excellent diastereoselectivities (3:1->20:1 d.r.), and high enantioselectivities (84-99%; Scheme 55).



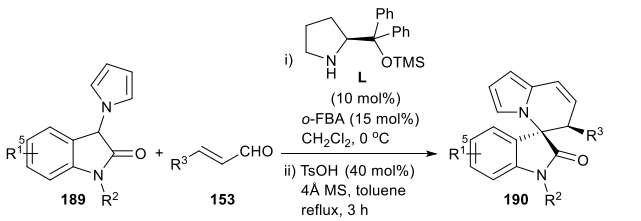
Scheme 55: Spirocyclization reported by Wang

Enders *et al*. reported a cascade reaction between oxindoles **186** and *N*-Boc isatin imines **109**, catalysed by cinchona derivative dimers [(DHQD)$_2$PHAL, **LVII**].[94] The cascade reaction comprises a two-step-one pot reaction starting with the Mannich reaction between the isatine imine and the oxindole. After completion, solvent evaporation and the addition of CH_2Cl_2 and TFA deprotect *N*-Boc amine. This undergoes an aza-Michael addition to form the tricyclo dispiro product **188** in moderate to good yields and excellent stereoselectivities (up to 20:1 d.r. and 98% ee; Scheme 56).



Scheme 56: Spirocyclization reported by Enders

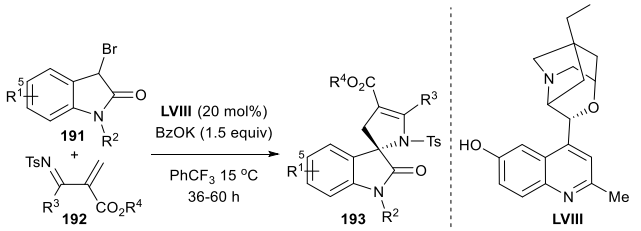
3-Pyrrolyl-oxindoles **189** have been reported as a convenient starting material for the synthesis of spirooxindoles through a Michael/Friedel-Crafts cascade reaction using enals **153** and catalyzed by TMS diphenylprolinol derivative **L**.[95] The reaction starts as a simple Michael addition of the oxindole to the iminium, followed by an acid catalysed intramolecular Friedel-Crafts reaction between the C2 position of the pyrrole and the aldehyde to furnish spiro ring **190**. The reaction displays good functional group tolerance with both aromatic and aliphatic enals and affords moderate to good yields (62-86%) and excellent stereoselectivities (up to 99:1 d.r. and up to 95% ee; Scheme 57).



R^1 = H, R^2 = H, R^3 = Ph; 72% yield, 92:8 dr, 92% ee
R^1 = H, R^2 = Me, R^3 = 4-Me-C_6H_4; 86% yield, 87:13 dr, 91% ee
R^1 = 5-F, R^2 = Me, R^3 = Ph; 80% yield, 86:14 dr, 89% ee

Scheme 57: Spirocyclization reported by Yuan

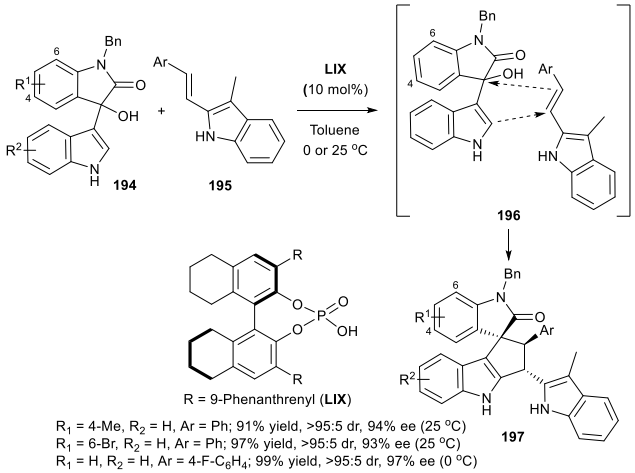
Under Lewis base catalysis, 3-bromo oxindoles **191** react with electron deficient 1-azadienes **192** through a [4+1] annulation to deliver spirooxindoles.[96] The reaction starts with the formation of the iminium ylide by substitution of the bromide by the nucleophilic nitrogen of the catalyst **LVIII**. This is followed by a Michael addition to the 1-azadiene and subsequently, an intramolecular nucleophilic substitution to build spirooxindole **193** in moderate yields (55-75%) and excellent enantioselectivities (82-99% ee; Scheme 58).



R^1 = H, R^2 = Me, R^3 = Ph, R^4 = Et; 75% yield, 98% ee
R^1 = H, R^2 = Me, R^3 = Ph, R^4 = Me; 74% yield, 99% ee
R^1 = 5-Cl, R^2 = Me, R^3 = Ph, R^4 = Et; 71% yield, 89% ee

Scheme 58: Spirocyclization reported by Chen and Liu

An interesting [3+2] cycloaddition reaction reported by Shi comprises a tandem reaction between 3-hydroxyoxindoles **194** decorated with an indolyl moiety and 3-methyl-2-vinylindoles **195**. The reaction is catalysed by chiral phosphoric acid derivative **LIX**, achieving the final spiro compounds **197** in good yields (72-99%) and excellent stereoselectivities (>95:5 d.r. and 90-98% ee).[97] The reported mechanism comprises an acid catalysed dehydration to form the carbocation, which subsequently forms an ion pair with the anion of the phosphoric acid. Due to the stabilization of the transition state through hydrogen bonding, the NH moiety in both indoles is crucial for high enantioselectivities (Scheme 59).

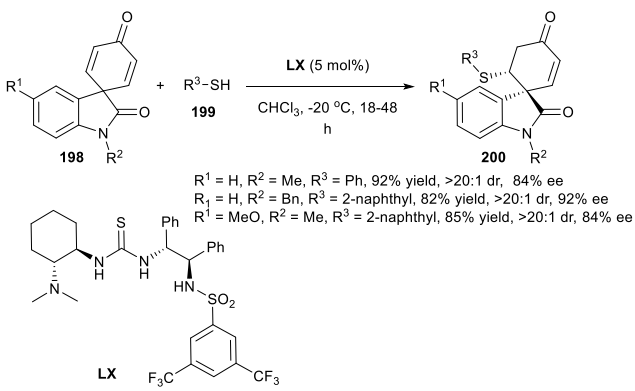


R_1 = 4-Me, R_2 = H, Ar = Ph; 91% yield, >95:5 dr, 94% ee (25 °C)
R_1 = 6-Br, R_2 = H, Ar = Ph; 97% yield, >95:5 dr, 93% ee (25 °C)
R_1 = H, R_2 = H, Ar = 4-F-C_6H_4; 99% yield, >95:5 dr, 97% ee (0 °C)

Scheme 59: Spirocyclization reported by Shi

A similar organocascade reaction, starting with 7-vinylindoles, was reported by Shi.[98] In the presence of chiral phosphoric acids, isatin-derived 3-indolylmethanols generate a vinyliminium ion. This then undergoes [3+2] cycloaddition with the 7-vinylinindole to afford the spirooxindole in moderate yields (43-68%), total diastereoselectivities, and excellent enantioselectivities (94-99% ee).

A double Michael addition between oxindoles and dienones was reported by Wang *et al*. for the synthesis of spirooxindoles, using Soos' catalyst, with excellent results (up to 98% yield, 20:1 d.r., and 99% ee).[99] Wang *et al*. reported the desymmetrization of achiral spirooxindoles by a sulfa-Michael addition.[100] Spiro cyclohexadienone oxindoles **198** react with thiols **199**, catalysed by bifunctional tertiary amine/thiourea catalyst **LX**. The reaction affords the spirooxinoles **200** in good yields (77-95%) and stereoselectivities (>20:1 d.r. and 82-95% ee; Scheme 60). Later on, Enders *et al*. exapanded the scope of this reaction by using spiro β-lactam derivatives.[101]

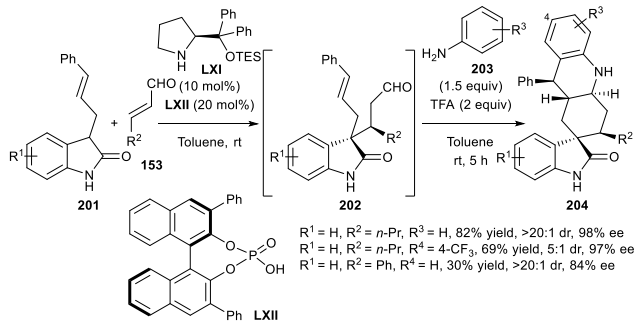


R^1 = H, R^2 = Me, R^3 = Ph, 92% yield, >20:1 dr, 84% ee
R_1 = H, R^2 = Bn, R^3 = 2-naphthyl, 82% yield, >20:1 dr, 92% ee
R^1 = MeO, R^2 = Me, R^3 = 2-naphthyl, 85% yield, >20:1 dr, 84% ee

Scheme 60: Desymmetrization reported by Wang

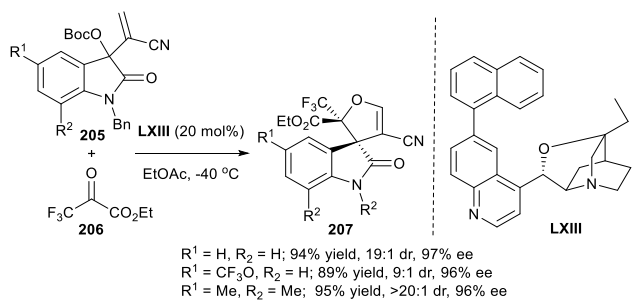
A formal [5+1] cycloaddition between oxindoles and ester-linked bisenones has been reported by Xu and Liang *et al*.[102] The double Michael addition, catalysed by a bifunctional tertiary amine/thiourea catalyst, provides access to spirooxindole-δ-lactones in good yields (71-94%) and excellent stereoselectivities (>25:1 d.r. and 88-97% ee).

An enantioselective Michael-Povarov cascade reaction was developed by Wang for the synthesis of spirooxindoles.[103] Thus, 3-allyl oxindoles derivatives **201** reacted with enals **153** in a reaction catalysed by Jørgensen-Hayashi catalyst **LXI** to form intermediate **202**. Next, aniline addition forms the imine, which then undergoes a Povarov reaction with the allyl moiety to generate spirooxindole **204**. The key towards achieving a high stereoselectivity is the π-π interaction between the aniline 203 and the Ph group located in the double bond. The final spirooxindoles **204** produced in good yields (68-86%) and excellent stereoselectivities (up to >20:1 d.r. and 98% ee; Scheme 61). A similar strategy was developed by Ding and Wang and comprises the use of oxindoles with a side chain in the 3 position bearing α,β-unsaturated esters and enals.[104] The enals are activated by a secondary amine and undergo a Michael addition with the oxindole. Next, the enamine formed *in situ* undergoes an intramolecular Michael addition to build the spiropyrazolone in good yields (70-86%) and excellent stereoselectivities (up to >99:1 d.r. and >99% ee).



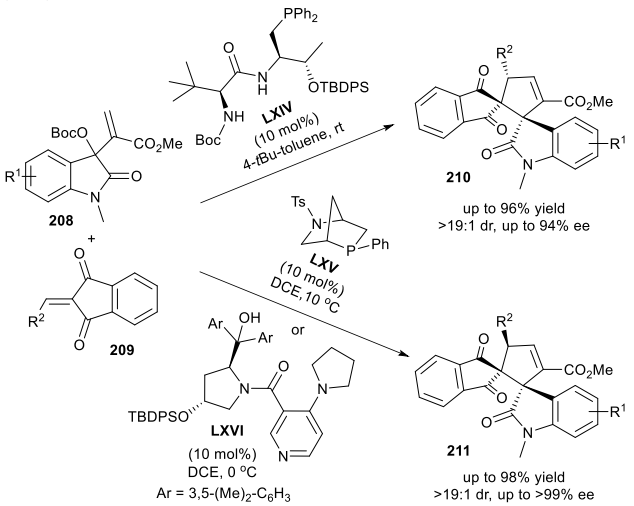
Scheme 61: Spirocyclization reported by Wang

MBH carbonates derived from oxindoles **205** were reported by Liu *et al*. as an excellent platform for the synthesis of spirooxindoles. They reported a [3+2] cycloaddition with maleimides using a diphosphine catalyst with excellent results (up to 84% yields and >99% ee).[105] Soon after, the same research group presented a similar approach to react trifluoropyruvate **206** with **205**. This reaction was catalysed by an isocupreinine derivative **LXIII**, furnishing the spirooxindoles **207** in good yields (76-94%) and excellent enantioselectivities (93-99% ee).[106] The catalyst activates the MBH carbonate, which reacts with trifluoropyruvate via an aldol fashion. Next, the alkoxide undergoes through an intramolecular Michael addition, followed by the release of the isocupreine derivative to generate the final compound (Scheme 62).



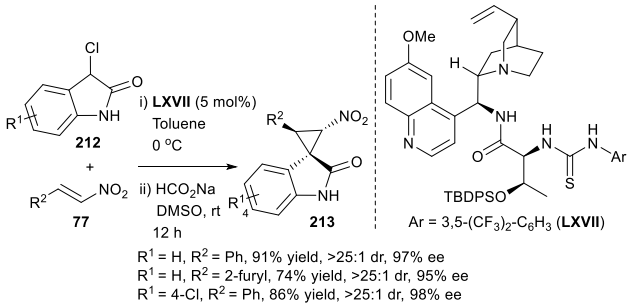
Scheme 62: Spirocyclization reported by Liu

Using a different approach, Quyang and Chen *et al*. reacted the MBH carbonates derived from oxindoles **208** with 2-alkylidene-1H-indene-1,3(2H)-diones **209**.[107] Remarkably, the reaction afforded different diastereomers when catalysed by phosphine derivative **LXIV**, phosphine **LXV**, or DMAP derivative **LXVI**; DFT calculations revealed the catalyst-based switch in the annulation mechanism. In both cases, the spirooxindoles **210**/**211** were produced with excellent results (Scheme 63). Soon afterwards, Quyang and Chen *et al*. reported the same approach using 1,2-benzoisothiazole 1,1-dioxide or 1,2,3-benzoxathiazine 2,2-dioxide derivatives as the activated alkene. After cycloaddition with the MBH carbonates derived from the oxindoles, the spirooxindoles were produced in good yields (75-97%) and excellent stereoselectivities (>19:1 d.r. and up to 99% ee).[108] A similar reaction was reported by Liu *et al*. using cyclic sulfonimine and catalysed by β-isocupreidine (**CII**).[109]



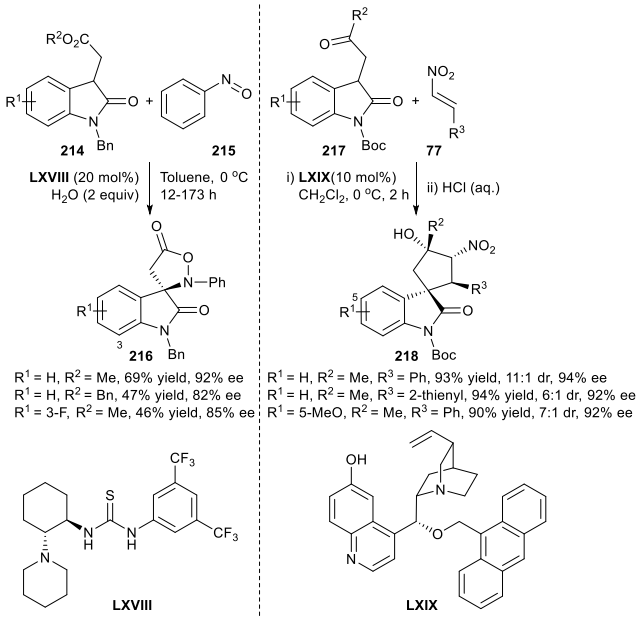
Scheme 63: Spirocyclization reported by Quyang and Chen

The 3-chloro oxindoles **212** have been reported as an excellent starting material for the synthesis of spirocyclopropane-fused oxindoles. Lu *et al*. reported the cycloaddition of 3-chloro oxindoles **212** to nitrostyrenes **77**.[110] The reaction is efficiently catalysed by the bifunctional thiourea/tertiary amine catalyst **LXVII**, affording the cyclopropanes **213** in a two-step one-pot procedure in good yields (74-96%) and excellent steroselectivities (up to >25:1 d.r. and 99% ee; Scheme 64). Later, Du *et al*. reported a similar reaction using alkylidene pyrazolones.[111] The Michael-α-alkylation cascade reaction was catalyzed by squaramides and produced the cyclopropanes in excellent yields (up to 99%) and moderate stereoselctivities (up to 87:13 d.r. and 74% ee).



Scheme 64: Spirocyclization reported by Lu

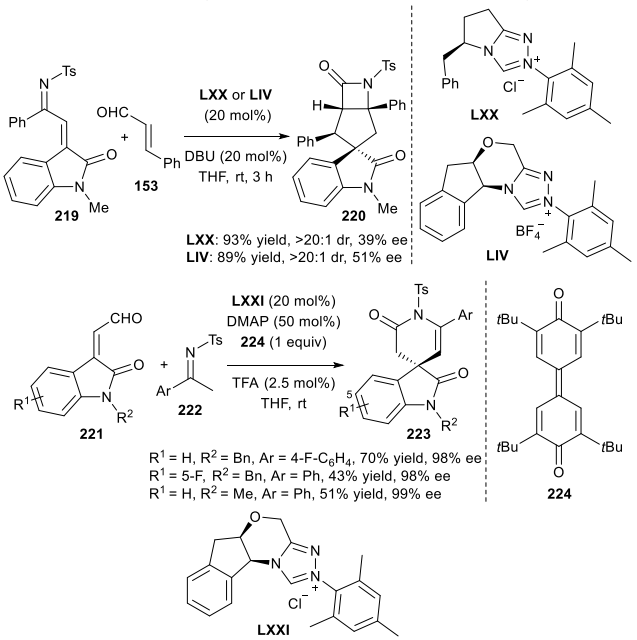
3-Substituted oxindoles decorated with an ester moiety, **214**, reacted with nitrosoaryl compounds **215** to furnish spirooxindoles **216** in moderate yields (31-69%) and good enantioselectivities (77-95% ee).[112] The method comprises a nitrosoaldol reaction, catalysed by a bifunctional tertiary amine/thiourea catalyst **LXVIII**, followed by intramolecular lactonization between NOH and the ester moiety (Scheme 65, left). Barbas *et al*. reported the addition of oxindoles decorated with a ketone moiety, **217**, to nitrostyrenes **77** to generate spirooxindoles **218**.[113] The reaction starts with the Michael addition of the oxindole to the nitrostyrene, catalysed by an *O*-desmethyl quinine-derived catalyst **LXIX**. This is followed by an intramolecular Henry reaction to afford the corresponding spirooxindoles in excellent yields (89-97%) and stereoselectivities (up to 18:1 d.r. and 97% ee; Scheme 65, right).



Scheme 65: Spirocyclization reported by Wang and Peng (left) and Barbas (right)

3.1.2 Organocatalytic methodologies starting with α,β-unsaturated oxindoles

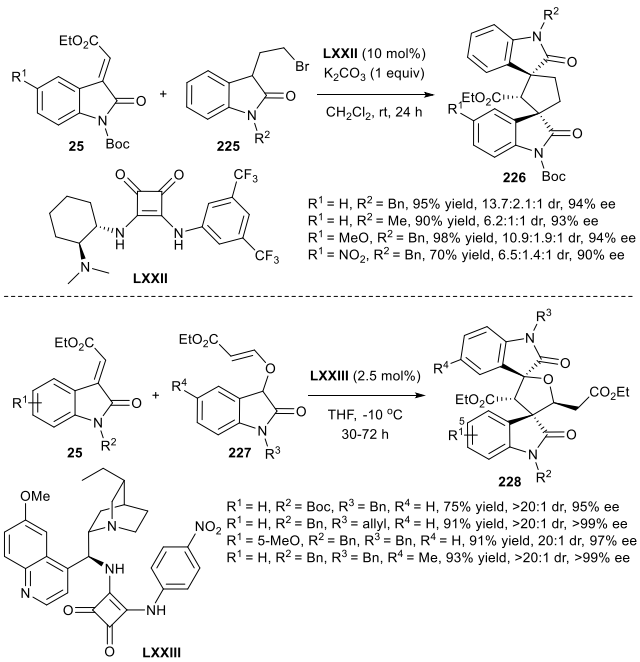
In 2012, Chi *et al*. reported the highly diastereoselective synthesis of spirooxindoles based on a NHC-catalysed reaction.[114] The procedure begins with Michael addition of a conjugated oxindole **219**, bearing a conjugated imine, reacts with the enal **153** in its homoenolate form (after addition of the NHC catalysts **LXX** or **LIV**) in a Michael addition. This is followed by 1,2-addition to the enamine to form the spirocyclic ring. The last step is the nucleophilic attack of the resulting Ts-amine to the carbonyl group, forming the β-lactam and releasing the NHC carbene. Only two chiral examples were reported and the final products were afforded in high yields (89 and 93%) and diastereoselectivities (>20:1 d.r.), albeit moderate to low enantioselectivities (39 and 51% ee; Scheme 66, top). Years later, a new NHC-catalysed reaction for the synthesis of spirooxindoles was developed by Yang, Zeng, and Zhong.[115] Oxindole-derived enals **221** and ketimines **222** undergo a [3+3] cycloaddition, using chiral NHC catalyst **LXXI** and 1 equiv. of oxidant **224** to achieve the final compounds **223** in moderate yields (40-69%) and excellent enantioselectivities (96-99% ee; Scheme 66, bottom).



Scheme 66: Spirocyclization reported by Chi (top) and Yang, Zeng, and Zhong (bottom)

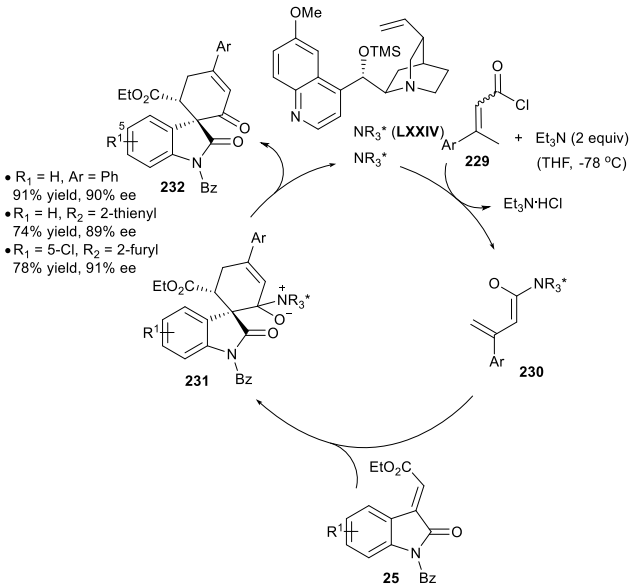
Wang and Hong *et al*. reported the reaction of methyleneindolinones **25** with oxindoles decorated at the C3 position with an alkyl chain containing a leaving group (Br) **225**.[116] The reaction comprised an initial Michael addition followed by intramolecular alkylation (5-*exo*-*tet*) to furnish the bispirobycycles **226**. The reaction was catalysed by a chiral bifunctional catalyst **LXXII** consisting of a squaramide unit (hydrogen bonding) and a tertiary amine (Brønsted base) to achieve the products in moderate to excellent yields (54-95%), good diastereoselectivities (up to 13.7:2:1 d.r.), and excellent enantioselectivities (up to 96% ee; Scheme 67, top). Soon after, the same research group reported a similar Michael-Michael cascade reaction using a Michael acceptor instead of the Br leaving group.[117] The reaction was catalysed by a bifunctional squaramide/tertiary amine catalyst, rendering the final dispiro

compounds in good yields (up to 76%) and excellent stereoselectivities (up to 15:1 d.r. and >99% ee). A different Michael-Michael cascade reaction for the formation of bis-spirooxindoles has been reported by Du *et al*. In this reaction, α,β-unsaturated oxindoles **25** react with 3-hydroxy oxindoles derivatives **227** bearing a α,β-unsaturated ester, which is directly bonded to the alcohol.[118] The reaction was efficiently catalysed by a bifunctional squaramide/tertiary amine catalyst **LXXIII**, affording the bis-spirooxindoles **228** with excellent results (up ro >20:1 d.r. and >99% ee; Scheme 67, bottom). Recently a similar approach has been reported where α-alkylidene succinimides were reacted with α,β-unsaturated oxindoles under squaramide/tertiary amine catalysts. The products were afforded in good to excellent yields (up to 93%) with excellent stereoselectivities (up to 99:1 d.r. and 98% ee).[119] The reaction was tested in multigram-scale to establish its practicality.



Scheme 67: Spirocyclization reported by Wang and Hong (top) and Du (bottom)

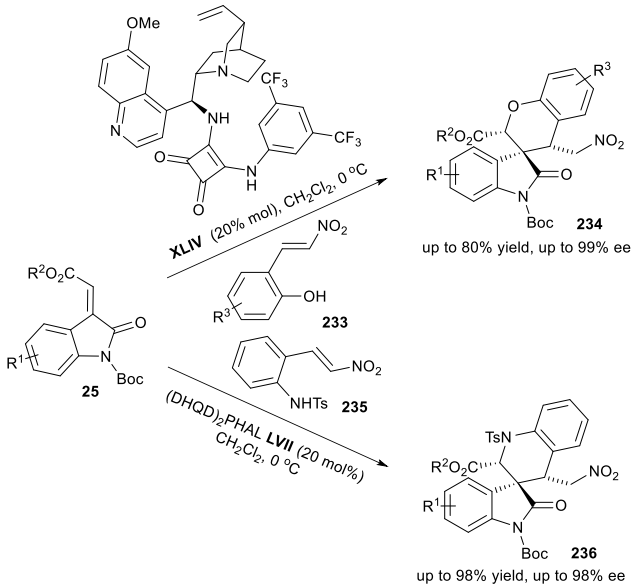
3-Alkylenyloxindoles **25** react with acyl chlorides **229**, under Lewis base catalysis, to generate spirooxindoles **232** in very good yields (74-91%) and enantioselectivities (87-93% ee).[120] The mechanism starts with the activation of the acid chloride with the Lewis base (cinchona alkaloid derivative; **LXXIV**). This forms the γ-enolate **230** that subsequently undergoes a Michael addition with the 3-alkylenyloxindole **25**. Next, intramolecular cyclization and the release of the catalysts lead to the formation of spiro compound **232** (Scheme 68).



Scheme 68: Spirocyclization reported by Ye

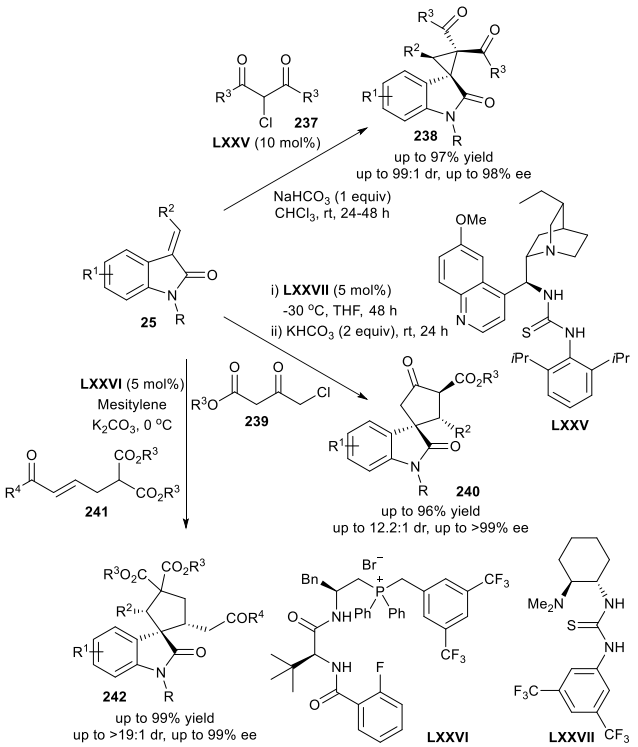
Ramachary *et al*. reported the synthesis of spirooxoindoles by the amino-catalysed reaction of enynes and alkylidene oxindoles.[121] Enynes react with cinchona alkaloid primary amine catalysts to generate the enamine, which undergoes a Michael addition with the alkylidene oxindole. Next, an intramolecular Michael addition between the formed enolate and the conjugated triple bond leads to the cyclohexene fused spiro oxindole in moderate yields (40-60%) and high enantioselectivities (81-96% ee).

Zhu *et al*. developed a cascade reaction between unsaturated oxindoles **25** and nitrostyrenes decorated with a hydroxyl **233** or amino-protected group **235**. This leads to chromanes **234** or tetrahydroquinolines **236**, respectively, through a Michael-Michael cascade reaction.[122] The reaction is catalysed by cinchona alkaloid derivatives for the former reaction. For chromanes formation, a cinchona alkaloid decorated with squaramide **XLIV** is necessary to achieve good yields (61-75%) and stereoselectivities (up to >99% ee). On the other hand, for the synthesis of tetrahydroquinolines, the Sharpless ligand [$(DHQD)_2PHAL$; **LVII**] emerged as the best organocatalyst, achieving excellent yields (87-96%) and enantioselectivities (up to 98% ee). The mechanism is the same for both cascade reaction: starting from a hetero-Michael addition between the hydroxyl or *N*-protected moiety to the alkylidene oxindole, followed by an intramolecular Michael addition between the previously formed enolate of the oxindole and the nitrostyrene (Scheme 69).



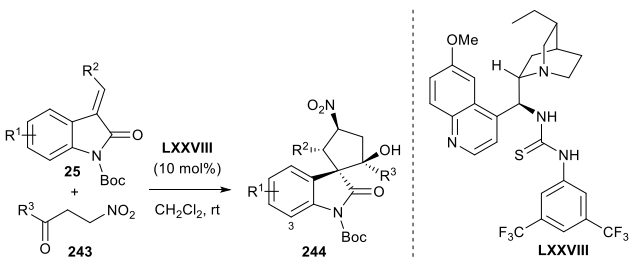
Scheme 69: Spirocyclization reported by Zhu

Alkylidene oxindoles **25** reacted with chloro-malonates **237** to render the corresponding spirooxindole cyclopropanes **238** in good yields (72-97%) and stereoselectivities (up to 93:7 d.r. and 94% ee) using the thiourea/tertiary amine bifunctional catalyst **LXXV**.[123] A similar cascade reaction between methylene indolines and γ-halogenated-β-ketoesters **239** was reported by Wang and Xu *et al.*[124] Inspired by the previous works of Córdova,[125] a domino Michael addition alkylation reaction, catalysed by a bifunctional tertiary amine/thiourea catalyst **LXXVII**, was developed, affording the final spiro compounds **240** in excellent yields (84-96%) and moderate to good stereoselectivities (up to 10:1 d.r. and 99% ee). The mechanism starts with the Michael addition of the keto ester to the methylene indoline followed by S_N2 alkylation of the enolate intermediate at the γ-position, decorated with a halogen. Shang and Zhao *et al*. reported a similar reaction with alkylidene oxindoles **25** and malonate derivatives bearing an enone in the side chain **241**.[126] The Michael-Michael cascade reaction was catalysed by a multifuncional quaternary phosphonium compound **LXXVI**, building the spirooxindoles **242** with excellent yields (80-98%) and stereoselectivities (up to >19:1 d.r. and 99% ee; Scheme 70).



Scheme 70: Several methodologies leading to spirooxindoles

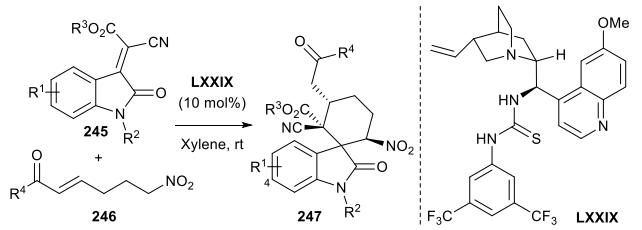
Kanger *et al*. reported another cascade reaction comprising a consecutive Michael addition/aldol reaction between nitro ketones **243** and alkylidene oxindoles **25**.[127] The reaction starts with a nitro alkyl Michael addition to the alkylidene oxindoles. Next, the formed enolate undergoes an aldol reaction with the ketone moiety to form a five-membered ring (Scheme 71). The reaction is efficiently catalysed by the bifunctional hydrogen bonding(thiourea)/Brønsted base catalyst **LXXVIII**, derived from cinchona alkaloids, rendering the final spiro compounds **244** in good yields (85-95%) and excellent stereoselectivities (up to d.r. 20:1 and up to 98% ee). The only limitation of this methodology is the size of the substituent in the ketone; sterically bulky substituents (R^3 = isobutyl) affored low yield (25%) and 10:1 d.r., while maintaining similar enantioselectivity (96% ee). Years later, Chen *et al*. reported the same reaction using 2-arylidene-1,3-indandiones instead of unsaturated oxindoles.[128]



Scheme 70: Spirocyclization reported by Kanger

A similar reaction comprising a Michael-Michael tandem

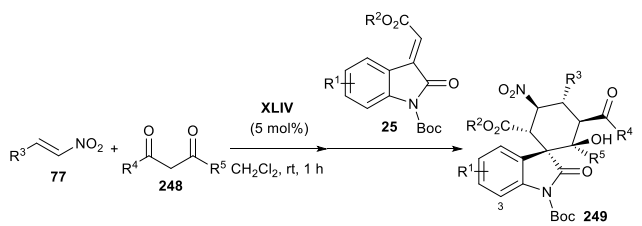
reaction using enones instead of ketones was reported years later by Zhao *et al*.[129] The reaction, catalysed by a bifunctional thiourea/tertiary amine catalyst derived from the cinchona alkaloid **LXXIX**, rendered the corresponding spirooixindoles in good yields (76-86%) and excellent stereoselectivities (up to 95:5 d.r. and 98% ee). The reaction begins with a first Michael addition between the nitroalkane **246** and the α,β-unsaturated oxindole **25**, promoted by the catalyst *via* hydrogen bonding. This is followed by an intramolecular Michael addition to render the final product **247** in good yields (86-78%) and excellent stereoselectivities (up to 95:5 d.r. and 98% ee; Scheme 72). Later, Quintivalla *et al*. reported the same reaction using unsaturated esters.[130]



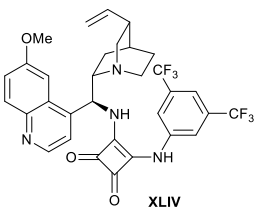
R^1 = H, R^2 = H, R^3 = Et, R^4 = Ph, 78% yield, 90:10 dr, 73% ee
R^1 = H, R^2 = Tr, R^3 = Me, R^4 = Ph, 86% yield, 95:5 dr, 96% ee
R^1 = 4-Cl, R^2 = Tr, R^3 = Me, R^4 = Ph, 82% yield, 91:9 dr, 93% ee

Scheme 72: Spirocyclization reported by Zhao

A multicascade Michael-Michael-aldol reaction was reported by Sun *et al*. in 2015.[131] The 1,2-dicarbonyl compounds **248**, nitroalkene **77**, and methyleneindolines **25** generated the spirooxindoles **249**, under squaramide catalysis, in excellent yields (up to 85%) and with excellent stereoselectivities (up to >20:1 d.r. and 99% ee; Scheme 73).

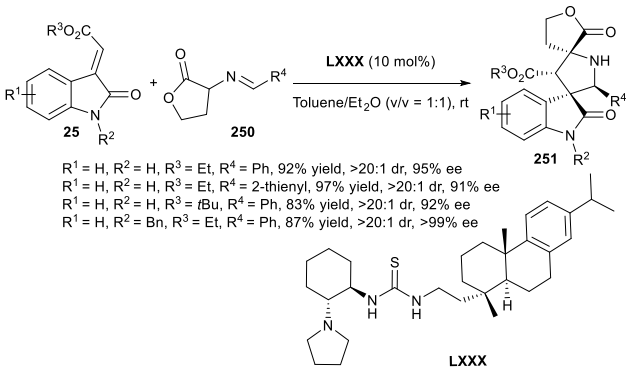


R^1 = H, R^2 = Et, R^3 = Ph, R^4 = Me, R^5 = Me; 85% yield, >20:1 dr, >99% ee
R^1 = 3-F, R^2 = Et, R^3 = Ph, R^4 = Me, R^5 = Me; 79% yield, >20:1 dr, >99% ee
R^1 = H, R^2 = Et, R^3 = Ph, R^4 = OEt, R^5 = Me; 89% yield, >20:1 dr, >99% ee
R^1 = H, R^2 = Et, R^3 = 2-thienyl, R^4 = OEt, R^5 = Me; 70% yield, >20:1 dr, >99% ee



Scheme 73: Spirocyclization reported by Sun

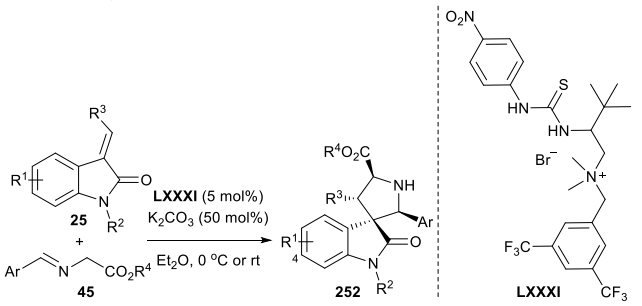
A [3+2] cycloaddition was reported by Wang *et al*. This comprised a 1,3-dipolar cycloaddition between alkylidene oxindoles **25** and cyclic imino esters **250** catalysed by a bifunctional thiourea/tertiary amine **LXXX**.[132] The reaction rendered the final spiro compounds **251** in good yields (83-97%) and excellent stereoselectivities (up to >20:1 d.r. and >99% ee; Scheme 74). Cheng *et al*. developed a similar [3+2] cycloaddition using nitrones as a 1,3-dipole.[133] The reaction was catalysed by bis-thiourea afford the final compounds in moderate yields (45-78%) and excellent stereoselectivities (up to 99:1 d.r. and 99% ee).



R^1 = H, R^2 = H, R^3 = Et, R^4 = Ph, 92% yield, >20:1 dr, 95% ee
R^1 = H, R^2 = H, R^3 = Et, R^4 = 2-thienyl, 97% yield, >20:1 dr, 91% ee
R^1 = H, R^2 = H, R^3 = *t*Bu, R^4 = Ph, 83% yield, >20:1 dr, 92% ee
R^1 = H, R^2 = Bn, R^3 = Et, R^4 = Ph, 87% yield, >20:1 dr, >99% ee

Scheme 74: Spirocyclization reported by Wang

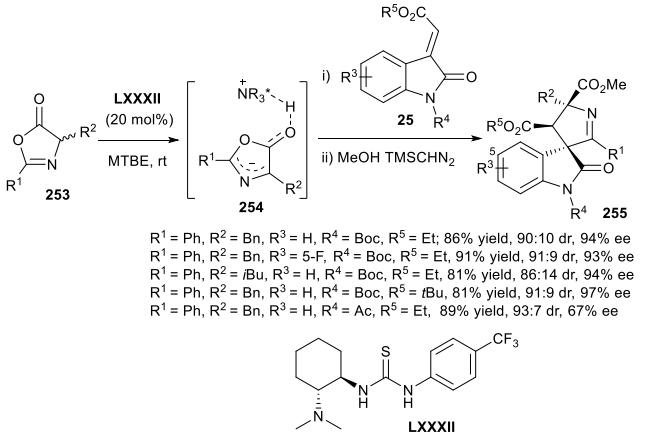
Later, noncyclic imino esters **45** were used in the 1,3-dipolar cycloaddition with alkylidene oxindoles **25** utilizing a thiourea/quaternary ammonium salt **LXXXI** as the catalyst. This reaction provided the final spiro compounds **252** with excellent results (up to 98% yield, >19:1 d.r., and 99% ee; Scheme 75).[134]



R^1 = H, R^2 = Bn, R^3 = Ph, R^4 = Et, Ar = Ph; 97% yield, 97:3 dr, 94% ee
R^1 = 4-F, R^2 = Bn, R^3 = Ph, R^4 = *t*Bu, Ar = Ph, 90% yield, 95:5 dr, 96% ee
R^1 = H, R^2 = Bn, R^3 = *n*-Pr, R^4 = *t*Bu, Ar = Ph, 90% yield, 84:16 dr, 96% ee
R^1 = H, R^2 = Boc, R^3 = Ph, R^4 = Me, Ar = Ph, 85% yield, 96:4 dr, 81% ee
R^1 = H, R^2 = Bn, R^3 = Ph, R^4 = *t*Bu, Ar = 2-naphthyl, 93% yield, 98:2 dr, 98% ee

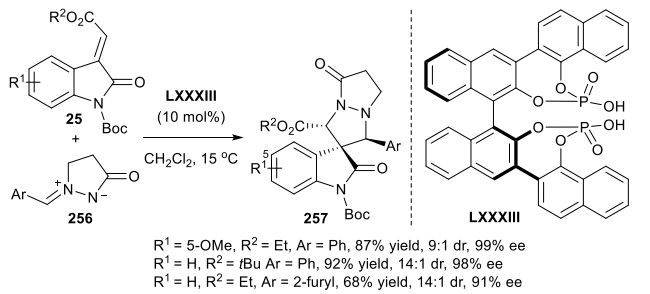
Scheme 75: Spirocyclization reported by Shang and Zhao

Alkylidene oxindoles **25** have also been used in a 1,3-dipolar cycloaddition with azalactones **253**.[135] A bifunctional thiourea/Brønsted base catalyst **LXXXII** deprotonates the azalactone to form an enolate species in which the C2 and C4 positions are activated. The enolate of the azalactone undergoes an enantioselective 1,3-dipolar cycloaddition with the alkylidene oxindole (dipolarophiles). The thiourea catalyst **LXXXII**, a slight modification of the Takemoto's catalyst, promotes the reaction, furnishing the spiro 3,3'-pyrrolidonyl spirooxindoles **255** in good yields (70-95%), excellent stereoselectivities (up to 93:7 d.r. and up to 98% ee), and good group compatibililty (Scheme 76). Later, the same research group reported the same reaction catalysed by chiral phosphoric acids with similar results.[136]



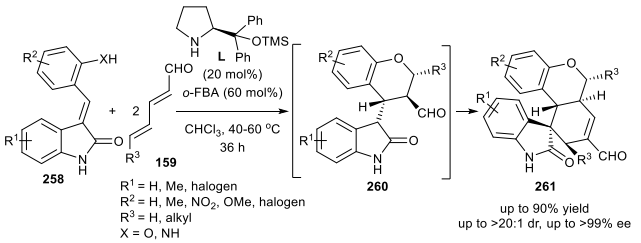
Scheme 76: Spirocyclization reported by Wang

N,*N*'-Cyclic azomethine imines **256** have been used in a similar approach for the synthesis of spirooxindoles.[137] Diphosphoric acid derivatives **LXXXIII** catalyse the 1,3-dipolar cycloaddition, producing the final spiro compounds **257** in excellent yields (84-94%) and good to excellent stereoselectivities (up to 20:1 d.r. and 99% ee; Scheme 77).



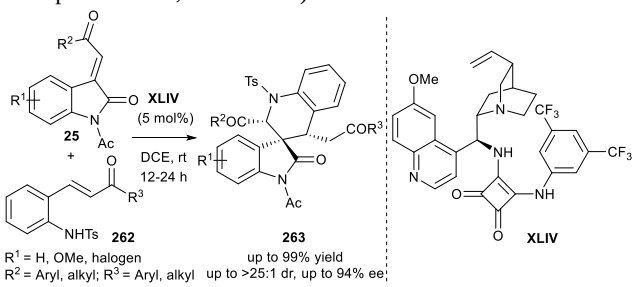
Scheme 77: Spirocyclization reported by Hong and Wang

A multicomponent cascade reaction was developed by Liu and Wang *et al*. using benzylidene oxindoles decorated with a hydroxyl group in the *ortho*-position of the phenyl ring **258**.[138] The reaction consists of an oxa-Michael addition with a subsequent intramolecular Michael addition. This is followed by an intermolecular Michael addition with a new molecule of enal occurs, followed by an intramolecular aldol reaction to form the cyclohexene ring after dehydration. The reaction renders the spirooxindoles **261** in moderate to good yields (31-90% yield) with good to excellent stereosecetivities (up to 12:1 d.r. and >99% ee). The reaction is limited to the use of aliphatic enals: when β,β-disubstituted enals were used, the reaction stopped after the intramolecular Michael addition, preventing the formation of the spirocentre (Scheme 78).



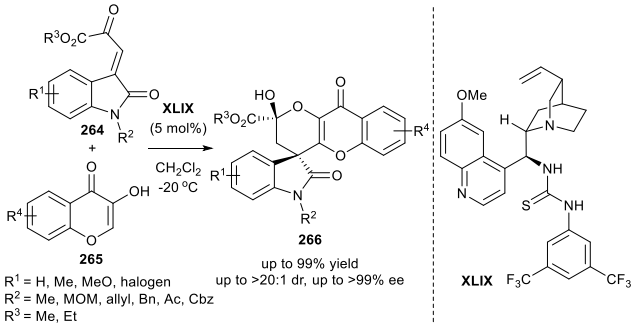
Scheme 78: Spirocyclization reported by Liu and Wang

Ortho-hydroxy chalcones react with alkylidene oxindoles, under a bifunctional tertiaryamine/thiourea catalyst, to furnish the spirooxindoles in good yields (60-95%) and moderate to high stereoselectivities (up to >20:1 d.r. and 90% ee).[139] Alkylidene oxindoles undergo an oxo-Michael addition to the *ortho*-hydroxy chalcones, followed by an intramolecular Michael addition between the enolate generate 'in situ' and the enone to build the spirooxindole. Du[140] and Zhao[141] independently reported a similar reaction, using *ortho*-amino chalcones **262** with excellent results (85-99% yields, >25:1 d.r., and up to 90% ee; Scheme 79).



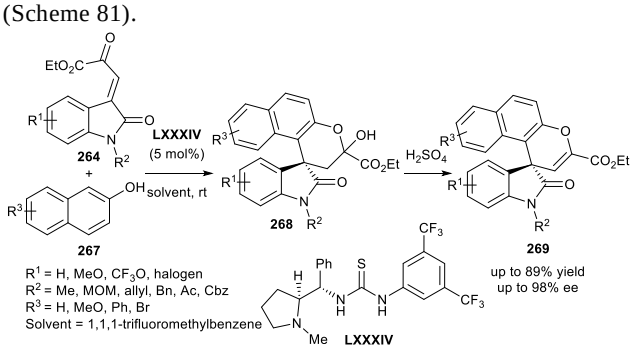
Scheme 79: Spirocyclization reported by Du and Zhao

Wang *et al*. reported a cascade reaction comprising the addition of 2-hydroxy-1,4-naphthoquinone or 3-hydroxy-4H-chromene-4-ones **265** to benzylidene oxindoles decorated with a ketoester (**264**).[142] The reaction mechanism comprises an initial Michael reaction between the enolate of the 2-hydroxy-1,4-naphthoquinone or 3-hydroxy-4H-chromen-4-ones to the benzylidene oxindole, followed an intramolecular hemiacetal formation to furnish the corresponding spiro oxindoles. The reaction is efficiently catalysed by a bifunctional thiourea/tertiary amine catalyst **XLIX**, affording the corresponding spiro compounds **266** in moderate to good yields (55-92%) and excellent stereoselectivities (up to >20:1 d.r. and >99% ee). The functional group tolerance is excellent, while the only limitation is the need of *N*-substituted oxindoles (Scheme 80). Almost simultaneously, Kesavan *et al*. reported similar methodologies, using 2-hydroxy-1,4-naphthoquinone[143] and pyrazolones.[144]



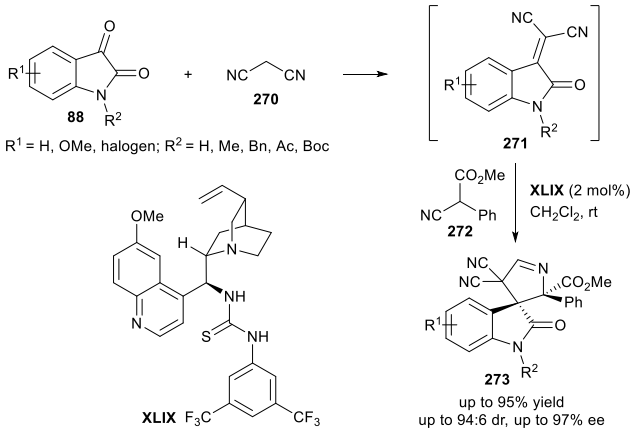
Scheme 80: Spirocyclization reported by Wang

A one pot-two-step reaction was reported by Kesavan *et al*. for the synthesis of naphthopyran-spirooxindoles.[145] The reaction is based on a tandem Friedel-Crafts/hemiketalization reaction. Taking advantage of the electron-rich nature of naphthol **267**, a Friedel-Crafts type reaction was employed between the most active *meta*-position of the 2-naphthol and the β-position of the alkylidene oxindole decorated with a ketoester **264**; the reaction was catalysed by a chiral thiourea/tertiary amine catalyst **LXXXIV**. The subsequent addition of sulfuric acid resulted in hemiacetal formation which, after dehydration, rendered the final product **269** in good yields (65-89%) and good to excellent enantioselectvities (70-98% ee). The tertiary amine acts as a base to activate the nucleophile, while the thiourea moiety activates the ketoester for Michael addition (Scheme 81).



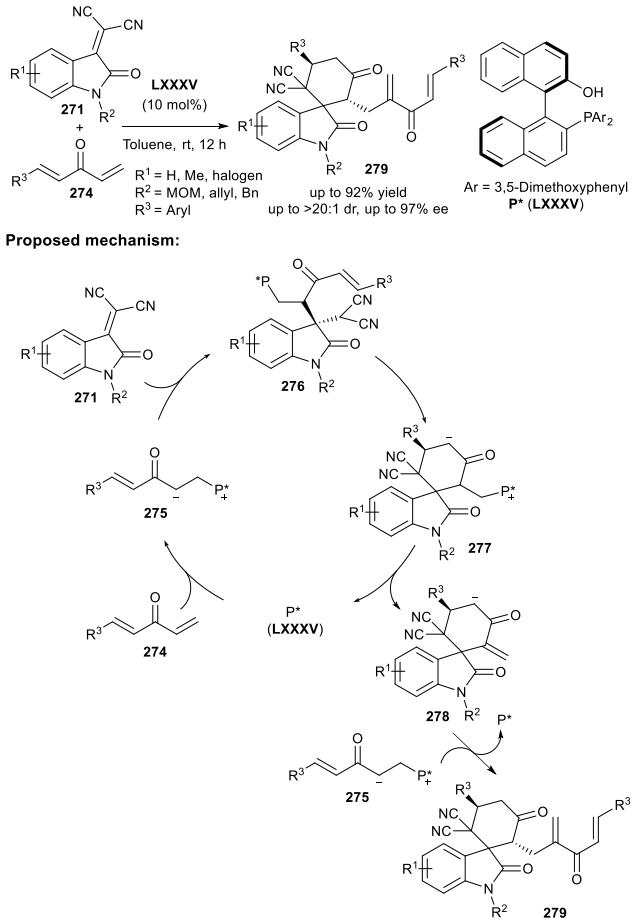
Scheme 81: Spirocyclization reported by Kesavan

N-Protected isatylidenemalononitriles have become popular reactants for the synthesis of spiropyrazolones. In 2012 a cycloaddition reaction between isocyanoacetates **272** and *N*-protected isatylidenemalononitriles, prepared *'in situ' via* the Knovenagel reaction between isatin **88** and malononitrile **270**, was reported by Yan *et al*.[146] The formal [3+2] cycloaddition is catalysed by a bifunctional tertiary amine/thiourea catalyst **XLIX**, to afford the final spiro compounds **273** in good yields (73-92%), moderate diastereoselectivities (up to 88:12 d.r.), and high enantioselectivities (80-97% ee; Scheme 82). A similar reaction under thiourea catalysis was reported by Wu *et al*., whereby *N*-protected isatylidenemalononitriles reacted with ketonitriles to afford spirooxindoles with moderate stereoselectivities.[147]



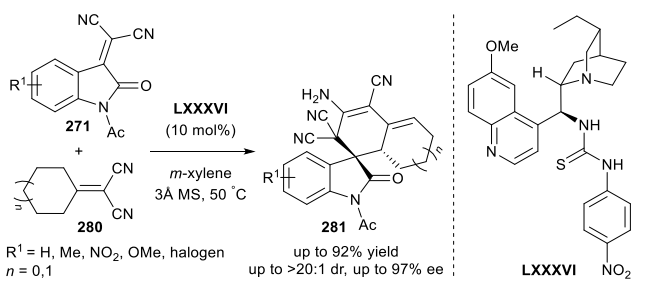
Scheme 82: Spirocyclization reported by Yan

Soon afterwards, Shi and Wei *et al*. reported a Rauhut-Currier/Michael/Rauhut-Currier cascade reaction of *N*-protected isatylidenemalononitriles **271** with dienones **274**, catalysed by chiral phosphine **LXXXV**.[148] The reported mechanism starts with the nucleophilic attack of the phosphine to the dienone, to form the enolate **275**, which attacks the *N*-protected isatylidenemalononitriles. Next, the formed enolate **273** undergoes an intramolecular Michael addition to the enone to form the spiro compound **276**. The release of the catalyst and an intermolecular Rauhut-Currier reaction render the final compounds **272** in good yields (63-92%) and excellent stereoselectivities (up to 20:1 d.r. and 97% ee; Scheme 83). The same group reported the use of similar alkylidenoxindoles reacting with MBH carbonates in a [4+1] cycloaddition, to generate spirooxindoles in good yields, moderate diastereoselectivities and high enantioselectivities.[149]



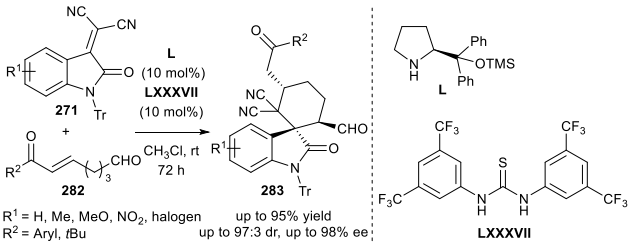
Scheme 83: Spirocyclization reported by Shi and Wei

N-Protected isatylidenemalononitriles **271** reacted with α,α-dicyanoalkenes **280**, catalysed by the cinchona alkaloid-derived bifunctional tertiary amine/thiourea **LXXXVI**.[150] The reported mechanism starts with the deprotonation of the cyclohexylidene malononitrile by the tertiary amine in the catalyst, which undergoes a Michael addition to the *N*-protected isatylidenemalononitrile. This latter compound is simultaneously activated through hydrogen bonding by the thiourea moiety of the catalyst. Next, the intermediate undergoes an intramolecular nucleophilic addition to the CN group to form the imine which, upon isomerization, generates the spirocyclic oxindole **281** in moderate to good yields (51-93%) and high enantioselectivities (74-95% ee; Scheme 84). A similar reaction was reported one year later by Kesavan *et al*. with similar results.[151]



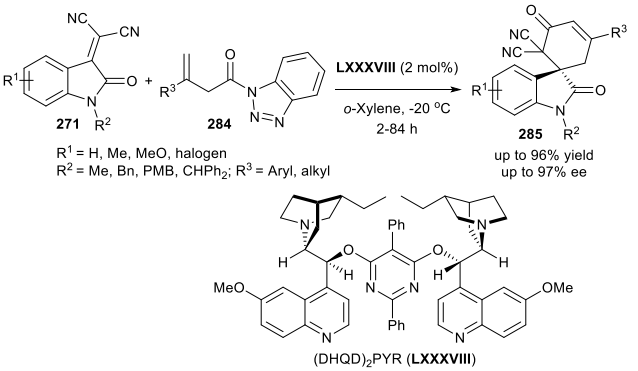
Scheme 84: Spirocyclization reported by Wang

Later, *N*-protected isatylidenemalononitriles **271** were employed in the synthesis of spirooxindoles through a double Michael cascade reaction with enolizable aldehydes decorated with a enone **282**.[152] The reaction is efficiently catalysed by TMS-protected diphenylprolinol **L** and requires the use of Schreiner thiourea **LXXXVII** for optimum results. Enamine first attacks the malononitrile moiety. The subsequent Michael addition between the recently formed enolate and the enone furnishes the final spirooxindole **283** in good yields (76-95%) and excellent stereoselectivities (up to 97:3 d.r. and 98% ee; Scheme 85).



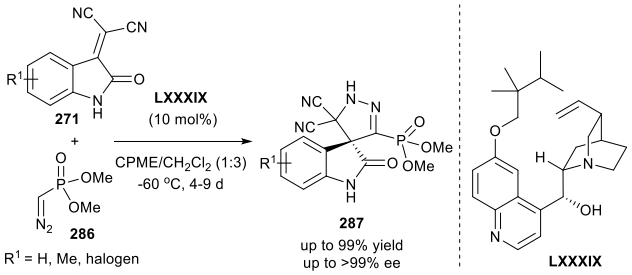
Scheme 85: Spirocyclization reported by Zhao

Wu and Sha *et al*. reported the vinylogous Michael/cyclization cascade reaction of acyclic β,γ-unsaturated amides **284** with isatylidene malonitriles **271** to build spirooxindoles **285**.[153] The reaction is catalysed by a Sharpless ligand [$(DHQD)_2PYR$, **LXXXVIII**] to afford the spiro compounds in good yields (84-96%) and enatioselectivities (85-97% ee; Scheme 86). Another example is the addition of pyrazolone to isatylidene malonitriles, catalysed by Sharpless ligand, which affords the spirooxindoles in quantitative yields and good enantioselectivities (63-91% ee).[154] The same research group expanded this reaction using *o*-quinones instead of isatylidene malonitriles.[155]



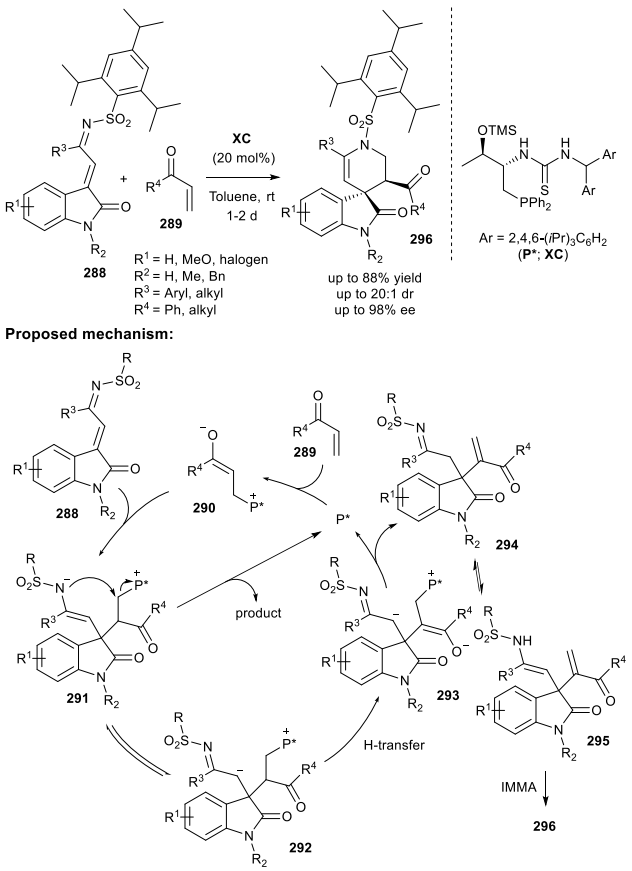
Scheme 86: Spirocyclization reported by Wu and Sha

Peng *et al*. reported a 1,3-dipolar cycloaddition between the Seyferth-Gilbert reagent **286** and isatylidene malononitriles **271**, catalysed by cinchona alkaloids **LXXXIX**.[156] The resulting spirooxindoles **287** were formed in good yields (up to 99%) and enantioselectivities (up to 99% ee; Scheme 87).



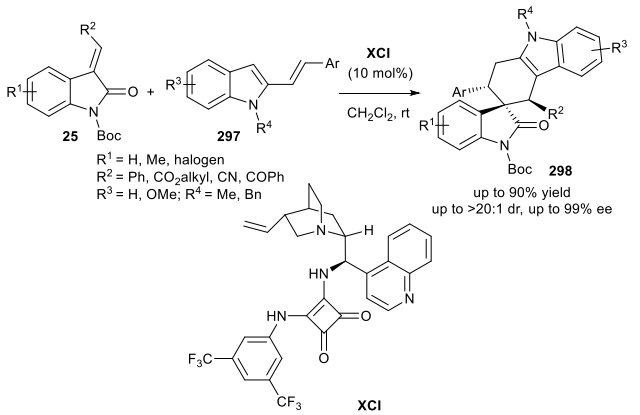
Scheme 87: Spirocyclization reported by Peng

A formal [4+2] cycloaddition for the synthesis of spirooxindoles, comprising the reaction between vinyl ketones **289** and oxindole-derived α,β-unsaturated imines **288**, was reported by Shi and Wei *et al*.[157] The multifunctional thiourea-phosphine catalyst **XC** efficiently promoted the reaction, achieving the spirocompounds **296** in good yields (67-87%) and excellent stereoselectivities (up to 20:1 d.r. and 98% ee). The reaction consists of the Rauhut-Currier reaction of the vinyl ketone **289** with the unsaturated imine **288** promoted by phosphine **XC**. This is followed by the Michael addition between the tosyl amine and the vinyl ketone. A limitation of this methodology is that only unsubstituted vinyl ketones can be used (Scheme 88).



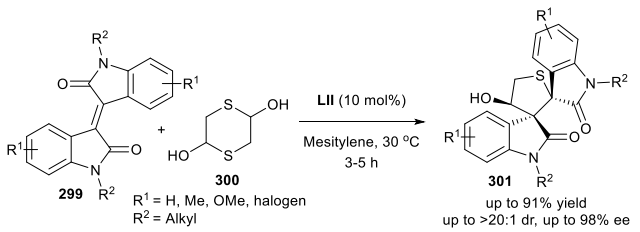
Scheme 88: Spirocyclization reported by Shi and Wei

A Diels-Alder reaction, catalysed by bifunctional tertiary amine/squaramide catalysts **XCI,** was reported by Weng and Lu *et al*.[158] Benzylidene oxindoles **25** react with 2-vinylindoles **297** *via* a [4+2] cycloaddition to efficiently build spiro[tetrahydrocarbazole-3,3'-oxindole] **298** in moderate yields (52-84%) and good stereoselectivities (4:1 to >20:1 d.r. and 65-99% ee; Scheme 89). Soon after, the same reaction was reported by Shi *et al*. using chiral phosphoric acid derivatives.[159] The spiro[tetrahydrocarbazole-3,3'-oxindole was afforded in high yields (71-96%) and excellent stereoselectivities (up to >95:5 d.r. and 97% ee). In the proposed transition state, the phosphoric acid coordinates with the oxindole carbonyl and the indole N-H. The final product is attained after isomerization to recover the indole aromaticity.



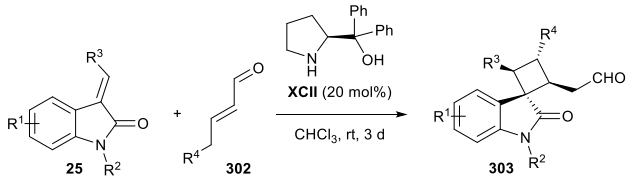
Scheme 89: Spirocyclization reported by Lu

Isoindigos **299** have been used in an organocascade reaction with 1,4-dithiane-2,5-diol **300**, catalysed by quinidine **LII**.[160] The reaction begins with a thio-Michael addition of the thiol moiety followed by an intramolecular aldol reaction to form the spiro tetrahydrothiophene ring **301** in good yields (70-91%) and high stereoselectivities (up to 20:1 d.r. and 90% ee; Scheme 90).



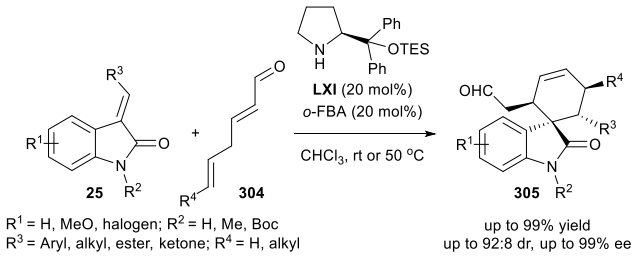
Scheme 90: Spirocyclization reported by Peng and Wang

Dienamine catalysis was used by Wang *et al*. in the synthesis of spirooxindoles through a formal [2+2] cycloaddition.[161] In this method, enals possessing a δ-hydrogen **302** reacted with diphenyl prolinol **XCII** to form the dienamine intermediate, which undergoes a formal [2+2] cycloaddition with alkylidene oxindoles **25** to furnish the butanocycle-bearing spirooxindoles **303** in good yields (66-83%) and excellent enantioselectivities (up to >19:1 d.r. and 97% ee). Surprisingly, the use of a silyl-protected diphenyl prolinol derivatives gave lower stereoselectivities, suggesting that H-bonding plays a crucial role in this reaction (Scheme 91).



Scheme 91: Spirocyclization reported by Wang

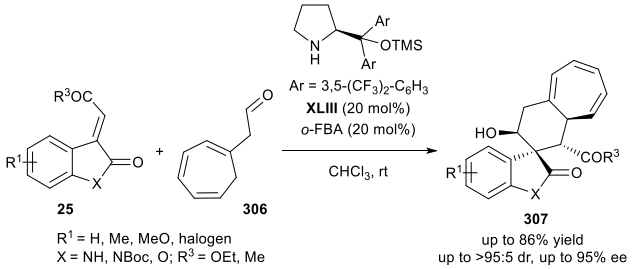
Trienamine catalysis was used by Chen and Jørgensen *et al*. for the synthesis of spirooxindoles.[162] Polyenals **304** react with the Jørgensen-Hayashi catalyst **LXI**, forming the trienamine intermediate. This undergoes a formal [4+2] cycloaddition with 3-olefinic oxindoles **25,** affording spirooxindoles **305** in good yields (60-99%) and excellent stereoselectivities (up to >95:5 d.r. and 98% ee; Scheme 92). Chen *et al*. reported a similar reaction, based on tetraenamine catalysis, with similar results.[163]



Scheme 92: Spirocyclization reported by Chen and Jørgensen

A similar trienamine activation strategy was used by Chen *et al*.[164] Primary amines derived from cinchona alkaloids acted as catalysts, forming the trienamine intermediate with linear 3,5-dienones. The trienamine undergos a Diels-Alder cycloaddition with 3-methylene oxindoles to render the spirooxindoles in high yields (81-94%) and excellent stereoselectivities (only one diastereomer, 91-99% ee).

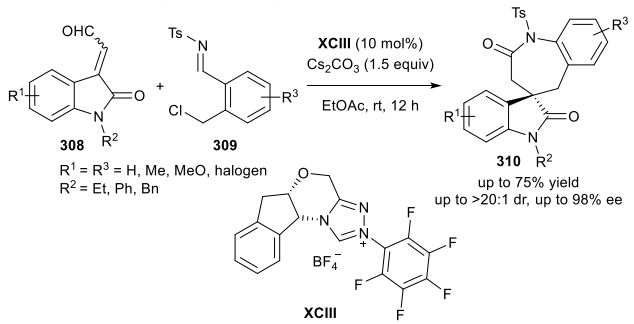
Soon after, Jørgensen *et al*. reported the use of tetraenamines for the synthesis of spirooxindoles.[165] Aldehyde 2-(cyclohepta-1,3,5-trien-1-yl)acetaldehyde **306** reacts with the Jørgensen-Hayashi catalyst **XLIII** to form the tetraenamine intermediate. This undergoes a formal [4+2] cycloaddition with alkylidene oxindoles **25** to form the spirooxindole **307** in good yields (51-84%) and good to excellent stereoselectivities (up to >95:5 d.r. and 95% ee). The scope of the reaction is quite narrow and only ester-substituted *N*-Boc-protected oxindoles render excellent stereoselectivities. On the other hand, ketones or non-protected oxindoles are used, the enantioselectivity drops considerably (Scheme 93).



Scheme 93: Spirocyclization reported by Jørgensen

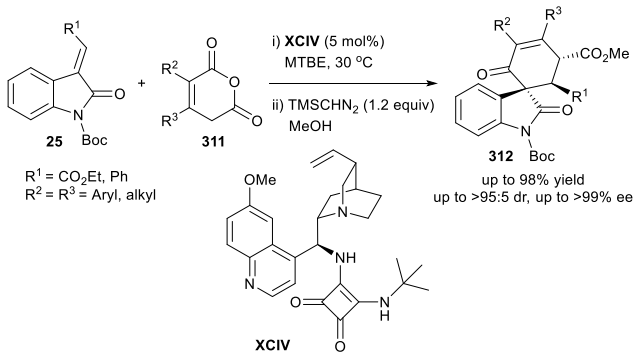
Jørgensen and Albrecht *et al*. developed a similar strategy consisting of a Diels-Alder reaction with MBH alcohols and benzylidene oxindoles.[166] The primary amine catalyst derived from cinchona alkaloids activates the MBH alcohol, generating a diene. This undergoes a [4+2] cycloaddition with the alkylidene oxindole to furnish spirooxindoles with four stereocentres in good yields (80-95%) and excellent stereoselectivities (up to >95:5 d.r. and 95% ee).

A formal [3+4] cycloaddition between alkylidene oxindoles **308** and aza-*o*-quinone methides (generated *in situ* from **309**), catalysed by chiral NHC carbenes, has been reported by Enders *et al*. for the synthesis of spirobenzazepinones **310**.[167] Isatin-derived enals **308** reacted with a NHC catalyst **XCIII** to generate the Breslow intermediate. The homoenolate the reacts with the *in situ*-formed aza-*o*-quinone methide to build a new C-C bond. Next, the acyl azolium species undergoes lactamization to release the NHC catalyst and furnish the spirobenzazepinone **310** in moderate yields (52-73%) and excellent enantioselectivities (up to 98% ee). They expanded the scope of the reaction by using hydrazones and oximes with similar results (Scheme 94).



Scheme 94: Spirocyclization reported by Enders

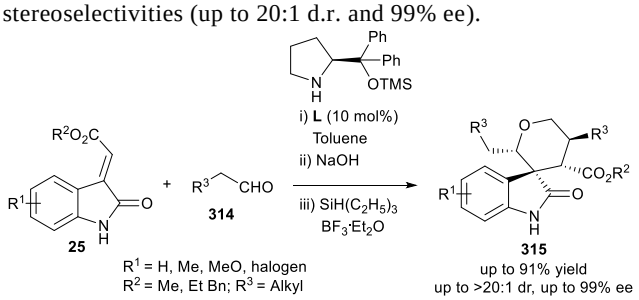
Connon *et al*. developed an enantioselective Tamura cycloaddition between cyclic anhydrides **311** and alkylidenoxindoles **25**.[168] The reaction is catalysed by a bifunctional tertiary amine/squaramide catalyst **XCIV**, affording the final spirooxindoles **312** in excellent yields (82-98%) and stereoselectivities (only 1 diastereomer and up to 99% ee; Scheme 95).



Scheme 95: Spirocyclization reported by Connon

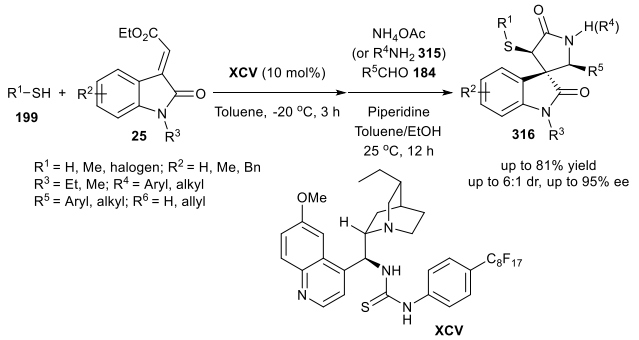
A multicomponent cascade reaction between alkylidene oxindoles and enolizable aldehydes was reported by Zeng and

Zhong *et al*.[169] The reaction consists of an initial Michael addition, catalysed by the Jørgensen-Hayashi catalyst **L**, between the enamine of aldehyde **314** and alkylidene oxindole **25**. This is followed by an aldol reaction between the *in situ*-generated enolate and another aliphatic aldehyde molecule. This is followed by intramolecular hemiacetal formation to furnish the spirooxindoles **315**. The reactions works well with short aldehydes (up to 91% yield >20:1 d.r., and 99% ee, Scheme 96). However, stereoselectivities decrease with longer chains. Enders reported a similar organocascade reaction using alkylidene oxindoles and aliphatic aldehydes catalysed by secondary amine catalysts.[170] The alphatic aldehyde in this enamine form undergoes a Michael addition with the unsaturated oxindole. Subsequently, another aliphatic aldehyde molecule undergoes oxidation to form the corresponding enal by reaction with IBX. This enal, which is in the iminium form, reacts with the *in situ*-formed enolate of the oxindole. Finally, an intramolecular aldol reaction and dehydration furnish the spiro compounds in moderate yields (50-78%) and excellent stereoselectivities (up to 20:1 d.r. and 99% ee).



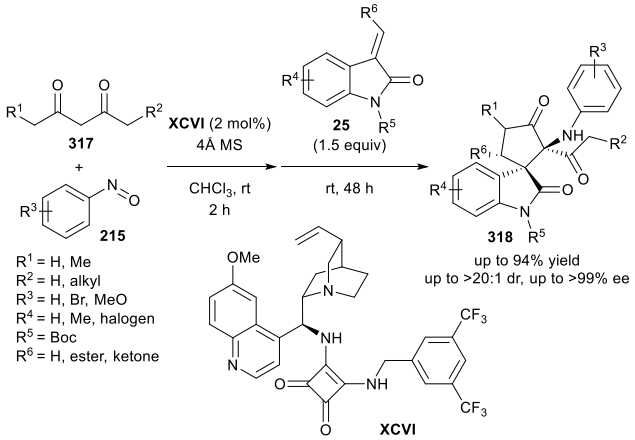
Scheme 96: Spirocyclization reported by Zeng and Zhong

A one-pot thia-Michael/Mannich/lactamization cascade reaction was reported by Zhang for the synthesis of spirooxindoles.[171] (*E*)-Ethyl 2-(1-methyl-2-oxoindolin-3-ylidene) acetate derivatives **25** reacted with thiols **199** *via* a thio-Michael addition. Next, the *in situ* formed enolate reacts with the formed imine (reaction of aromatic aldehydes **184** and NH_4OAc). The resulting amine attacks the ester moiety to form the final lactam-spirooxindole **316** in reasonable yields (59-81%) and good stereoselectivities (up to 6:1 d.r. and 95% ee; Scheme 97).



Scheme 97: Spirocyclization reported by Zhang

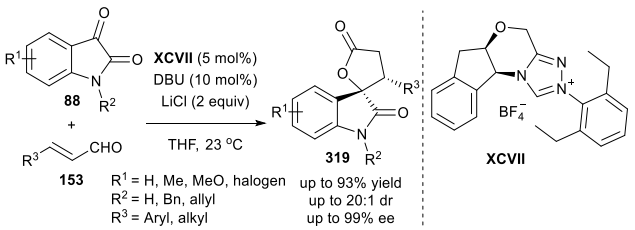
A cascade cycloaddition comprising the reaction between ketimines and alkylidene oxindoles **25**, catalysed by bifunctional quinine-derived squaramide **XCVI**, was reported by Sun *et al*.[172] The ketimines generated *in situ* by 1,3-diketones **317** and nitrosobenzene **215** react with alkylidene oxindoles through a Michael-Mannich cascade reaction, to furnish the spiro oxindoles **318** in moderate to good yields (41-94%) and excellent stereoselectivities (4:1 to >20:1 d.r. and 92-99% ee; Scheme 98).



Scheme 98: Spirocyclization reported by Sun

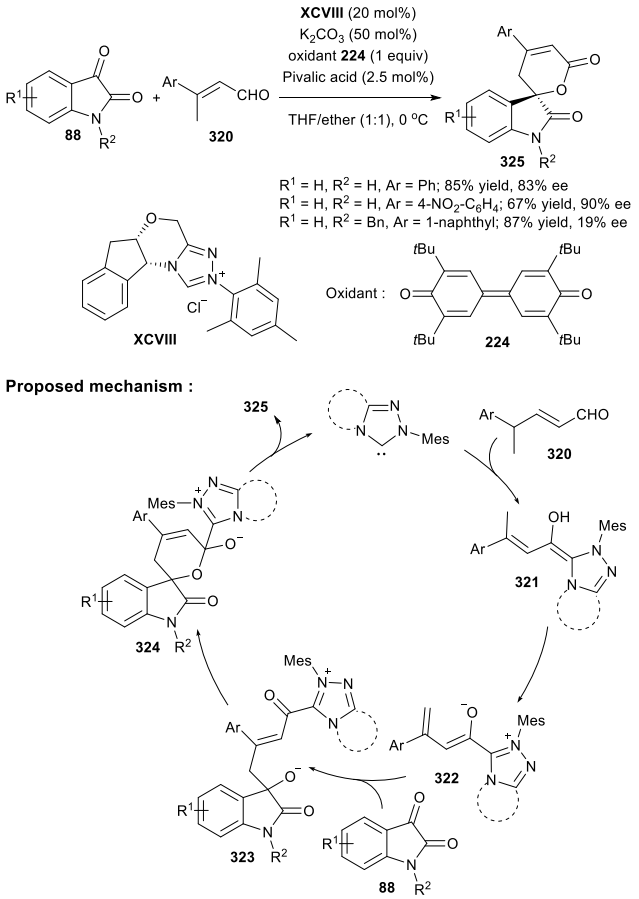
3.1.3 Organocatalytic methodologies starting with isatin

Scheidt *et al*.[173] reported NHC (**XCVII**) catalysed reaction with enals **153** and isatin **88** with a Lewis acid (LiCl) as cocatalyst. The final spirooxindoles **319** were achieved in good yields (73-93%), moderate diastereoselectivities (up to 5:1 d.r.) and excellent enantioselectivities (up to 99% ee; Scheme 99).



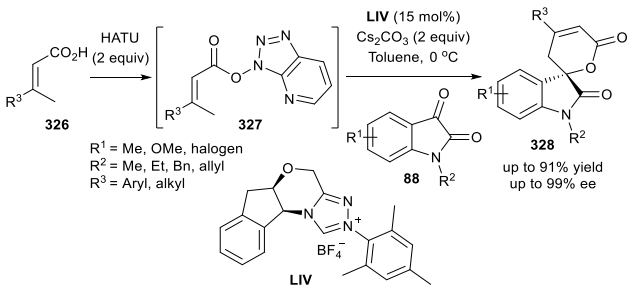
Scheme 99: Spirocyclization reported by Scheidt

Soon afterwards, Yang and Zhong *et al*. reported the same reaction using NHC catalyst **XCVIII** / Brønsted acid combination (Scheme 100).[174]



Scheme 100: Spirocyclization reported by Yang and Zhong

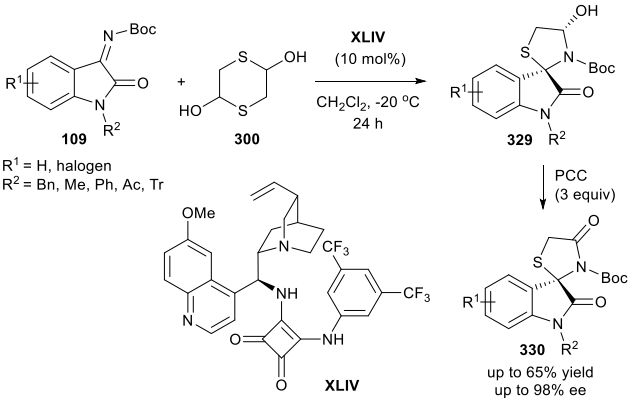
In 2016, inspired by these reactions, Yao *et al*. employed a similar strategy for the synthesis of spirooxindoles **328** using γ-hydrogen-bearing α,β-unsaturated carboxylic acids **326** with NHC as the catalyst **LIV**.[175] The reaction comprised the activation of the carboxylic acid by HATU (**327**), followed by the addition of the NHC catalyst, which formed the vinylogous enolate with the base. Subsequently, the ketone of the isatin **88** undergoes a nucleophilic attack by the formed enolate. Next, intramolecular lactonization affords the spirooxindole **328** in good yields (73-91%) and enantioselectivities (73-99% ee). Almost simultaneously, Ye *et al*. reported the same reaction with slighly inferior results (Scheme 101).[176]



Scheme 101: Spirocyclization reported by Yao

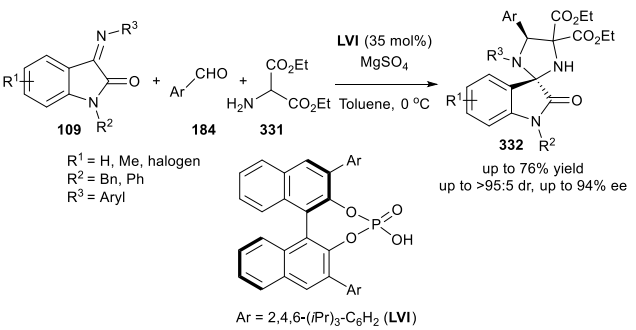
N-Boc-isatin imines reacted with enals under NHC catalysis to afford the spirooxindoles in good yields (66-83%) and steroselectivities (up to >20:1 d.r. and 99% ee).[177] The reaction exhibits broad group compatibility, the only limitation being requirement of *N*-methyl-protected oxindoles.

N-Boc-isatin imines **109** have also been used for the synthesis of spirooxindoles **330** by their reaction with 1,4-dithiane-2,5-diol **300**.[178] The reaction comprises thiol addition to the imine, followed by hemiaminal formation **329** between the resulting amine and the aldehyde and PCC oxidation of hemiaminal **329**. The reaction was catalysed by a bifunctional tertiary amine/squaramide catalyst **XLIV,** achieving the spirooxindoles in moderate yields (53-65%) and excellent enantioselectivities (90-97% ee, after oxidation of the hemiaminal to amide), with good functional group compatibility (Scheme 102).



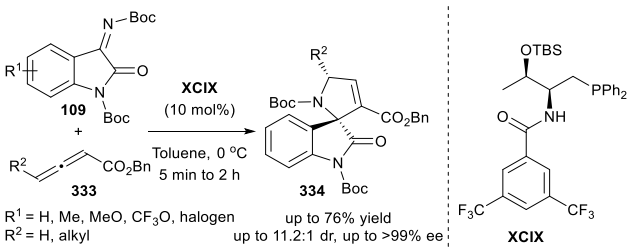
Scheme 102: Spirocyclization reported by Lu, Du, and Li

Isatin imines were also used in 1,3-dipolar cycloadditions to generate spirooxindoles.[179] Under chiral phosphoric acid (**LVI**) catalysis, aromatic aldehydes **184**, 2-aminomalonate **331**, and isatin imines **109** generated the spirooxindoles **332** in good yields (64-76%) and excellent stereoselectivities (>95:5 d.r. and up to 94% ee; Scheme 103).



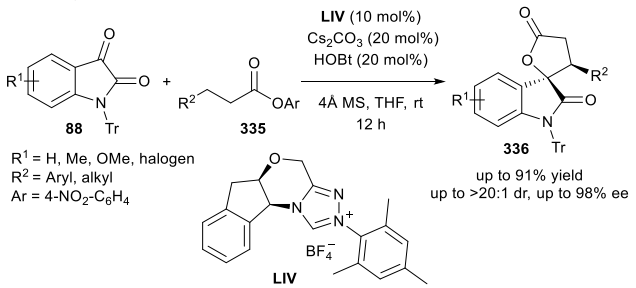
Scheme 103: Spirocyclization reported by Shi

Lu, Han *et al*. developed a [3+2] cycloaddition between *N*-Boc isatin imines **109** and allenoates **333**, catalysed by a phosphine catalyst **XCIX**.[180] The reaction starts with the addition of the phosphine to the allenoate, leading to the zwitterion intermediate. This acts as a dipole and undergoes a [3+2] cycloaddition with the alkylidene benzofuranone to afford the phosphorous ylide *via* a γ-addition or α-addition. Following intramolecular proton transfer and elimination, the spirooxindoles **334** were produced in good yields (56-81%) and diastereoselectivities (up to 9:1 d.r.), and excellent enantioselectivities (up to 99% ee; Scheme 104).



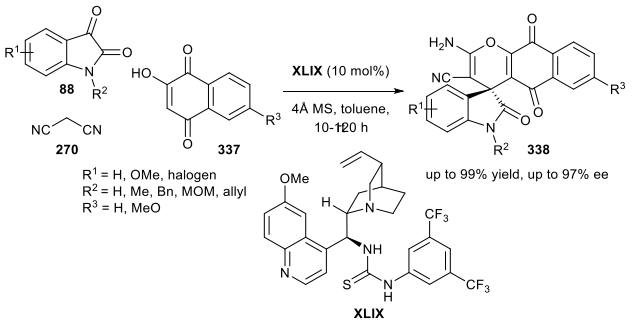
Scheme 104: Spirocyclization reported by Lu and Han

Aliphatic esters **335** were used with isatins **88** to generate spirooxindoles **336** under NHC catalysis.[181] The proposed mechanism starts with the addition of the NHC catalyst to the ester, using HOBt to generate the acyl azolium intermediate. Subsequent enolate formation and proton transfer led to the homoenolate intermediate. Next, the isatin undergoes a nucleophilic attack by this intermediate. This is followed by intramolecular lactonization to afford the spirooxindole in good yields (71-92%) and excellent stereoselectivities (>20:1 d.r. and 84-98% ee; Scheme 105). A similar reaction, comprising the use of *N*-hydroxybenzotriazole unsaturated esters was reported by Yao with similar results.[182] Almost simutaneously, Yao reported a similar reaction starting with saturated acids and isatins using NHC as the catalyst.[183] This was followed by the addition of the NHC catalyst to the *in situ*- formed activated ester (using HATU). This is followed by and subsequent nucleophilic attack on the isatin by the homoenolate formed via a proton transfer. Finally, intramolecular lactonization releases the NHC catalyst and form the spirocompounds in good yields (78-90%), excellent stereoselectivities (6:1 - 20:1 d.r. and 94-97% ee).



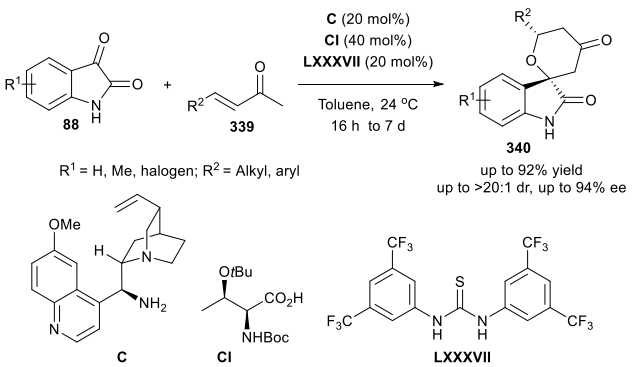
Scheme 105: Spirocyclization reported by Xu

A multicomponent reaction was developed by Zhao *et al.*[184] Isatins **88** react with malononitrile **270** and the resultant Michael acceptor reacts with 2-hydroxynaphthalene-1,4-diones **337** catalysed by a bifunctional thiourea/tertiary amine catalyst **XLIX**. The reaction renders the final spiro compounds **338** in good to excellent yields (81-99%) and enantioselectivities (81-97% ee; Scheme 106).



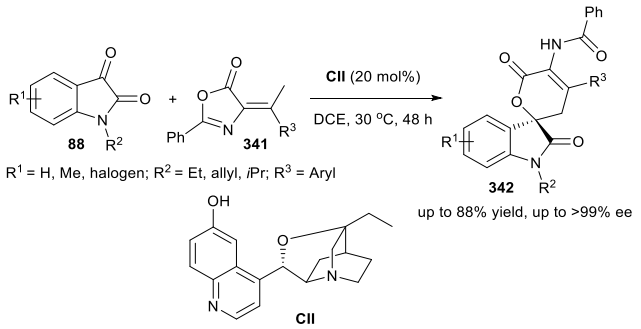
Scheme 106: Spirocyclization reported by Zhao

A different approach was developed by Tanaka in 2013 for the synthesis of spirooxindoles.[185,186] The fused ring **340** was generated with isatins **88** *via* a aldol-Michael cascade reaction of enones **339**, catalysed by **C**, **CI**, and **LXXXVII**. The formal hetero-Diels-Alder reaction starts with enamine formation between the catalyst and the enone (Scheme 107).



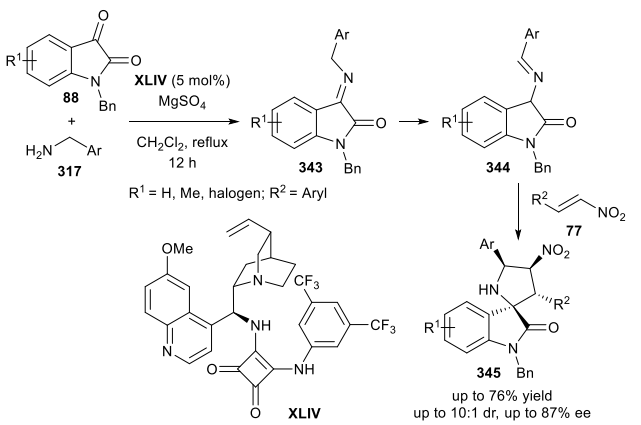
Scheme 107: Spirocyclization reported by Tanaka

Another hetero-Diels-Alder reaction with isatins was reported by Xu *et al.*[187] Isatins **88** react with olefinic azlactones **341**, catalysed by a bifunctional tertiary amine hydrogen bond catalyst **CII**. β-Isocupreidine (**CII)** forms the vinylogous enolate of the olefinic azlactone, while isatin is activated by hydrogen bonding between its carbonyl and the isocupreine 6-OH group. The subsequent [4+2] cycloaddition is followed by tautomerization and protonation to give the spirooxindoles **342** in good yields (69-83%) and excellent enantioselectivities (up to 99% ee; Scheme 108). A similar approach was reported by Han. This comprised the vinylogous addition of γ-H-bearing 3-alkylidene oxindoles to the isatins through an aldol-Michael cascade reaction.[188] The reaction was efficiently catalysed by bifunctional tertiary amine/squaramide catalyst with excellent yields (80-99%) and enantioselectivities (87-99% ee).



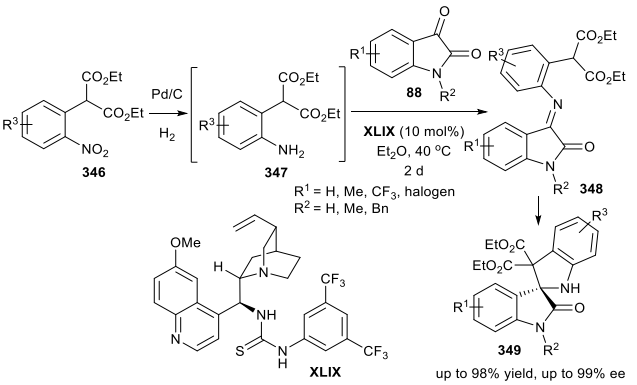
Scheme 108: Spirocyclization reported by Xu

Xu *et al*. developed a new multicomponent organocascade reaction (formal [3+2] cycloaddition) for the synthesis of spirooxindoles starting with isatins.[189] In their work, the first step was the formation of the imine **343** using isatin **88** and a primary amine **317**, followed by a [1,3]-proton shift **344** to generate the dipole. The subsequent organocascade reaction was catalysed by a bifunctional hydrogen bond/Brønsted base **XLIV** combination, where the previously generated dipole reacts with nitrostyrene to form the pyrrolidine ring **345** in good yields (up to 77%) and stereoselectivities (up to 11:1 d.r. and 87% ee; Scheme 109). Later, Zhao *et al*. employed the same strategy, using maleimides as the dipolarophile, with good results.[190]



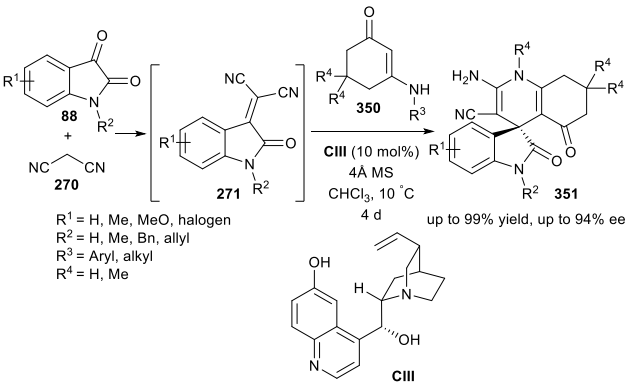
Scheme 109: Spirocyclization reported by Xu

Zhou *et al.* reported a triple relay catalysis cascade reaction starting with isatins for the synthesis of spirooxindoles.[191] The triple relay catalysis begins with the reduction of the nitrobenzene **346** by a palladium-catalysed hydrogenation. A ketimine **348** is then formed when the resulting amine **347** reacts with isatin **88**. Finally, 6π electrocyclization of **348** takes place to form the five-membered ring **349**. This final reaction is catalysed by a bifunctional thiourea/tertiary amine catalyst **XLIX**, which exhibits excellent enantioselectivities (up to 99% ee; Scheme 110).



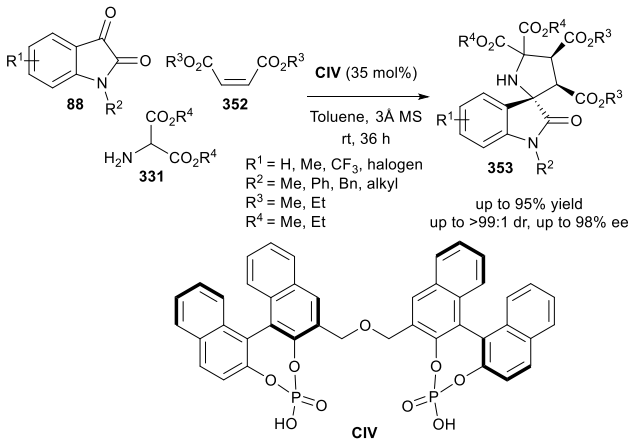
Scheme 110: Spirocyclization reported by Zhou

Shi *et al*. reported a multicomponent [3+3] cyclization, using cinchona alkaloid **CIII** as the catalyst for the enantioselective synthesis of spirooxindoles bearing a tetrahydroquinolin-3-one scaffold.[192] The reaction starts with the condensation of malononitrile **270** with isatin **88**. Next, enaminone **350** attacks the newly formed Michael acceptor **271** under base catalysis. This is followed by isomerization and intramolecular nucleophilic addition to form spiro compound **351** in moderate to excellent yields (43-99%) and high enantioselectivities (80-92% ee; Scheme 111).



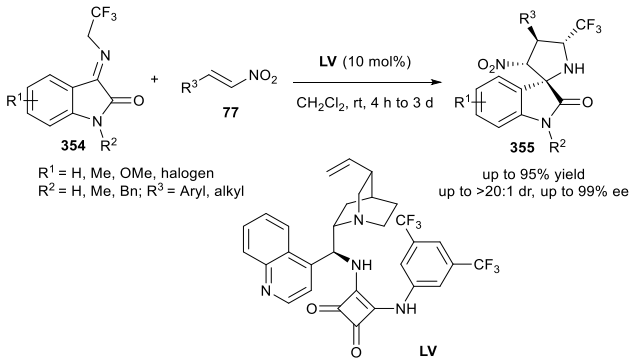
Scheme 111: Spirocyclization reported by Shi

Gong and Luo *et al*. reported a multicomponent 1,3-dipolar cycloaddition between isatins **88**, 2-amino malonates **331**, and maleates **352**, catalysed by chiral phosphoric acid **CIV**.[193] The reaction starts with the condensation of 2-aminomalonate with isatin to generate the dipole. This then reacts with the maleate, under acid catalysis, to generate the spirooxindole **353** in good yields (72-94%) and high stereoselectivities (>99:1 d.r. and 83-94% ee; Scheme 112). Inspired by this report, Shi and Tu *et al*. reported a similar reaction using alkynes and chiral phosphoric acids as the catalyst. This reaction also afforded good yields (69-99%) and high enantioselectivities (82-97% ee).[194] The same research group expanded this reaction by using alkylidene oxindoles instead of maleates with excellent results.[195]



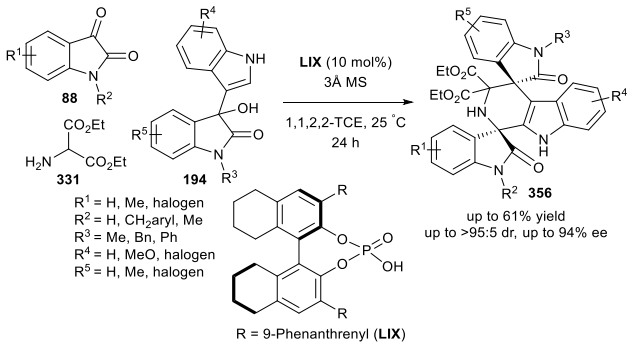
Scheme 112: Spirocyclization reported by Luo and Gong

Wang, Yan, and Wang *et al*. reported the 1,3-dipolar cycloaddition of nitroalkenes **77** with *N*-2,2,2-trifluoroethylisatin ketimines **354**, catalysed by a bifunctional tertiary amine/squaramide catalyst **LV**.[196] In the proposed mechanism, the ketimine reacts with a base to form the azomethine ylide. This then undergoes a [3+2] cycloaddition with β-nitroalkene, which is activated through hydrogen bonding by the squaramide moiety. The reaction exhibits good functional group tolerance and generates the corresponding spirooxindoles **355** in good yields (70-95%) and excellent stereoselectivities (up to >20:1 d.r. and >99% ee; Scheme 113). The same group reported near-identical reaction using enals as the counterpart and TMS-protected diphenylprolinol as the catalyst with excellent results.[197] Soon after, Yuan and Xu *et al*. reported a similar [3+2] cycloaddition between *N*-2,2,2-trifluoroethylisatin ketimines with 3-alkenyl-5-arylfuran-2(3*H*)-ones to afford spirooxindole derivatives.[198] The reaction was catalysed by a bifunctional thiourea/tertiary amine derived from cinchona alkaloids. The reaction tolerates several functional groups, including halogens and MeO, in the aromatic rings, achieving the final compounds in excellent yields (81-99%) and stereoselectivities (>20:1 d.r. and up to >99% ee).



Scheme 113: Spirocyclization reported by Yan, Kairong Wang, and Rui Wang

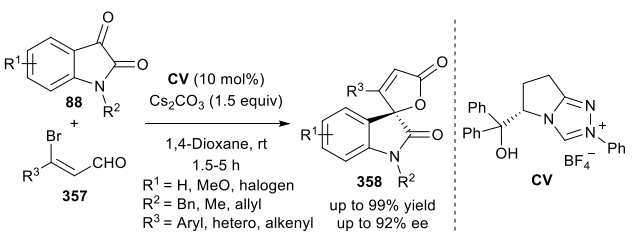
A multicomponent cascade reaction was reported by Shi *et al*.[199] Isatins **88** react with 2-aminomalonates **331** to form the dipole. This subsequently reacts with isatin-derived 3-indolyl methanol **194** in a Michael/Pictet-Spengler cascade reaction. The reaction furnished the spiro bis-oxindoles **356** in moderate yields (47-61%) and excellent stereoselectivities (up to >95:5 d.r. and 94% ee) when chiral phosphoric acid **LIX** was used as a catalyst (Scheme 114). Shi and Tu *et al*. reported a similar formal [3+3] cycloaddition between isatin-derived 3-indolyl methanol, aromatic aldehydes, and aminomalonate. This reaction was catalysed by chiral phosphoric acids to furnish the final spirooxindoles with good results.[200]



Scheme 114: Spirocyclization reported by Shi

A similar methodology, comprising the reaction of the same dipole formed by the condensation of isatin and aminomalonate with 2-cyclohexenone, was developed by Yang *et al*.[201] The formal 1,3-dipolar cycloaddition was catalysed by proline sulfonamide (Hua catalyst) to render the final spirooxindole in high yields (up to 95%) and excellent stereoselectivities (up to >20:1 d.r. and 99% ee). Shi *et al*. reported a similar multicascade reaction using allenes instead of cyclohexanones with good results.[202]

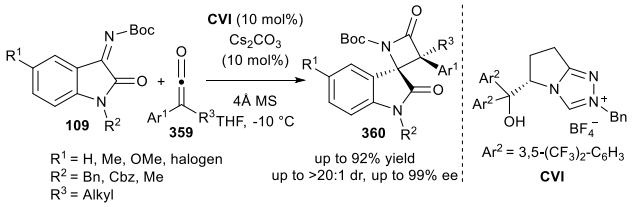
The reaction of isatins **88** with 3-bromoenals **357**, catalysed by NHC carbene **CV**, was reported by Ma *et al*. in 2014.[203] The asymmetric formal [3+2] cycloaddition furnished chiral spirooxindole-butenolides **358** in good yields (88-99%) and enantioselectivities (up to 92% ee). The NHC catalyst reacts with the enal, forming the Breslow intermediate, which undergoes nucleophilic addition to the isatin. Next, bromide elimination and *O*-acylation lead to the final spiro butenolide. Hui later expanded the scope of the reaction to *N*-Boc isatin imines (Scheme 115).[204]



Scheme 115: Spirocyclization reported by Ma

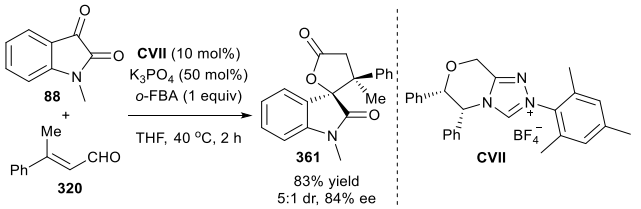
Almost simultaneously, Ye *et al*. reported a formal [2+2] cycloaddition between isatin imines **109** and ketenes **359**, catalysed by chiral NHC **CVI** with a free hydroxyl group.[205] The free hydroxyl in the NHC catalyst plays an important role in the Staundinger reaction, achieving high diastereo- and enantioselectivities. The reaction exhibits good group tolerance

and affords the oxindolo-β-lactams **360** in good yields (74-90%) and excellent stereoselectivities (up to >20:1 d.r. and 99% ee; Scheme 116).



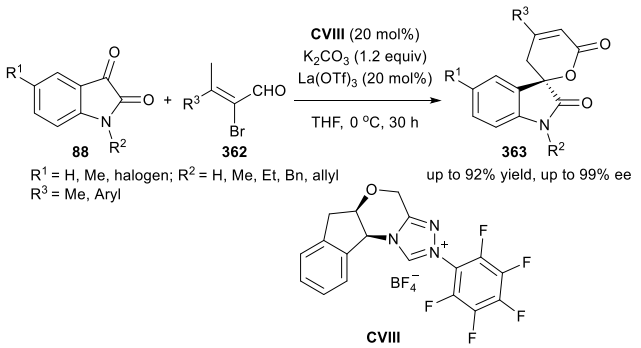
Scheme 116: Spirocyclization reported by Ye

Glorius *et al*. reported the NHC/Brønsted acid-catalysed reaction between isatins **88** with β,β-disubstituted enals **320** for the construction of spirooxindoles **361**; a single enantioselective example was reported.[206] The NHC catalyst **CVII** reacts with the enal to form the Breslow intermediate. The catalyst allows the reaction between the isatin and the Breslow intermediate *via* the presence of two stabilizing H-bonds. The subsequent intramolecular lactonization renders the final spirooxindole in good yield (83%) and good stereoselectivities (5:1 d.r. and 84% ee; Scheme 117).



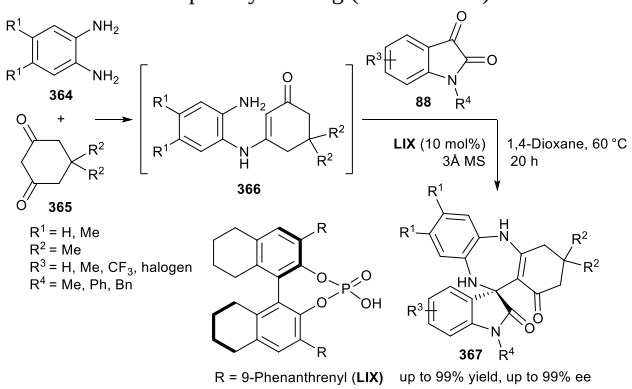
Scheme 117: Spirocyclization reported by Glorius

A similar reaction, based on the reaction of α-bromo-α,β-unsaturated aldehydes **362** with isatin derivatives **88** was reported by Yao *et al*. almost simultaneously.[207] The reaction was efficiently catalysed by a combined of Lewis acid / chiral NHC catalyst **CVIII** to afford the spirooxindole derivatives in good yields (71-92%) and enantioselectivities (85-99% ee). The proposed mechanism starts with the addition of the NHC catalyst to the 2-bromo-2-enal to form the Breslow intermediate. After debromination, the intermediate generates the vinyl enolate, which undergoes a nucleophilic addition to the isatin activated by the Lewis acid. Finally, lactonization releases the NHC catalyst and generates the spirooxindole **363**. A similar approach was reported by Liu *et al*. using simple enals.[208] The main difference was that his reaction required an oxidant to generate the γ-enolate (Scheme 118).



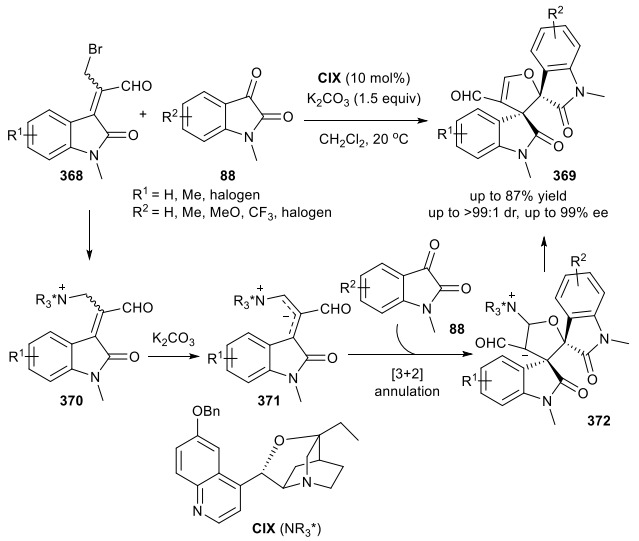
Scheme 118: Spirocyclization reported by Yao

Shi *et al*. developed the synthetic procedure for 3,3'-spirooxindoles fused with seven-membered rings, based on a tandem reaction.[209] Isatin **88**, 1,2-diamino benzene **364**, and 1,3 diketones **365**, catalysed by chiral phosphoric acid **LIX**, furnished the final spiro compounds **367** in moderate yields (19-83%) and high enantioselectivities (72-94% ee). The proposed mechanism starts with enamine formation from the reaction of 1,2-aminobenzene and 1,3-diketone. This is followed by imine formation with the other amino substituent in the benzene and the isatin. Finally, the intramolecular Mannich reaction, catalysed by phosphoric acid, produced the seven-membered spiro cyclic ring (Scheme 119).



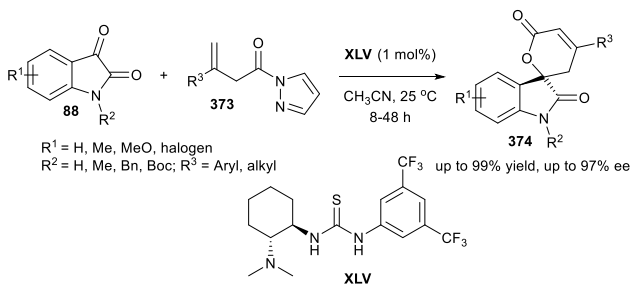
Scheme 119: Spirocyclization reported by Shi

Zhou *et al*. reported an organocascade reaction starting from isatins **88**, for the synthesis of spirooxindoles.[210] Isatin reacts with crotonaldehyde via the Morita-Baylis-Hillman (MBH) reaction. This is followed by bromination and finally, a [3+2] cycloaddition with another molecule of isatin or trifluoromethyl ketone derivative. The cascade reaction comprises three intermolecular reactions and involves two distinct catalytic steps that use the same catalyst **CIX**. The reaction allows the formation of spiro oxindoles **369** in moderate to good yields (44-83%), excellent enantioselectivities (90-99% ee), and good group tolerance (Scheme 120).



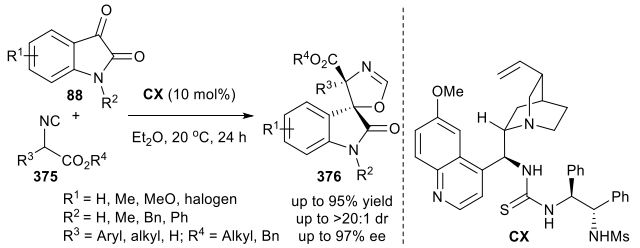
Scheme 120: Spirocyclization reported by Zhou

The reaction between allyl pyrazoleamides **373** with isatin **88** is efficiently catalysed by the Takemoto catalyst, to generate spirodihydropyranones in excellent yields (93-99%), high enantioselectivities (84-97% ee) with good group tolerance.[211] The mechanism comprises the activation of the allyl pyrazoleamides by the tertiary amine of the catalyst **XLV** to form the vinylogous enolate, which attacks the isatin activated by the thiourea moiety. Next, intramolecular lactonization produces the dihydropyranone derivatives **374** (Scheme 121).



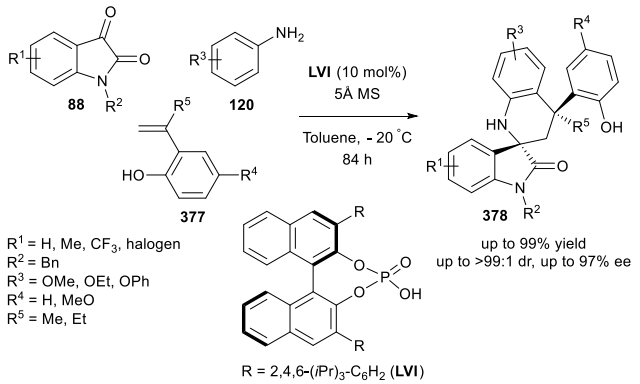
Scheme 121: Spirocyclization reported by Sha and Wu

Zhao and Shi *et al.* reported the combination of isocyanoacetates **375** with isatins **88** to generate spirooxindoles **376** in a highly enantioselective process.[212] The reaction begins with the addition of the isocyanate acetate to isatin, catalysed by a bifunctional tertiary amine/thiourea catalyst **CX**. In this step, the tertiary amine deprotonates the isocyanate, while the thiourea moiety activates the isatin through hydrogen bonding. Next, the formed enolate reacts with the isocyanate *via* a 5-*endo*-dig fashion to form the spiro compound in generally good yields (63-95%) and good to excellent stereoselectivities (up to 20:1 d.r. and 96% ee; Scheme 122). Later, the same research group developed a similar reaction using *N*-Boc isatin imines instead of isatins with similar results.[213]



Scheme 122: Spirocyclization reported by Zhao and Shi

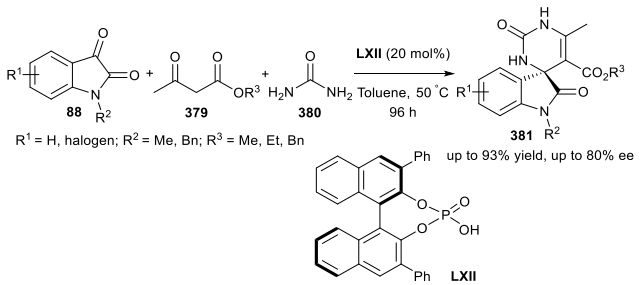
Shi and Tu *et al.* reported a multicomponent Povarov- type reaction between isatin **88**, aromatic amines **120**, and *o*-hydroxystyrenes **377**, catalysed by phopsphoric acid **LVI**.[214] The reaction afforded the spiropoxindoles **378** in excellent yields (70-99%) and diastereoselectivities (>99:1 in all examples), and good to excellent enantioselectivities (78-97% ee; Scheme 123).



Scheme 123: Spirocyclization reported by Shi and Tu

Isatines have been reacted with homophthalic anhydrides under thiourea/tertiary amine catalysis, to furnish 3,4-dihydroisocoumarin spirooxindoles in moderate to good yields (50-99%) and excellent stereoselectivities (>95:5 d.r. and 84-94% ee).[215]

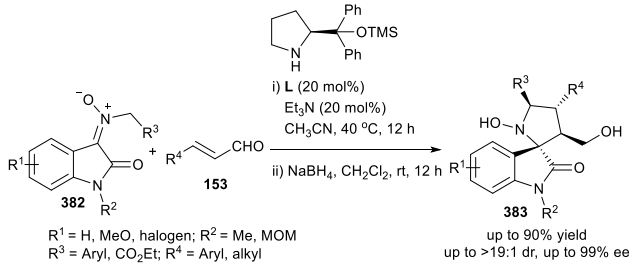
Silvani *et al.* developed a Biginelli-like reaction with isatines.[216] β-Ketoesters **379**, urea **380**, and isatine **88** were reacted, under chiral phosphoric acid (**LXII**) catalysis, to afford the spiropyrazolones **381** in moderate yields (49-93%) and enantioselectivities (50-80% ee) with limited reaction scope (Scheme 124).



Scheme 124: Spirocyclization reported by Silvani

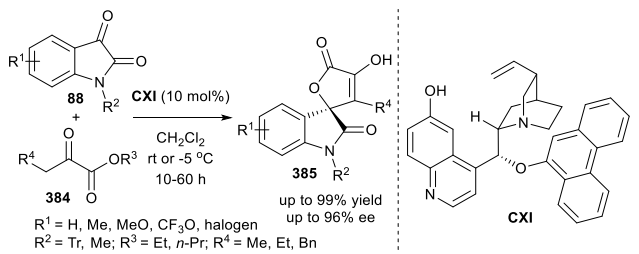
Nitrone ylides **382** derived from isatin were successfully used

for the formation of spirooxindoles through a [3+2] cycloaddition with enals **153**.[217] The reaction was catalysed by TMS-protected diphenylprolinol (**L**), to produce the spirooxindoles **383** in good yields (69-90%), total diastereoselectivities and excellent enantioselectivities (93-99% ee; Scheme 125).



Scheme 125: Spirocyclization reported by Chen and Du

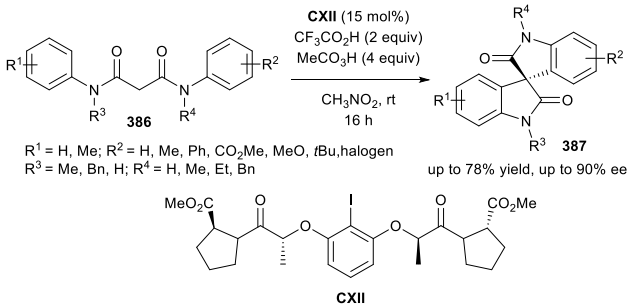
Spirooxindole-isotetronic acids have been synthesised by Liu and Li *et al*. through a cascade reaction: α-ketoesters react with isatin derivatives catalysed by a bifunctional Brønsted acid/tertiary amine catalyst **CXI**.[218] The reaction starts with the base- catalysed formation of the enolate of the α-ketoester **384**, which undergoes an aldol addition with the isatin **88**. This is followed by intramolecular lactonization to furnish the spirooxindole **385** in excellent yields (85-95%) and good enantioselectivities (77-96% ee). The 6'-OH group of the cinchona alkaloid catalyst plays an important role in the activity and stereocontrol of the reaction, through H-bonding with isatin carbonyl (Scheme 126).



Scheme 126: Spirocyclization reported by Liu and Li

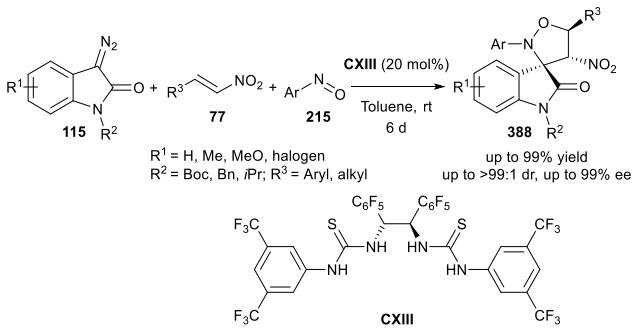
3.1.4 Organocatalytic methodologies for the synthesis of spiro oxindoles starting with other compounds

Gong *et al*. reported the synthesis of bis-spirooxindoles through an organocatalytic direct Csp^2-H/Csp^3-H oxidative cross coupling reaction using a chiral iodine reagent as the catalysts.[219] The *N1*,*N3*-diphenylmalonamides **386** undergoes an intramolecular C(sp^2)-H/C(sp^3)-H oxidative cross coupling reaction in the presence of chiral iodine reagent **CXII**, using the stoichiometric oxidant $MeCO_3H$. The reaction affords the bis-spirooxindoles **387** in moderate to good yields (40-78%) and high enantioselectivities (81-90% ee; Scheme 127). A similar approach was reported by Du *et al*., using 3-oxopentanedioate monoamide derivatives, leading to the final spiro compounds in good yields (up to 77%) and enantioselectivities (up to 91% ee).[220]



Scheme 127: Spirocyclization reported by Gong

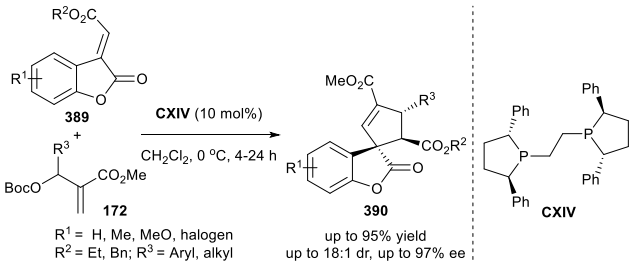
Another approach comprises the use of diazooxindoles **115** in a multicomponent cascade reaction. Dioazooxindoles undergo a nitrosoaldol reaction with nitrosobenzene **215** under H-bonding catalyst **CXIII**.[221] This is followed by an oxo-Michael addition to nitrostyrene **77** with subsequent intramolecular alkylation to build the spirooxindole **388** in good yields (57-99%) and excellent stereoselectivities (>99:1 d.r. and 90-99% ee; Scheme 128).



Scheme 128: Spirocyclization reported by Tan and Liu

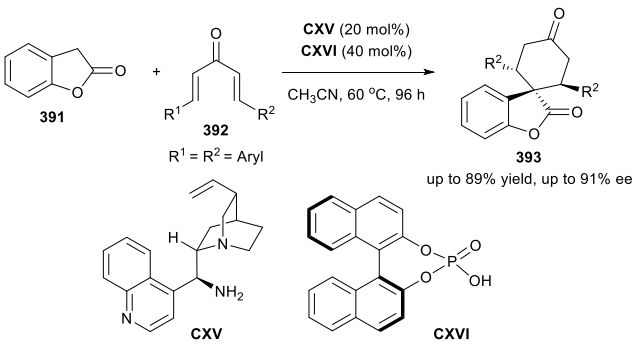
3.2 Organocatalytic methodologies for the synthesis of spirobenzofuranes

Barbas *et al*. reported a Diels-Alder reaction between MBH carbonates **391** and benzylidene benzofuranones **389**.[222] The diphosphine **CXIV** activates the MBH carbonate **172** through an S_N2' reaction, generating an allyl that undergoes a [3+2] cycloaddition with the alkylidene oxindole. The final benzofuranones **390**, bearing three stereocentres, were attained in good yields (86-95%), moderate to good diastereoselectivities (2:1-19:1 d.r.), and high enantioselectives (up to 95% ee; Scheme 129). Years later, Guo *et al*. reported a similar reaction using barbiturate-derived alkenes instead of benzylidene benzofuranones with similar results.[223]



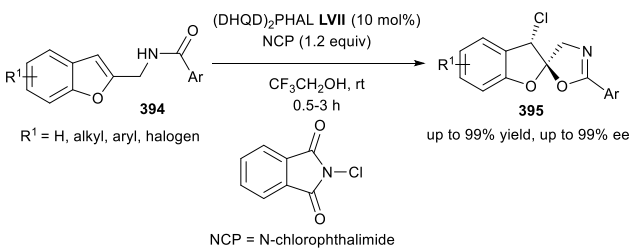
Scheme 129: Spirocyclization reported by Barbas

A double Michael addition between benzofuranones **391** and dienones **392**, using the Soos' catalyst **CXV**, was reported by Wang and Xu *et al*. for the synthesis of spirobenzofuranones **393** with good results (up to 89% yield, 20:1 d.r., and 91% ee).[224] Remarkably, high stereoselectivities was achieved when BINOL-derived phosphoric acid **CXVI** was added as additive (Scheme 130).



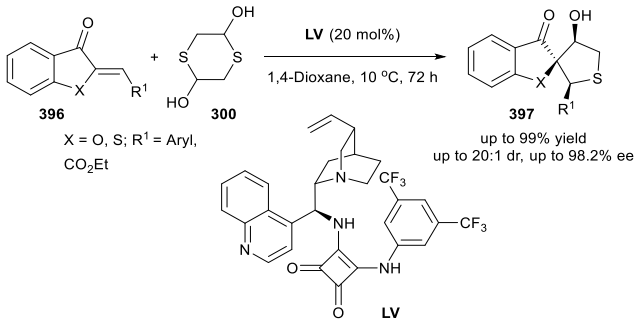
Scheme 130: Spirocyclization reported by Wang and Xu

You *et al*. reported an elegant chlorinative dearomatization of benzofurans to synthesise spirobenzofuranes with excellent stereoselectivities.[225] Benzofuranes **394**, bearing an amide in position 2, were reacted with *N*-chlorophthalimide (NCP), catalysed by Sharpless ligand **LVII**. The spirobenzofuranes **395**, which formed after intramolecular cyclization of the amide moiety, were afforded excellent yields (80-99%) and stereoselectivities (up to 99:1 d.r. and 99% ee; Scheme 131).



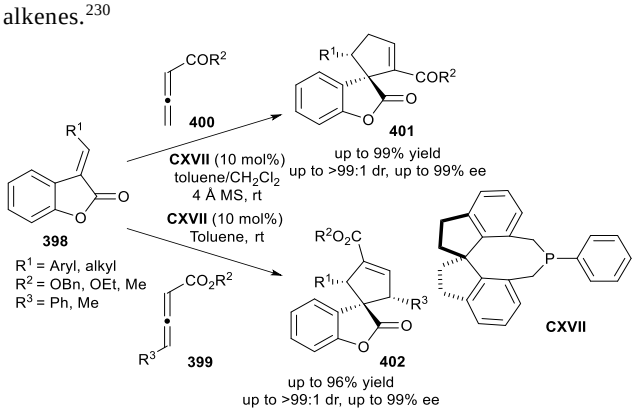
Scheme 131: Spirocyclization reported by You

Albrecht *et al*. reported the organocascade reaction of 2-arylidenbenzofuranones **396** (X = O) with 1,4-dithiane-2,5-diol **300** (form *in situ* 2-thioacetaldehyde) promoted by the bifunctional tertiary amine/squaramide catalyst **LV**.[226] The reaction was initiated by the thio-Michael addition of the thiol moiety, followed by an intramolecular aldol reaction to form the spiro benzofuranes **397** (X = O) in excellent yields (89-99%) and good stereoselectivities (up to 20:1 d.r. and 96% ee; Scheme 132). Almost simultaneously, Enders *et al*. reported the same reaction with 2-arylidene-1,3-indandiones,[227] while Du *et al*. reported the same reaction with cyclic enones.[228]



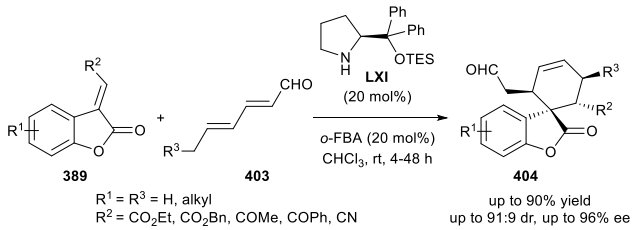
Scheme 132: Spirocyclization reported by Albrecht

Wei, Zhou, and Shi *et al*. developed a [3+2] cycloaddition between alkylidene benzofuranones **398** and allenoates **400**, catalysed by the phosphine catalyst **CXVII**.[229] The reaction starts with the addition of the phosphine to the allenoate leading to the zwitterion intermediate. This acts as a dipole and undergoes a [3+2] cycloaddition with the alkylidene benzofuranone to afford the phosphorous ylide via a γ- or α-addition. The subsequent intramolecular proton transfer and elimination afforded the two regioisomeric spirobenzofuranones **401** and **402**. The reaction is controlled by the nature of the allenoate: terminal allenoates undergo a γ-addition while Ph-substituted allenoates undergo an α-addition. In both cases, the final spiro compounds were afforded in good yields (68-99%) and excellent reagio-, diastereo-, and enantioselectivities (up to 99:1 r.r., 99:1 d.r., and 99% ee; (Scheme 133). A similar reaction was reported years later by Zhou and Guo *et al*. using barbiturate-derived alkenes.[230]



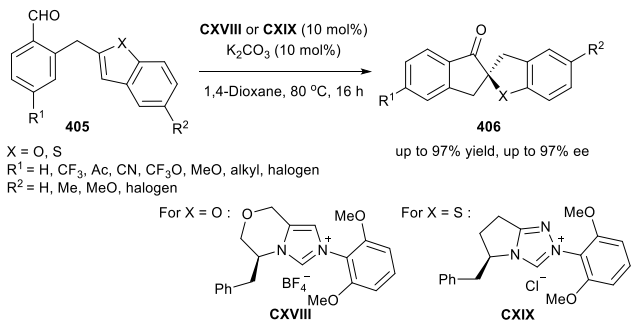
Scheme 133: Spirocyclization reported by Wei, Zhou, and Shi

A Diels-Alder reaction between alkylidene benzofuranes **389** and polyenals **403** was reported by Li and Cheng *et al*.[231] Polyenals react with **LXI** to form the trienamine. This then undergoes [4+2] cycloaddition with the alkylidene benzofurane to afford the spirobenzofuranes **404** in good yields (72-90%) and stereoselectivities (up to 91:9 d.r. and 91-96% ee; Scheme 134).



Scheme 134: Spirocyclization reported by Li and Cheng

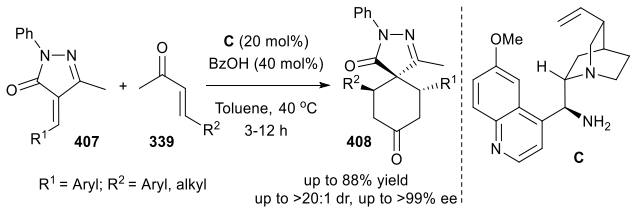
A NHC-catalyzed dearomatizating hydroacylation for the synthesis of spirobenzofuranes was reported by Glorius *et al*. in 2016.[232] In this work, benzo(thio)furanes **405** (X = S) decorated with a benzyl 2-carbaldehyde react with the NHC catalyst **CXIX** and undergo a 5-*exo*-trig cyclization to form spiro benzo(thio)furanes **406** (X = S) in good yields (55-92%) and excellent enantioselectivities (78-97% ee; Scheme 135).



Scheme 135: Spirocyclization reported by Neugebauer and Glorius

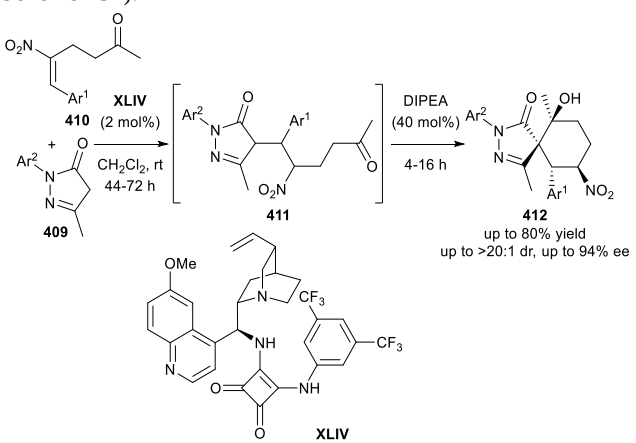
3.3 Organocatalytic methodologies for the synthesis of spiropyrazolones

A double Michael cascade reaction was developed by Wang *et al*. for the synthesis of spiropyrazolones.[233] Enones **339** were reacted with unsaturated pyrazolones **407** under primary amine catalysis. First, the primary amine derived from a cinchona alkaloid (**C**) forms the dienamine intermediate with the enone, which subsequently undergoes a Michael addition with the unsaturated pyrazolone. Next, intramolecular Michael addition with the *in situ* formed enolate and the enone in its iminium form, delivers the spiro-pyrazolone **408** in good yields (55-88%) and excellent stereoselectivities (up to 20:1 d.r. and 99% ee). Almost simultaneously, another Wang's group reported the same reaction using a combination of Soos' catalyst and 2-fluorobenzoic acid as cocatalyst with excellent results (Scheme 136).[234] The same reaction using 2-arylidene-1,3-indandiones was developed later.[235]



Scheme 136: Spirocyclization reported by Wang

Chen *et al*. developed a Michael-aldol cascade reaction between pyrazolones **409** and nitroalkenes **410** decorated with an alkyl chain bearing a ketone in the β-position.[236] The reaction is catalysed by a bifunctional tertiary amine/squaramide **XLIV** combination and comprises a Michael addition of the pyrazolone to the nitroalkene followed by an intramolecular aldol reaction catalysed by a base. The resulting spiro- pyrazolones **412** were produced in moderate yields (40-80%) and excellent stereoselectivities (up to 20:1 and 94% ee; Scheme 137).

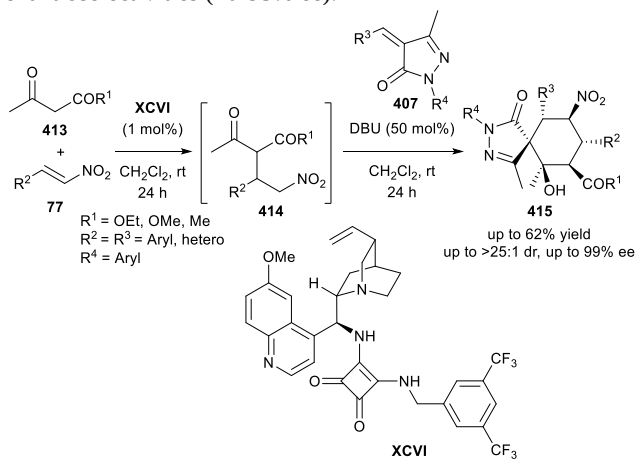


Scheme 137: Spirocyclization reported by Chen

Unsaturated pyrazolones reacted with allenoates under phosphine catalysis to afford spiropyrazolones in good yields (64-97%), moderate diastereoselectivities (up to 78:22 d.r.), and excellent enantioselectivities (89-94% ee) through a [4+2] cycloaddition.[237]

Enders *et al*. reported a multicascade Michael/Michael/aldol reaction for the construction of six vicinal stereogenic centres on spiropyrazolones.[238] The reaction starts with the addition of β-dicarbonyl compounds **413** to nitroalkenes **77**, promoted by a bifunctional tertiary amine/squaramide catalyst **XCVI**. Next, the resulting nitro compound **414** undergoes a Michael addition with the unsaturated pyrazolone **407** and the *in situ* formed enolate attacks the ketone moiety intramolecularly to afford the spiro pyrazolone **415** in moderate yields (53-62%) and excellent stereoselectivities (99% ee, only one diastereomer; Scheme 138). Soon after, Xie *et al*. reported a similar reaction employing enals instead of nitrostyrene.[239] The main difference in the mechansim was that the ketoester first reacts with the unsaturated pyrazolone promoted by the bifunctional thiourea/tertiary amine catalyst. This was followed by the cascade Michael/aldol reaction with the enal, promoted by piperidine. The final spiro compounds were produced as a single diastereomer in good yields (43-85%) and

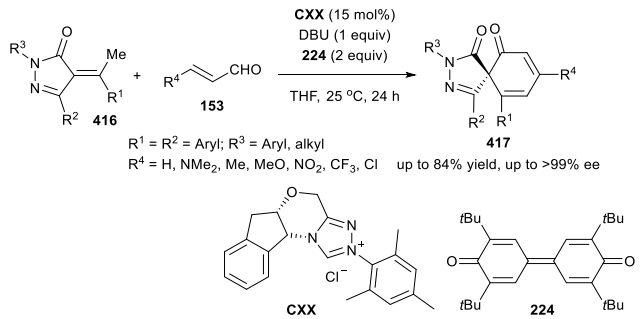
enantioselectivities (70-95% ee).



Scheme 138: Spirocyclization reported by Enders

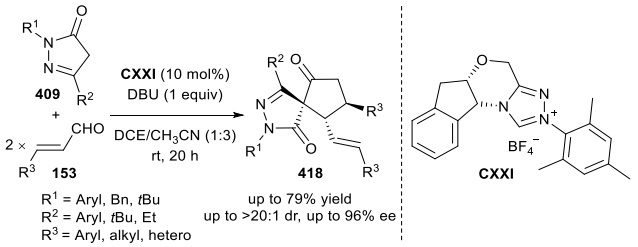
A similar multicomponent Michael-Michael-aldol cascade reaction for the formation of spiropyrazolones was reported by Peng *et al*. in 2015.[240] Aliphatic aldehydes undergo a Michael addition with nitrostyrenes under secondary amine catalysis to afford the nitroaldehyde. This then undergoes a Michael-aldol cascade reaction with the unsaturated pyrazolones, rendering the spiropyrazolones in moderate yields (30-70%) and excellent stereoselectivities (up to 92:8 d.r. and 93-95% ee).

A [3+3] cycloaddition has been reported between unsaturated pyrazolones **416** bearing a γ-hydrogen and enals **153**. The reaction is catalysed by the NHC catalyst **CXX**.[241] and starts with the formation of the Breslow intermediate between the enal and the NHC catalyst. This is followed by oxidation of the Breslow intermediate, with quinone **224** as the oxidant. Next, the dienolate intermediate, generated by α-arylidene pyrazolinone, under basic conditions, undergoes a vinylogous Michael addition to the α,β-unsaturated acyl azolium salt. The subsequent intramolecular proton transfer generates the acylazolium and finally, intramolecular alkylation leads to spiro compound **417** and the release of the NHC catalyst. The spiropyrazolones are synthesised in good yields (50-77%) and excellent enantioselectivities (94-99% ee; Scheme 139).



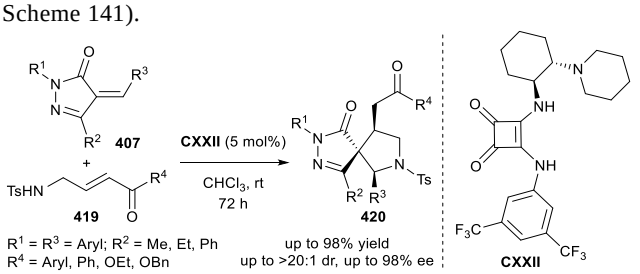
Scheme 139: Spirocyclization reported by Biju

Enders *et al*. reported a three-component aldol/NHC-catalysed annulation cascade reaction for the synthesis of spiropyrazolones. The reaction was catalysed by chiral NHC **CXXI**.[242] The proposed mechanism consists of a base-catalysed aldol reaction between the pyrazolone **409** and enal **153** to form the diene product after dehydration. On the other hand, the enal reacts with the NHC catalyst to form the Breslow intermediate, which undergoes a Michael/cyclization reaction with the previously formed diene, to afford the spiropyrazolones **418** in moderate yields (52-79%), excellent diastereoselectivities (up to 20:1 d.r.), and high enantioselectivities (76-94% ee; Scheme 140).



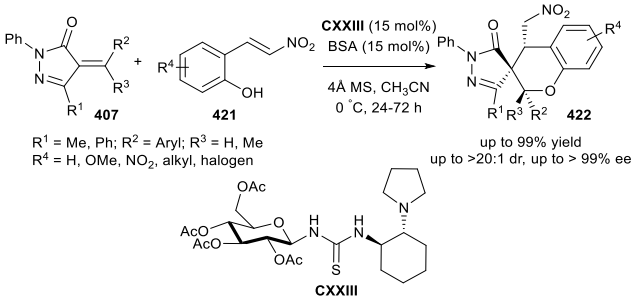
Scheme 140: Spirocyclization reported by Enders

Unsaturated pyrazolones **407** react with enones **419** decorated with an *N*-tosyl amine to build spiropyrazolones **420** under bifunctional tertiary amine/squaramide catalysis.[243] The reaction starts with an aza-Michael reaction between the tosylamine and the unsaturated pyrazolone. This is followed by an intramolecular Michael reaction between the *in situ* formed enolate of the pyrazolone and the enone, achieving the final spiro compounds in generally good yields (49-98%), total diastereoselectivity, and high enantioselectivities (71-98% ee; Scheme 141).



Scheme 141: Spirocyclization reported by Du

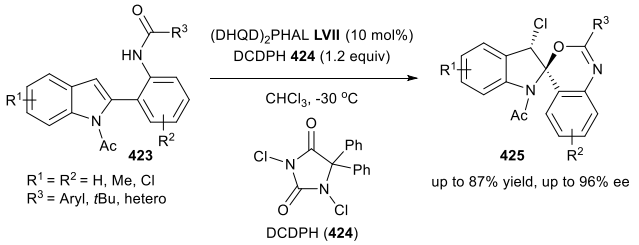
Another approach for the synthesis of spiropyrazolones, comprising the reaction between *o*-hydroxynitrostyrenes **421** and alkylidene pyrazolones **407** was reported by Miao *et al*.[244] The reaction is promoted by the bifunctional thiourea/tertiary amine catalyst **CXXIII**, affording the spiro compounds **422** *via* an oxo-Michael/ intramolecular Michael addition in excellent yields (83-99%) and enantioselectivities (up to 99% ee), but moderate diastereoselectivities (up to 5:1 d.r.; Scheme 142).



Scheme 142: Spirocyclization reported by Miao

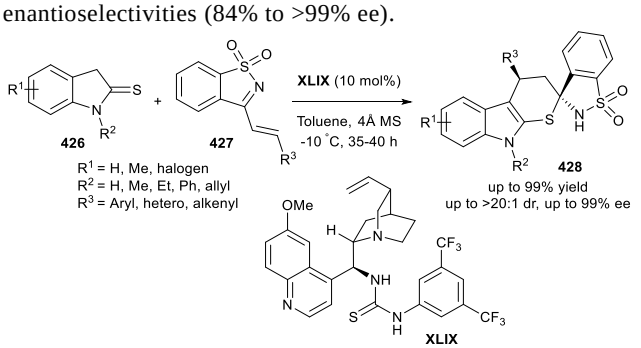
3.4 Organocatalytic methodologies for the synthesis of indoles

The synthesis of spiroindolines, mediated by the enantioselective chlorocyclization of indoles, has been reported.[245] Indole-derived benzamides **423** reacted with 1,3-dichloro-5,5-diphenylhydantoin (DCDPH, **424**) promoted by the Sharpless ligand **LVII**, to generate the chloro-spiroindoline **425** in good yield (70-90%) and excellent enantioselectivities (up to 96% ee; Scheme 143).



Scheme 143: Spirocyclization reported by You

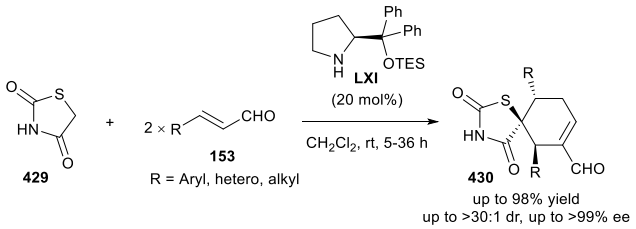
Wang and Zhou *et al.* reported the construction of spirothiopyranoindole derivatives by a formal [3+3] cascade reaction.[246] Thioindoles **426** reacted with 1-azadienes **427** *via* a Michael reaction, promoted by a bifunctional tertiary amine/thiourea catalyst **XLIX**. This is followed by intramolecular thio-acetal formation, leading to the formation of the spiroindoline derivatives **428** in excellent yields (82-99%), total diastereoselectivity, and good to excellent enantioselectivities (74-99% ee) with excellent substrate scope (Scheme 144). One year later, Ye *et al.* developed a similar reaction using enones instead of 1-azadienes.[247] The reaction was catalysed by chiral primary amines in moderate yields (50-72%) and diastereoselectivities (3:1-19:1 d.r.), and excellent enantioselectivities (84% to >99% ee).



Scheme 144: Spirocyclization reported by Zhou and Wang

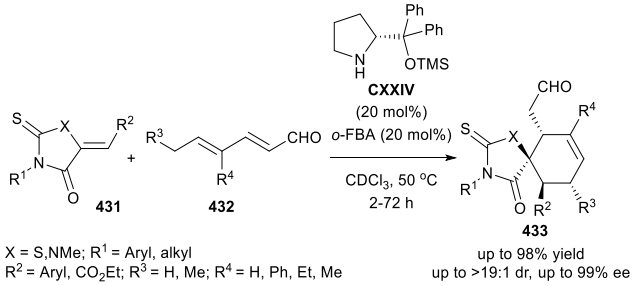
3.5 Organocatalytic methodologies for the synthesis of other spirocycles

A double Michael/aldol organocascade, similar to the ones reported by Rios and Melchiorre, were used by Wang, Zhang and Sheng *et al.* for the synthesis of spirothiazolidinedione derivatives.[248] The reaction between thiazolidinediones **429** and enals **153** was efficiently catalysed by TES-protected diphenyl prolinol **LXI**, affording the spiro compounds **430** in good yields (44-96%) and diastereoselectivities (up to 30:1 d.r.) , and in an enantiopure form (Scheme 145).



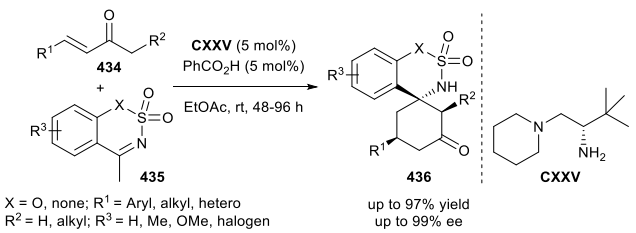
Scheme 145: Spirocyclization reported by Zhang, Sheng, and Wang

Ye *et al.* reported the reaction of 2,4-dienals **432** with unsaturated rhodanines **431** (X = S) or hydantoines, for the synthesis of spiro compounds **433**.[249] The formal Diels-Alder cyclization was catalysed by the Jørgensen-Hayashi catalyst **CXXIV** *via* a trienamine intermediate, affording the spirocompounds in good yields (64-98%) and excellent diastereo- and enantioselectivities (up to 19:1 d.r. and 99% ee; Scheme 146). A similar reaction was reported by the same research group, using enones instead of dienals and primary amine as the catalyst, achieved similar results.[250]



Scheme 146: Spirocyclization reported by Ye

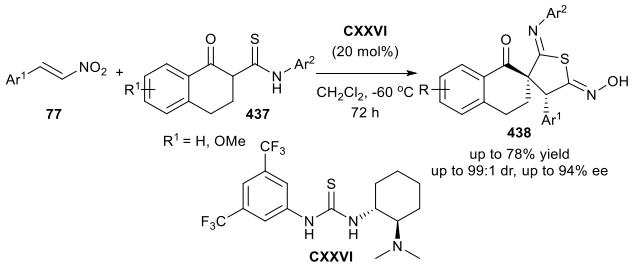
Cyclic sulfonyl imines **435** reacted with enones **434** *via* a Michael-Mannich cascade reaction leading to the spiro compounds **436** in good yields (81-90%) and excellent enantioselectivities (95-97% ee) under primary amine catalysis.[251] The reaction starts with the formation of the sulfonyl enamine, which attacks the conjugate iminium intermediate. This is followed by an intramolecular Mannich reaction (Scheme 147). The authors also developed the same reaction using methylene chromenes with moderate yields (46-60%) and good enantioselectivities (84-90% ee).



Scheme 147: Spirocyclization reported by Ye

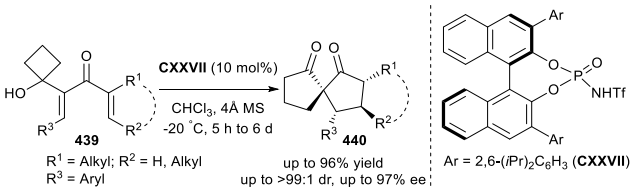
Xie *et al.* reported the synthesis of spirodihydrothiophenes.[252] Nitrostyrenes **77** react with ketothioamides **437** in a Michael

addition promoted by Takemoto's catalyst **CXXVI**. Next, nucleophilic attack by the sulfur atom on the α-carbon atom of the nitro group leads to the final spiro products **438** in moderate yields (55-78%), excellent diastereoselectivities (up to 99:1 d.r.), and high enatioselectivities (82-94% ee; Scheme 148).



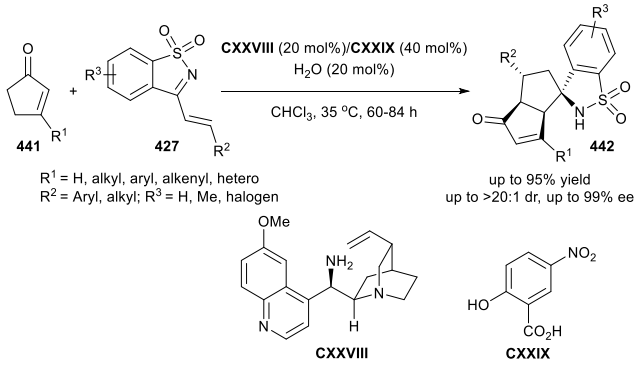
Scheme 148: Spirocyclization reported by Xie

An organocatalystic asymmetric tandem Nazarov cyclization/semipinacol rearrangement was reported for the easy synthesis of chiral spiro[4.4]nonane-1,6-diones.[253] The 1,4-dien-3-ones **439**, decorated at the α-position with a cyclobutanol motif, reacted under the chiral acid catalyst **CXXVII** to form the oxoallyl intermediate typical of the Nazarov reaction. This induces a semipinacol rearrangement with the hydroxy cyclobutane motif, affording the spiro compound **440** in good yields (72-92%) and excellent stereoselectivities (up to 99:1 d.r. and 97% ee; Scheme 149).



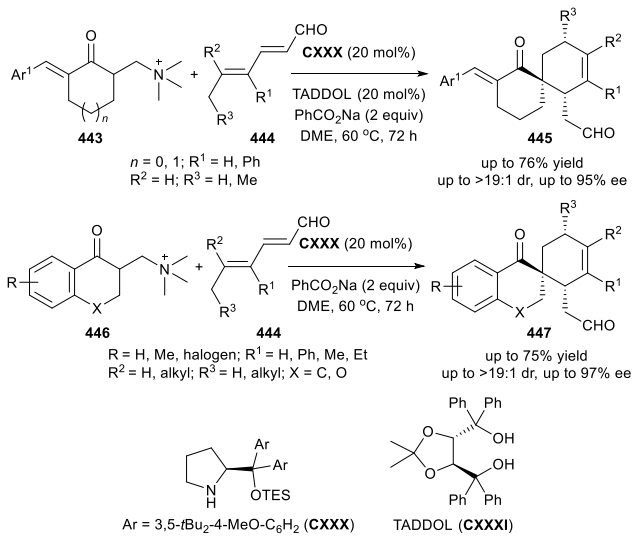
Scheme 149: Spirocyclization reported by Tu

Chen and Gao *et al*. reported the reaction between 1-azadienes **427** and cyclic pentenones **441**, catalysed by the primary amine **CVII** via a dieneamine/dienamine cascade reaction.[254] 3-Arylcyclopentenones form the cross conjugated dienamine when treated with a chiral primary amine **CXXVIII** and Brønsted acid (**CXXIX**). The dienamine then reacts with the 1-azadiene *via* a Michael addition. Subsequently, formation of the endo-type dienamine in the cyclopentenone, followed by intramolecular Mannich addition render the spiro compounds **442** in good yields (58-95%), total diastereoselectivity, and excellent enantioselectivities (up to 99% ee). The reaction require the use of an acid to achieve high enantioselectivities. When cyclohexene derivatives were used, a bridged [5+3] product was produced in low yields and enantioselectivities. A formal [3+3] cascade reaction between the ketones and 1-azadienes was reported by the same research group for the synthesis of spiro compounds.[255] The reaction comprises the activation of the ketone in its enamine form by chiral primary amines. The enamine undergoes a Michael addition with the 1-azadiene, followed by intramolecular 1,2- addition to furnish the spiro ring in good yields (62-88%) and excellent enantioselectivities (89-99% ee; Scheme 150).



Scheme 150: Spirocyclization reported by Chen and Gao

Trienamine activation has been used in conjunction with the methyliodide salts of Mannich bases for the synthesis of spirocycles.[256] Dienals **444** react with **CXXX** forming the trienamine. This undergoes a *exo*-Diels-Alder reaction with the methyliodide salt of the Mannich base **443**, which previously undergoes elimination, to furnish the enone. The final spirocycles **445** and **447** were synthesized with reasonable group compatibility in moderate yields (41-72%), excellent diastereoselectivities (up to 19:1 d.r.), and high enantioselectivities (83-96% ee). For some substrates, 20 mol% TADDOL **CXXXI** must be added to achieve good conversions through the H-bonding activation of the dienophile (Scheme 151).

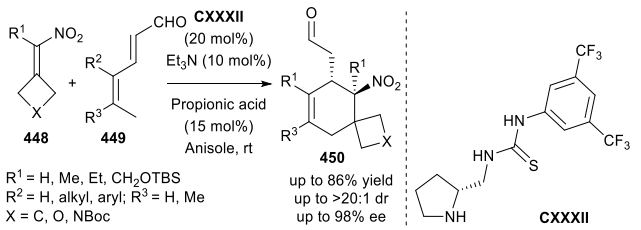


Scheme 151: Spirocyclization reported by Chen

Another example of trienamine catalysis was developed by Albrecht.[257] In this process, dienals reacted with (*E*)-3-alkylidene-5-arylfuran-2(3H)-ones in a [4+2] Diels-Alder reaction using TES-protected diphenylprolinol as the catalyst. The construction of the spirocyclic butenolides was achieved with moderate yields (28-65%) and diastereoselectivities (up to 3:1 d.r.), and excellent enantioselectivities (89-99% ee).

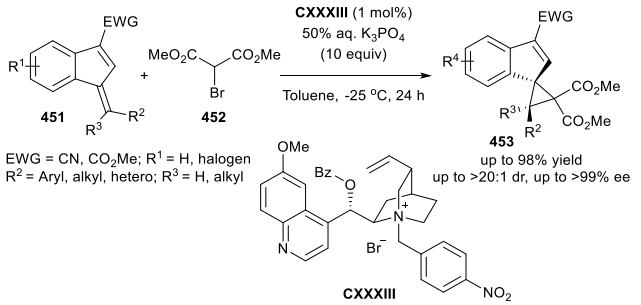
Jørgensen *et al*. developed a procedure for the synthesis of spiro compounds via a formal Diels-Alder reaction based on trienamine chemistry.[258] Thus, α,β,β-trisubstituted nitroolefins

448 reacted with 2,4-dienals **449**, promoted by a bifunctional secondary amine/thiourea catalyst **CXXXII**, to afford the spirocompounds **450** in good yields (61-82%) and excellent stereoselectivities (up to 20:1 d.r. and 96% ee; Scheme 152). The same research group developed another spiro reaction using trienamine catalysis with benzofulvenes with similar results.[259]



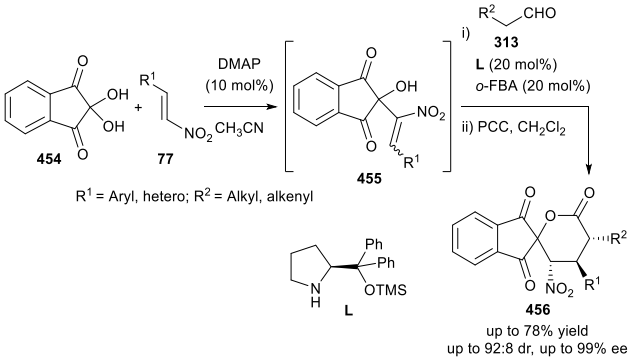
Scheme 152: Spirocyclization reported by Jørgensen

Benzofulvenes were also used with bromo-malonates **452** to generate spirocyclopropanes **453**, under the chiral phase-transfer catalyst **CXXXIII**, *via* a Michael/intramolecular alkylation sequence.[260] The reaction afforded excellent yields (88-98%) and diastereoselectivities (up to 20:1 d.r.), and good enantioselectivities (68-98% ee). The authors also attempted the reaction with 2-bromoketoesters; however, lower yields and enantioselectivities were recorded (Scheme 153).



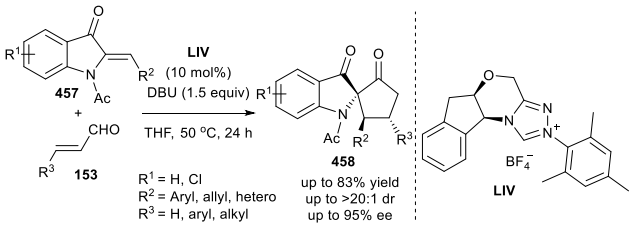
Scheme 153: Spirocyclization reported by Jørgensen

Han and Huang *et al*. reported the synthesis of spiroindanones based on a one-pot cascade reaction between oxoindanones **454**, nitrostyrenes **77**, and aliphatic aldehydes **313**, catalysed by DMAP and diphenyl prolinol derivative **L**.[261, 262] The reaction proceeds *via* the Morita-Bailys-Hillman/Michael/hemi-acetal formation, affording the final spiroindanones in good yields (60-78%) and excellent stereoselectivities (up to 92:8 d.r. and 99% ee; Scheme 154).



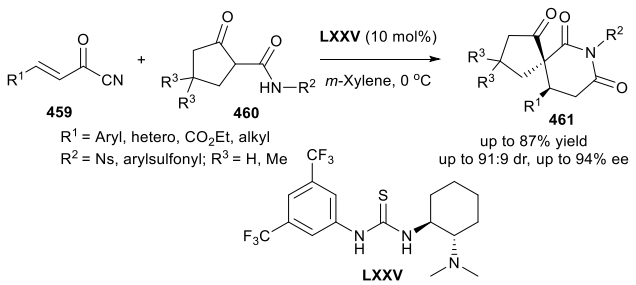
Scheme 154: Spirocyclization reported by Han and Huang

Glorius *et al*. reported the synthesis of spirocylces **458** through a formal [3+2] cycloaddition between unsaturated aza-aurones **457** and enals **153**, catalysed by the chiral NHC catalyst **LIV** with good yields (58-77%) and good diastereoselectivities (up to 17:1 d.r.), and enantioselectivities (up to 95% ee).[263] The proposed mechanism comprises the formation of the NHC-homoenolate from the enal and the NHC catalyst, which leads to a 1,4-addition to the azaaurone. Next, intramolcular alkylation of the acyl azolium intermediate leads to the formation of the spirocycle and the release of the catalyst (Scheme 155).



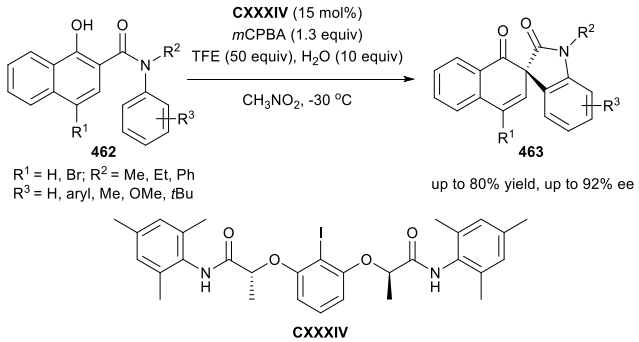
Scheme 155: Spirocyclization reported by Glorius

Bonne and Rodriguez *et al*. reported the synthesis of spirolactams **461** based on the reaction of cyclic ketoamides **460** with α,β-unsaturated acyl cyanides **459**.[264] 1,3-Cyclic ketoamides undergo a Michael addition with unsaturated acyl cyanides, catalysed by bifunctional tertiary amine/thiourea **LXXV**. This is followed by intramolecular nucleophilic displacement of the cyanide by the amide moiety, through a formal [3+3] spiroannulation. The spirolactames were afforded in good yields (73-82%) and stereoselectivities (up to 91:9 d.r. and 94% ee; Scheme 156). Years later, Rios and Vesely *et al*. reported a similar reaction catalysed by secondary amines, using enals instead of α,β-unsaturated acyl cyanides, and with similar results.[265]



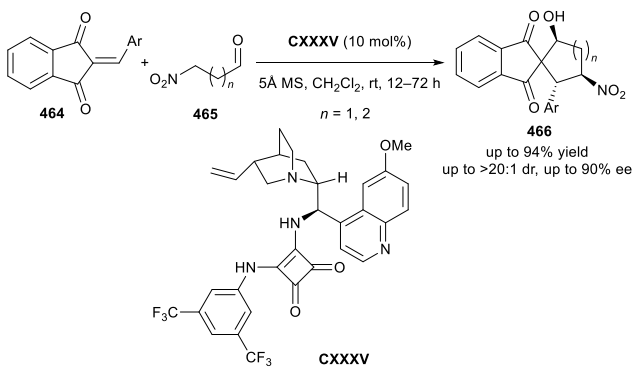
Scheme 156: Spirocyclization reported by Rodriguez and

Chiral hypervalent iodines **CXXXIV** promote the oxidative dearomatizing spirolactonization of naphthols bearing a carboxylic acid on the side chain.[266, 267] The reaction requires *m*CPBA as a stoichiometric oxidant and affords the spiro compounds in good yields (52-94%) and enantioselectivities (85-92% ee). Years later, Gong *et al*. reported a similar reaction using 1-hydroxy-*N*-aryl-2-naphthamide derivatives **462**, affording the spiro compounds **463** in moderate to good yields (42-80%) and high enantioselectivities (80-91% ee; Scheme 157).[268]



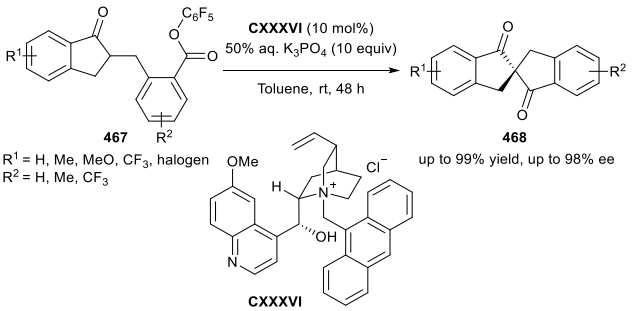
Scheme 157: Spirocyclization reported by Gong

2-Arylideneindane-1,3-diones **464** reacted with nitroadehydes **465** in a Michael-aldol reaction to render spiroindanones **466**.[269] The reaction was promoted by the bifunctional squaramide/Brønsted base catalyst **CXXXV**, affording the [5,6,0]spirocycles in good yields (up to 84%) and stereoselectivities (up to 20:1 d.r. and 88% ee). Using the same approach, [5,5,0]spirocycles were produced with near-identical results (Scheme 158). The same research group also reported a similar cascade reaction using 4-mercapto-2-butenoates with similar results.[270]



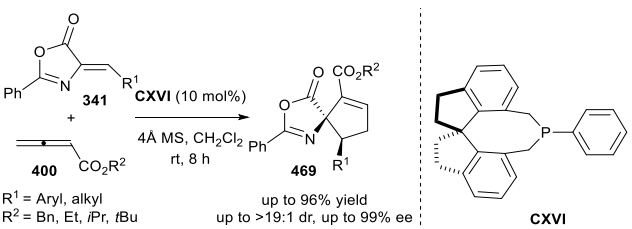
Scheme 158: Spirocyclization reported by Li

Another approach for the synthesis of spirobiindanones was reported by Smith *et al*.[271] In this approach, the key step is an intramolecular C-acylation. Taking advantage of the good leaving group (OC_6F_5), the formed enolate attacks the ester, catalysed by a chiral ammonium salt **CXXXVI**, to afford the spiro indanones **468** with excellent yields (94-99%) and enantioselectivities (84-98% ee; Scheme 159).



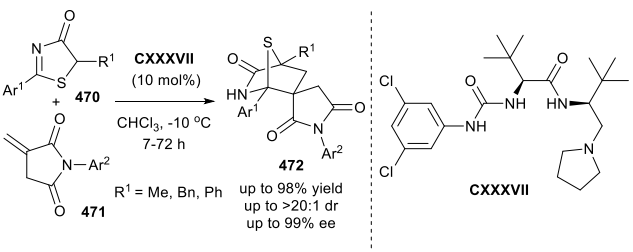
Scheme 159: Spirocyclization reported by Smith

Shi *et al*. reported the synthesis of spiroazalactones, comprising the [3+2] annulation of allenoates **400** with alkylidene azlactones **341**, catalysed by chiral phosphines.[272] The proposed mechanism starts with the addition of the chiral phosphine **CXVI** to the allene, followed by γ attack of the formed dipole on the azalactone in a Michael addition. Next the *in situ*-formed enolate reacts intramolecularly *via* Michael addition. After elimination of the phosphine, the final spiro compounds bearing consecutive quaternary and tertiary stereocentres, are formed in good yields (65-96%) and excellent stereoselectivities when aryl-derived unsaturated azalactones are used, while lower values were observed when aliphatic substituents were employed (up to 19:1 d.r. and 99% ee; Scheme 160). A similar reaction was reported by Marinetti *et al*. in 2012, employing dienones instead of unsaturated azlactones with similar results.[273]



Scheme 160: Spirocyclization reported by Shi

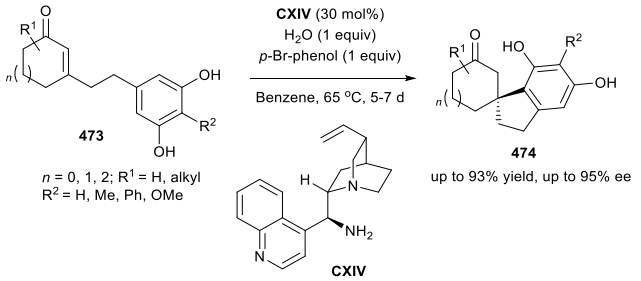
A formal Diels-Alder reaction between 5*H*-thiazol-4-ones **470** and *N*-itaconimides **471** was reported by Jiang and Tan *et al*.[274] The reaction is efficiently catalysed by **CXXXVII**, affording the corresponding spiro compounds **472** in excellent yields (81-96%) and enantioselectivities (90-99% ee; Scheme 161).



Scheme 161: Spirocyclization reported by Jiang and Tan

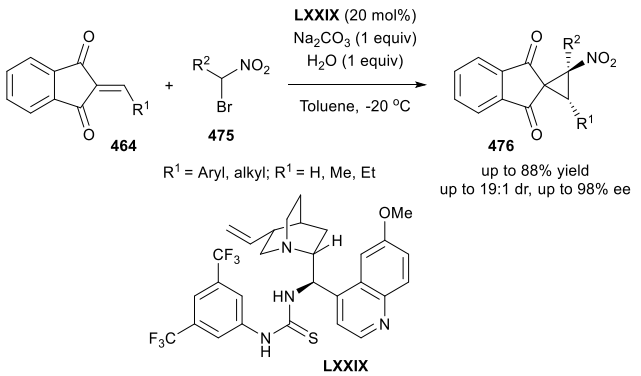
Yoshida and Takao *et al*. reported an intramolecular Friedel-Crafts-type 1,4-addition for the enantioselective constructionof spiroindanes.[275] Under primary amine cataysis, cyclic enones **473** bearing a carbon chain decorated with an electron-rich

benzene ring in their β-position undergo an intramolecular Michael addition to the *o*-position of the aromatic ring. The use of water and *p*-bromophenol as additive is crucial to produce high yields. Under the optimized conditions, the reaction renders the spiroindanones **474** in good yields (52-93%) and good enantioselectivities (74-95% ee). In the case of [5,5] spirobicycles, the enantioselectivity decreased dramatically (Scheme 162).



Scheme 162: Spirocyclization reported by Yoshida and Takao

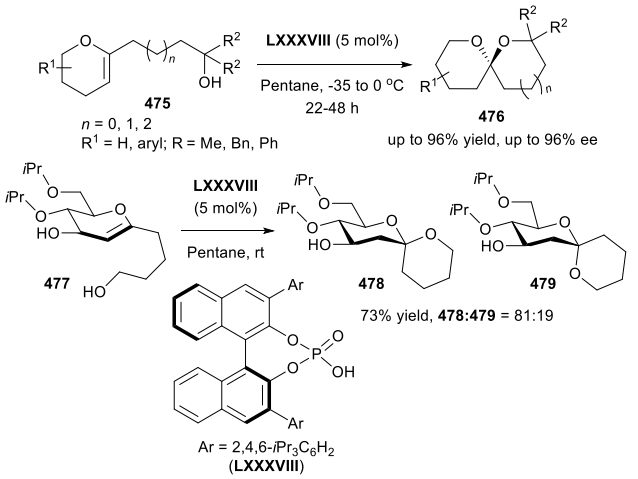
An enantioselective spirocyclopropanation was developed by Lin *et al*. This comprised an organocascade reaction (a Michael/intramolecular alkylation) between 2-arylidene-1,3-indandiones **464** and 1-bromo nitroalkanes **475**,[276] efficiently catalysed by the bifunctional tertiary amine/thiourea catalyst **LXXIX**. The reaction afforded the spirocyclopropanes **476** in good yields (63-88%) and excellent stereoselectivities (up to 19:1 d.r. and 98% ee). The main limitation of the reaction is the substitution in 1-bromonitromethane, whereby longer groups reduced the enantioselectivities (Scheme 163). A similar reaction was reported by Du *et al*., employing 3-arylenechroman-4-ones and affording the spironitrocyclopropanes in good yields and excellent stereoselectivities.[277]



Scheme 163: Spirocyclization reported by Lin

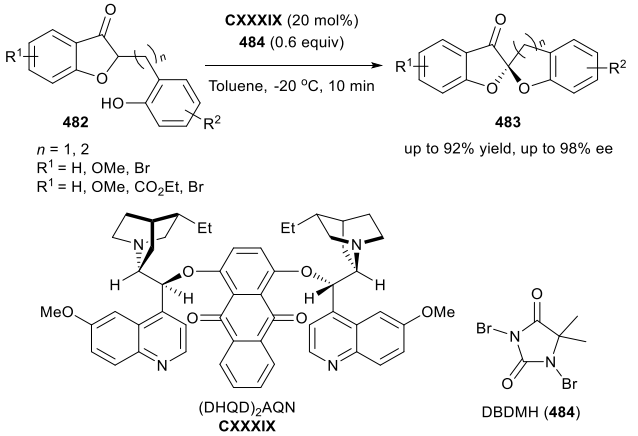
3.6 Organocatalytic methodologies for the synthesis of spiroketals

Nagorny *et al*. reported a spiroketalization reaction catalysed by the chiral phosphoric acid derivative **CXXXVIII**.[278] Cyclic enol ethers **475** bearing an alcohol in the alkyl chain form the corresponding spiroketals **476** under BINOL-derived phosphoric acid catalysis. The products are afforded in excellent yields (up to 96%) and enantioselectivities (up to 96% ee). Moreover, the authors expanded the substrate scope of the spiroketalization, using cyclic enol ethers **477** derived from sugars, with excellent results (Scheme 164).



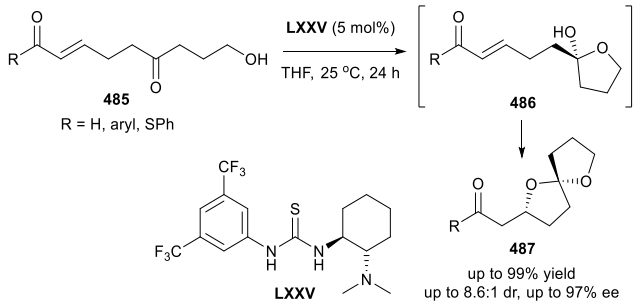
Scheme 164: Spirocyclization reported by Nagorny

A different spiroketalization comprising an organohalogenite-mediated reaction was reported by Xue, Jiang, and Li *et al*.. Benzofuranones **482** bearing a phenol were reacted with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH, **484**), promoted by the Sharpless ligand [$(DHQD)_2AQN$, **CXXXIX**], to afford the spiroketals **483** in good yields (70-92%) and excellent enantioselectivities (95-98% ee).[279] This methodology gives access to the bioactive core of rubromycins in a single step (Scheme 165).



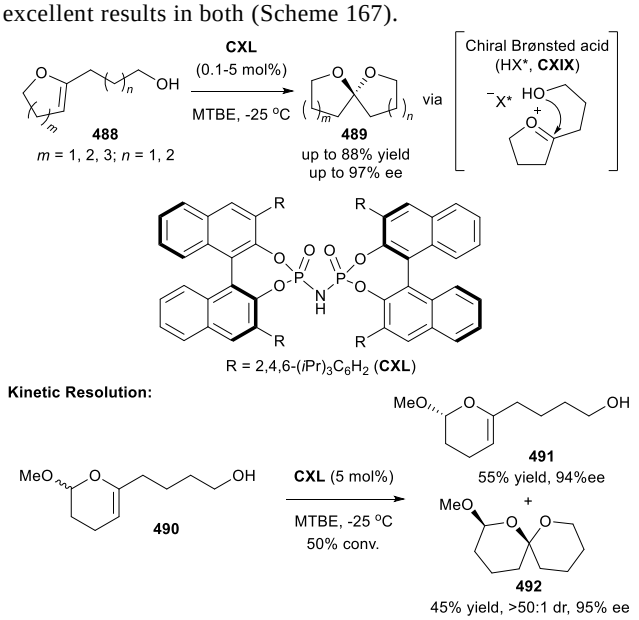
Scheme 165: Spirocyclization reported by Xue, Jiang, and Li

Matsubara and Asano *et al*. reported a ketalization reaction catalysed by chiral aminothiourea **LXXV**.[280] The reaction comprises an intramolecular hemiacetalization (**486**)/oxo-Michael addition cascade reaction, affording the spiroketals **487** in moderate to excellent yields (40-99%), moderate to good diastereoselectivities (up to 8:1 d.r.), and excellent enantioselectivities (94-97% ee; Scheme 166).



Scheme 166: Spirocyclization reported by Matsubara and Asano

List *et al*. developed a spiroacetalization catalysed by a confined Brønsted acid.[281] They tested the reaction with readily available hydroxyenol ethers using the C2 symmetric imidophosphoric acid **CXL** as a catalyst; this rationally constructed Brønsted acid displays a significant sterically demanding chiral environment, with only one catalytic relevant and geometrically constrained bifunctional active site. The reaction affords the bicyclic spiroketals **489** in good yields (up to 88%) and excellent enantioselectivities (up to 97% ee). Moreover, the authors tested the reaction with chiral substrates and in the kinetic resolution of racemate **490**, achieving excellent results in both (Scheme 167).

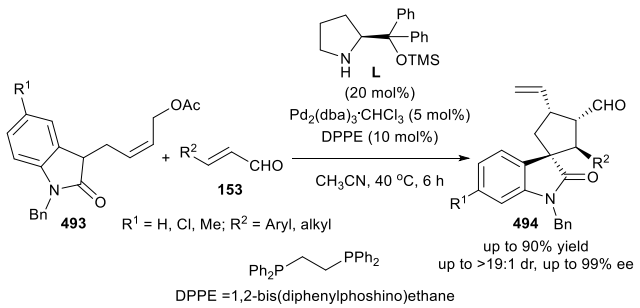


Scheme 167: Spirocyclization reported by List

4. Synergistic methodologies for the synthesis of spiro compounds

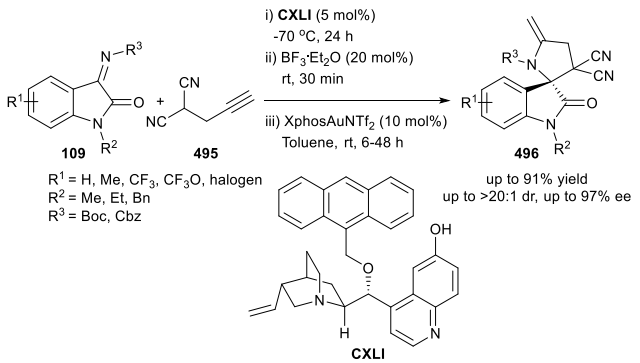
At the beginning of this decade, a new system for the synthesis of complex products became popular in organic synthesis. This new approach comprises the coexistence of two catalytic cycles that work concurrently to generate one or more new bonds. A commonly used approach when a metal catalyst and an organocatalyst are employed. In this way, the rich chemistry of the metals is combined with the cheap and easy stereoprediction of the organocatalysts.

In 2015, Córdova *et al*. developed a synergistic approach for the synthesis of spirooxindoles based on the combination of imine/enamine activation together with Pd-allylation.[282] Oxindoles **493** decorated with an allylic acetate were reacted with enals **153** *via* Michael/Tsuji-Trost allylation, rendering the final spirooxindoles **494** in good yields (90-76%), moderate diastereoselectivities (up to 5:1 d.r.), and excellent enenatioselectivities (up to 99% ee; Scheme 168).



Scheme 168: Spirocyclization reported by Córdova

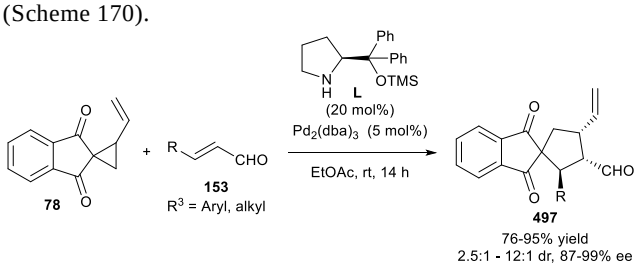
In 2013, Liu and Jiang *et al*. developed a one-pot cascade reaction for the synthesis of spirooxindoles comprising in the reaction between isatin imines **109** and malononitriles **495** decorated with an alkyne.[283] The reaction is catalysed by a cinchona alkaloid **CXLI** (Brønsted base) / gold catalyst. The first reaction is the addition of the malononitrile to the isatin amine catalysed by the organocatalyst. This is followed by intramolecular cyclization between the previously formed amine and the triple bond activated by gold. The spiro compounds **496** were produced in high yields (up to 91%) and excellent stereoselectivities (up to 97% ee and >20:1 *exo*/*endo*; Scheme 169).



Scheme 169: Spirocyclization reported by Liu and Jiang

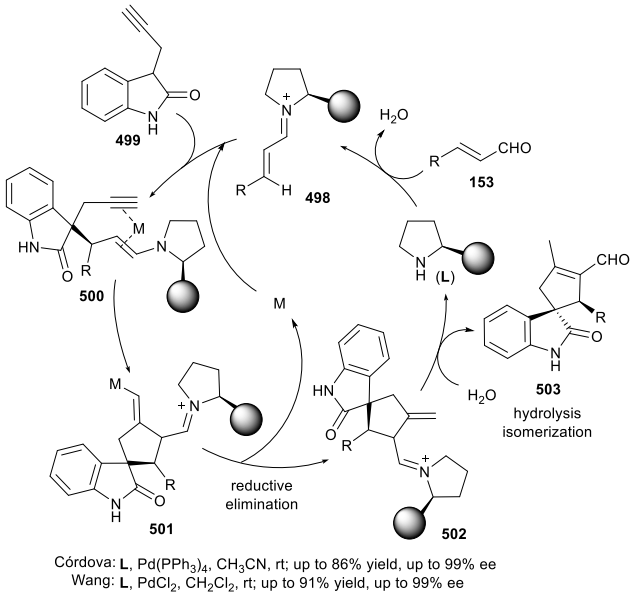
Almost simultaneously, in 2016, the research groups of Michelet,[284] Jørgensen,[285] and Rios[286] developed a synergistic reaction based on the ring opening of vinyl cyclopropanes **78** *via* an allyl palladium complex and cycloaddition with enals **153**, activated by a secondary amine **L**. Michelet and Rios independently employed vinyl cyclopropanes **78** derived from

indanones, achieving the final compounds **497** in good yields (76-99%) and diastereoselectivities (up to 12:1 d.r.), and excellent enantioselectivities (87-99% ee). In the same study, Rios *et al*. expanded the scope of the reaction, synthesising spirobenzofuranones and spirooxindoles with good results (Scheme 170).



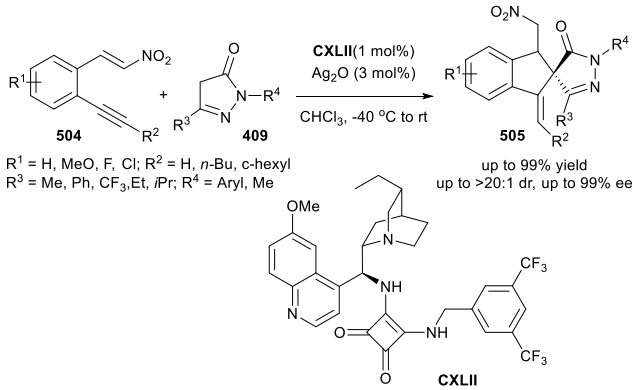
Scheme 170: Spirocyclization reported by Rios

Liu and Feng *et al*. developed a cycloaddition reaction between isatins and isocyanoacetates to build spirooxindoles under guanidine/Ag catalysis.[287] The reaction comprises an initial aldol reaction between isocyanoacetate and isatin, with guanidine acting as a bifunctional catalyst, activating the isatin and the isocyanoacetate through organized multipoint hydrogen bonding. Next, intramolecular cyclization between the hydroxyl and isocyano groups, activated by the Ag salt, affords the final spirooxindole in good yields (60-99%), moderate diastereoslectivities (up to 88:12 d.r.), and good enantioselectivities (76-90% ee). Wang *et al.*[288] reported a combination of Pd(II) salts with a secondary amine catalyst (**L**) for the synthesis of spirooxindoles **503**. Propargylated oxindoles **499** were reacted with enals **153** *via* a Michael/Conia-ene reaction pathway. The procedure began with a Michael reaction, followed by intramolecular 5-*exo*-dig cyclization (**501**) between the enamine intermediate and the triple bond activated by the Pd salt to produce intermediate **502** after reductive elimination. Subsequent isomerization of the double bond and hydrolysis provide the most stable conjugated product **503**. The reaction afforded the spirooxindoles derivatives in good yields and with excellent enantioselectivities. Later, Córdova *et al*. reported a similar cascade reaction starting from allylic alcohols that were oxidized to enals. These then reacted with propargylated oxindoles in the same way as that reported by Liu and Feng *et al.* Recently, the authors confirmed the mechanism by DFT studies.[289] The same authors expanded the substrate scope of the reaction with supported secondary amines and/or supported Pd catalysts (Scheme 171).[290]



Scheme 171: Spirocyclization reported by Córdova and Wang

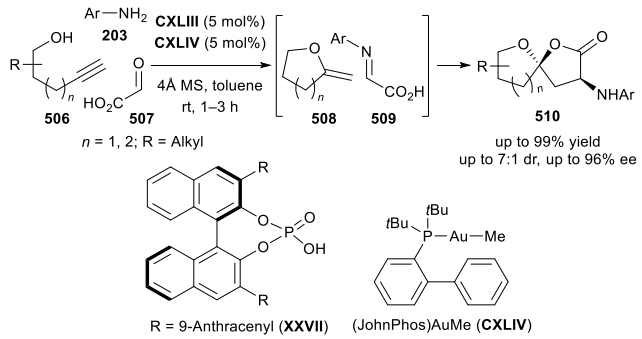
Enders and Schoenebeck *et al*. reported the synthesis of spiropyrazolones based on the concurrent activation of nitrostyrenes and alkynes.[291] Nitrostyrenes, decorated in the *orto* position of the benzene ring with an alkyne, react with pyrazolones under dual catalysis. First the pyrazolones **409** undergo a Michael addition with the nitrostyrenes **504**, a reaction catalysed by the bifunctional tertiary amine/squaramide catalyst **CXLII**. Subsequently, a second pyrazolone attack, this time to the triple bond activated by Ag, leads to the final spiropyrazolones **505** in good yields (42-99%), excellent diastereoselectivities (10:1-20:1 d.r.), and enantioselectivities (76-99% ee; Scheme 172).



Scheme 172: Spirocyclization reported by Enders and Schoenebeck

The enantioselective synthesis of spiroketals **510**, comprising the reaction of aliphatic alcohols **506** bearing a triple bond, 1,2-ketoacids **507**, and amines **203**, was reported by Rodríguez and Fañanás *et al*.[292] The reaction requires the use of Au(I) salts and chiral phosphoric acids. The proposed mechanism begins with the reaction of the Au salt [(JohnPhos)AuMe, **CXLIV**] with phosphoric acid **CXLIII**, forming the gold phosphate complex.

Next, coordination of the gold cation to the triple bond and intramolecular *exo*-addition of the alcohol to the alkyne, furnish the enol ether **508** after protodemetallation. On the other hand, the glyoxylic acid **507** reacts with aniline **203** to furnish the imine **509**, which is activated by the phosphoric acid **XXVII**. Subsequent nucleophilic addition of the enol ether produces the oxonium intermediate. This is trapped by the acid to deliver the spiroketal **510** in good yields (77-99%), moderate to good diastereoselectivities (2:1-7:1 d.r.), and good enantioselectivities (60-96% ee; Scheme 173).



Scheme 173: Spirocyclization reported by Rodríguez and Fañanás

5. Conclusions

The enantioselective synthesis of spirocyclic compounds has long pursued by organic chemists. The difficulties associated with their synthesis have made these compounds underrepresented in screening libraries, despite their unique 3D properties and presence in several biological active natural products. Since the development of asymmetric organometallic chemistry and with the advent of organo and synergistic catalysis, a plethora of new methodologies has emerged to fill this gap in organic synthesis. As we have shown in this review, desymmetrization, ring-closing, cycloaddition, annulation and multicomponent reactions are methods that have been efficiently used for this purpose. Clearly, the highlighted methodologies have several drawbacks, including poor structural diversity and the need to use highly complex starting materials. Nevertheless, the achievements have been immense. In the last five years, the development of new methodologies has increased exponentially, with many improvements, such as new multicomponent reactions and the synthesis of spiro compounds using supported or flow chemistry, expected in the future. Thus, spiro compounds show great potential not only for the interest in the challenge of their synthesis but also for the creation of new libraries that could lead to the development of new drugs and active compounds.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

[a] *Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, Fudan, People's Republic of China. Email: Hao_Guo@fudan.edu.cn*

[b] *School of Chemistry. University of Southampton. Highfield Campus, SO17 1BJ, Southampton, UK. Email: rrt1f11@soton.ac.uk*

[c] *Department of Energy Science, Sungkyunkwan University, Suwon 16419, South Korea. Email: jwyang@skku.edu*

[§] *These authors contributed equally to this work*

Dedicated to Professor Benjamin List on the occasion of his 50th birthday

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