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COMPREHENSIVE REVIEW

Molecular diversity of spirooxindoles. Synthesis and biological activity

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Abstract Spirooxindoles are important synthetic targets possessing extended biological activity and drug discovery applications. This review focuses on the various strategies for the enantioselective synthesis of spirocyclic oxindoles relying on reports over the past decade and from earlier work. The spirooxindoles in this review are separated into three structural classes, and then further categorized into the method type from which the spirocycle is generated.

Keywords Spiroheterocyclic systems · Isatin · Oxindoles · Multicomponent reactions (MCRs) · Cycloadditions · Highly functionalised molecules · Diversity-oriented synthesis · DOS

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Introduction

Spirooxindole systems are of great interest in a modern organic, medicinal, and natural product chemistry. This type of framework has been found as a core structure of many alkaloids with promising pharmacological activity, such as horsfiline, gelsemine, mitraphylline, spirotryprotatins A, B, and others. The indole scaffold of these compounds is a spiro-ring fused with non-planar bicyclic or polycyclic units of saturated or partially saturated heterocycles. Non-planar structures particularly rigid spatial organized spiro heterocyclic systems have a higher affinity to three-dimensional sites of proteins acting as biotargets than flat aromatic compounds. However, in the modern broad range of pharmaceuticals, spiro compounds are not widely used, and spirooxindoles are absent. At the same time, this type of core is prevalent in a number of spiro leader-compounds and drug candidates with different directions of action [1]. For this reason, investigations of the efficient synthetic routes to compounds with spiroheterocycles or spirocarbocycles at C-2 or C-3 positions of the indole system have increasingly appeared in recent publications. Evidently, among the different synthetic strategies, multicomponent reactions (MCRs) are dominating. For the formation of spirooxindole scaffolds, the three-component condensation of isatin, amino acids and 1,3-dipolarophils, Heck reactions, Michael-Michael-aldol cascades, and many others domino reactions have been used [2]. The regio- and stereoselectivity of these processes are the most discussed in the literature. The highly stereoselective construction of the spirooxindole skeletons with unusual regioselectivity suggests a new avenue of great importance to medicinal chemistry and diversity-oriented synthesis. This review is devoted to diverse methods for the synthesis of compounds containing spirooxindole ring systems, including the ones mimicking specific structures of the natural products.

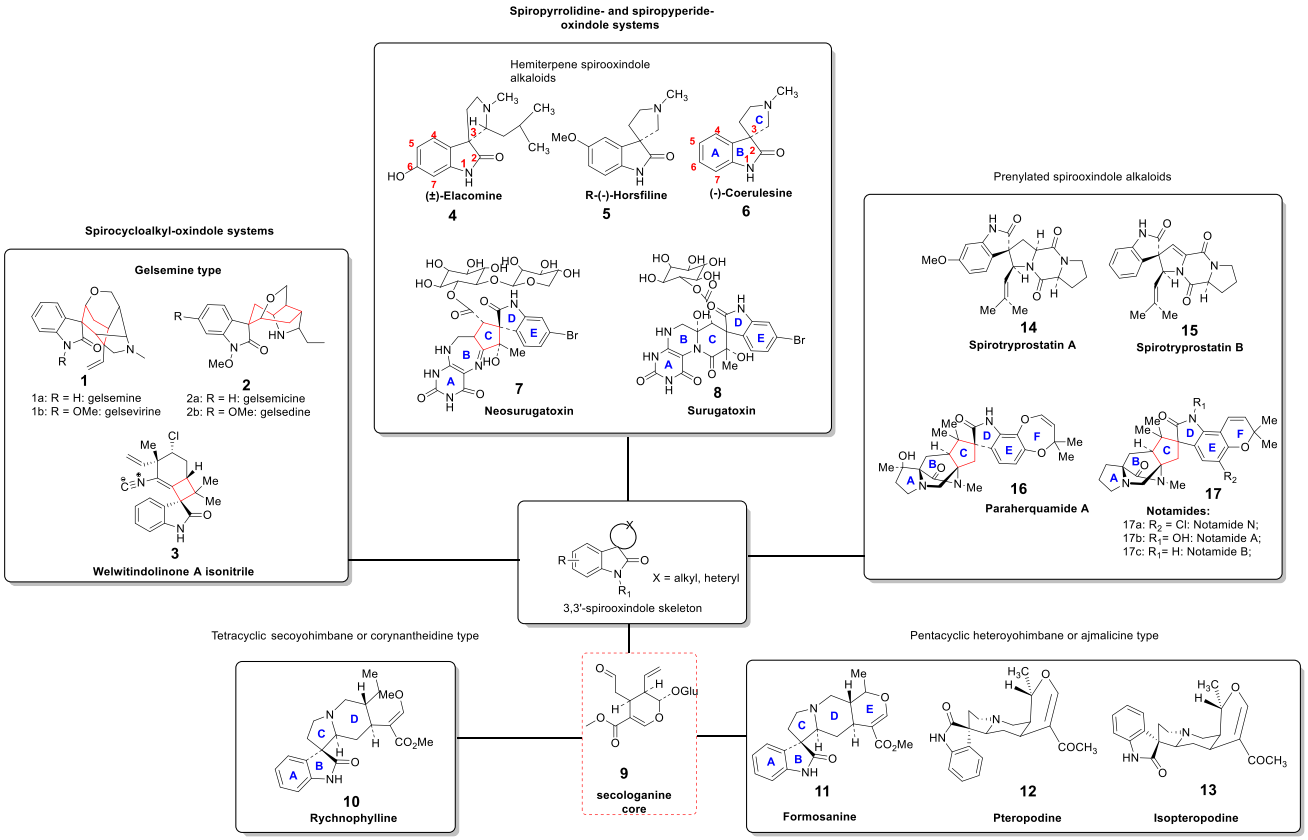


Fig. 1 Natural products containing 3,3′-disubstituted oxindole motifs

Naturally occurring s spirooxindoles

The first isolated spirooxindole alkaloids were spirocycloalkyl-oxindole systems of type **1**,**2** (gelsemine **1a**, gelsevirine **1b**, gelsemicine **2a**, gelsedine **2b**), which were found in the roots of *Gelsemium sempervirens* and were classified as *Gelsemium* species [3,4]. The 3,3′-spirooxindole skeleton of these compounds is formed by the 2-oxindolic core linked to the cycloalkyl moiety [5] (Fig. 1).

Welwitindolinone A isonitrile **3** is a spirooxindole-containing alkaloid with an antifungal activity derived from the blue-green algae reported by Moore et al. in 1994 [6], which includes a highly functionalized spirocyclobutane oxindole carbon skeleton.

The first hemiterpene spirooxindole alkaloid was isolated in 1968 from the roots of the bush *Elaeagnus commutata*, *Elaegnaceae*. X-ray diffraction studies helped to determine the structure of compound **4** named (±)-elacomine [7]. The total synthesis of (±)-elacomine and establishing of its absolute configuration was achieved by Pellegrini and co-workers [8].

Another simple alkaloid of this group, (-)-horsfiline **5**, was originally obtained from the Malaysian medicinal plant *Horsfildea Superba* (*Myristicaceae*) by Bodo et al. in 1991 [9]. This compound possesses analgesic properties as well as its synthetic spiro[piperidino-3,3′-oxindole] analogs [10]. (-)-Horsfiline **5** is closely related to alkaloid (-)-coerulescine **6** which was isolated in 1997 by Anderton et al. from toxic plants of the South Australian *Phalaris coerulescens (Poaceae)* [11].

Neosurugatoxin **7** contains a spiro[indoline-3,4′-pyperidine] system. It was extracted by Kosuge et al. from the toxic Japanese *Ivory Shell* and its structure was determined by X-ray crystallographic analysis [12]. It has about 100 times greater antagonistic nicotinic-receptor activity than relative surugatoxin **8**, which contains a piperidone cycle **C** instead of the cyclopentane ring.

The spiropyrrolidine type of indole alkaloids possessing the same basic terpenoid framework derived from tryptamine and secologanine **9** were discovered in the *Mitragyna* species and tropical lianas of the genus *Uncaria (Ouroupariа).* They can be further classified into two substructural classes: (1) the tetracyclic secoyohimbane or corynantheidine type (e.g., rhynchophylline **10**), and (2) the pentacyclic heteroyohimbane or ajmalicine type (e.g., formosanine **11**) [13]. General traditional medicinal uses of *Uncaria* include treatments for a wide variety of diseases, such as fever, colic, muscular pains, and worm infestations [14–16].

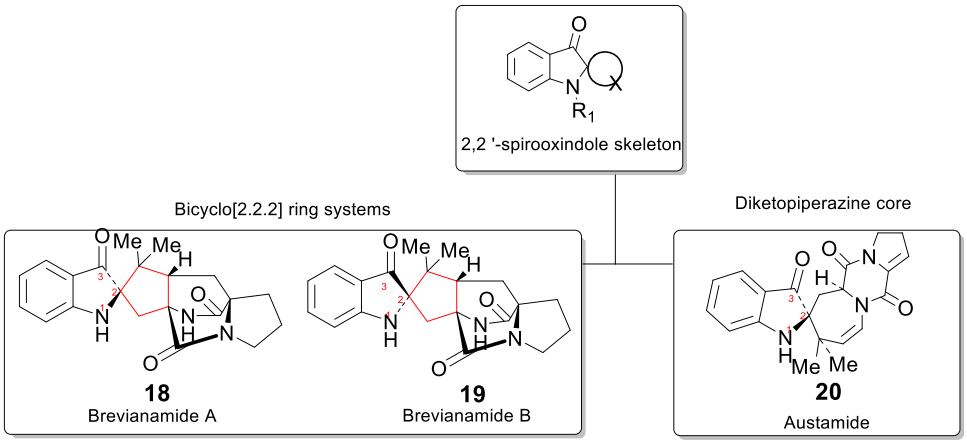


Fig. 2 Natural products containing 2,2′-disubstituted oxindole core

Pteropodine **12** and isopteropodine **13** represent another heteroyohimbine type of oxindole alkaloids with 8-azabicyclo [3.2.1]nonane fragments and act as positive modulators of G protein-coupled muscarinic M_1 acetylcholine and $5-HT_2$ (5-hydroxytryptamine) receptors. These compounds can be found in *Uncaria tomentosa*, a Peruvian medicinal plant known as "cat's claw" [17].

A number of prenylated indole alkaloids containing a diketopiperazine or a bicyclo[2.2.2]diazaoctane ring were derived from various *Aspergillus* and *Penicillium* fungi. The study of their biosynthetic pathways has recently become an area of significant interest. The secondary fungal metabolites spirotryprostatins A **14** and B **15** were found by Osada et al. in *Aspergillus fumigatus* culture medium [18] and were shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells with IC_{50} values of 197.5 μM and 14.0 μM, respectively [19]. This, in turn, has attracted interest in the synthesis and search of new antitumor agents of this class of compounds [20–22].

Paraherquamide A **16** and notamides **17** contain the unique bicyclo[2.2.2]diazaoctane ring system that is common to this family of natural products and biosynthetically can be the result of an intramolecular Diels-Alder cycloaddition reaction [23].

Spirooxindole systems containing spiro-substituent at position 2 in the 3-oxindole nucleus form a separate group of natural fungal metabolites and are less common than the 3,3′-spirooxindole alkaloids (Fig. 2). Brevianamide A **18** was isolated as the major fluorescent metabolite from culture extracts of the fungus *Penicillium brevicompactum* in 1969 by A. Birch and J. Wright [24]. These compounds possess modest insecticidal activity [25]. Austamide **20** is a cyclo-*L*-Trp-*L*-Pro derivative and contains only one reverse prenyl moiety at position C-2 of the indole ring.

A biological Diels-Alder reaction was proposed as a main route for formation of a unique bicyclo[2.2.2]diazaoctane ring system spirpofused with the oxindole skeleton of brevianamides **18**, **19** [26,27]. Brevianamides **18**, **19** can also be attributed to the group spirocycloalkyl-oxindole systems. Structurally and biosynthetically they are related to paraherquamides **16** and notamides **17** that can act as their metabolites (Fig. 1).

Examples of 3-heteroatom-substituted spirooxindoles are also found in nature, e.g., spiroindoline[3,5′]thiazolidine-type phytoalexins from some plants of the family *Cruciferae*, cultivated worldwide. Thus, in 1987 the first oxindole phytoalexin $(S)-(-)$-spirobrassinin **21** was isolated from Japanese radish (*Raphanus sativus*) by Monde et al. [28,29]. Later the (R)-(+)-1-methoxyspirobrassinin **22** from kohlrabi (*Brassica oleracea var. gongylodes*) [30], $(2R,3R)-(-)$-1-methoxyspirobrassinol methyl ether **23** and N-methoxyspirobrassinol **24** from Japanese radish (*R. sativus*) have been described as stress metabolites. They possess a heteroatom-rich spirocycle with a sulfur atom in the 3-C position (Fig. 3). N-Methoxyspirobrassinol **24** has an unusual hemi-aminal structure and occurs as a mixture of diastereomers [31].

The appealing molecular diversity of the naturally occurring spirooxindole systems increases interest in the design of novel spirooxindole skeletons. In the present review we report on the different approaches for the synthesis of the spirooxindoles depending on the recent advantages of the natural product synthesis.

Synthesis of the spiro[pyrrolidine-3,3′-oxindole] and spiro[pyrrolidine-3,2′-oxindole] systems

Spiropyrrolidinyl-oxindoles can be classified into spiro [pyrrolidine-3,3′-oxindole] and spiro[pyrrolidine-3,2′-oxindole] systems. The spiro[pyrrolidine-3,2′-oxindole] derivatives **B** are synthetically accessible analogs of the alkaloids with the spiro[pyrrolidine-3,3′-oxindole] skeleton **A** (Fig. 4).

The approaches for the design of the spiro[pyrrolidine-3,3′-oxindole] alkaloids were summarized in some recent

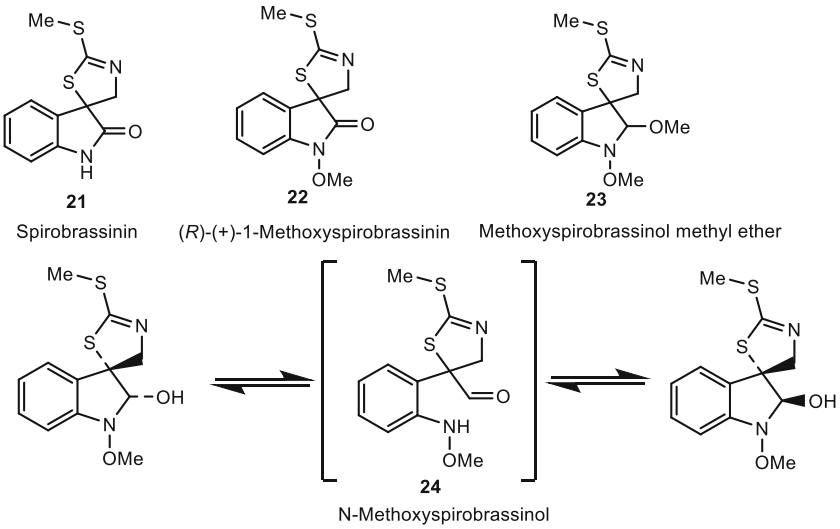


Fig. 3 Examples of 3-heteroatom-substituted spirooxindoles

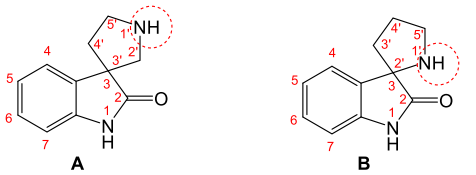
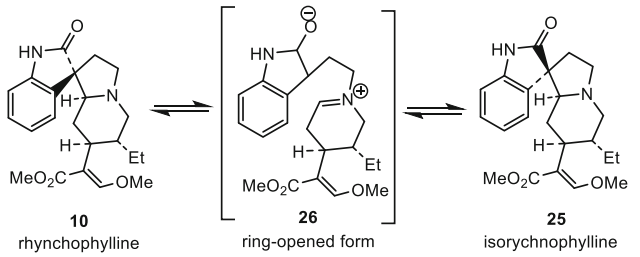


Fig. 4 Spiropyrrolidinyl-oxindole systems



Scheme 1 Isomerisation of the spirooxindole alkaloids via retro-Mannich mechanism

reviews. Marti et al. categorized only the spiro[pyrrolidine-3,3′-oxindoles] construction methods [32], Sh-M. Li presented the report on the prenylated fungal indole derivatives [33], D. Hart classified spiroquinazoline family of alkaloids [34], and G. Singh and Z. Desta focused on the construction of the spirooxindoles derived from isatins [35]. The most recent reviews were devoted to the asymmetric organocatalytic strategies for the synthesis of the spirocyclic oxindoles and to the demonstration of the brief use of spirocyclic scaffolds in drug discovery [36,37].

Mannich reactions and related transformations

The Mannich reaction successfully found application in the construction of a number of the naturally discovered spirooxindol alkaloids. The biosynthetic pathways of the isomerisation reactions of the oxindol alkaloids are based on the retro-Mannich reaction mechanism that was noted by Wenkert et al. in 1959 [38]. The isomerisation of the spiro center of the alkaloids rhynchophylline **10** and isorychnophylline **25** involves the ring-open form **26** (Scheme 1) [39]. The same situation was observed in the case of hemiterpene spirooxindole alkaloid (±)-elacomine **4** [40].

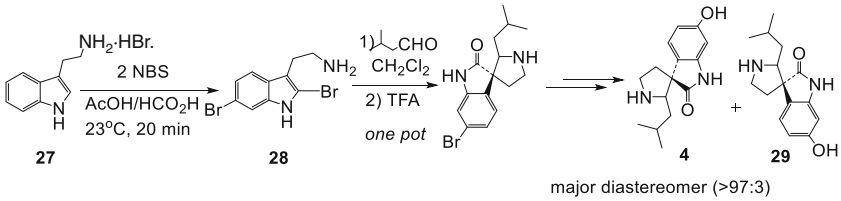
The construction of the spiro[pyrrolidine-3,3′-oxindole] core via an intramolecular Mannich reaction faces problems mostly in controlling the stereochemistry at the quaternary spiro carbon center and neighboring alkyl groups. Recently, a number of successful attempts were made to solve this problem [32]. The Pictet-Spengler/oxidative rearrangement sequence involving β-carbolines and the intramolecular Mannich-type condensation of tryptamine- and tryptophan-based oxindoles represent the classical routes of the indole-based natural compound synthesis. Miyake et al. reported the synthesis of elacomine **4** and isoelacomine **29** from 2,6-dibromotryptamine **28** as a new stereoselective method for the spiro[pyrrolidine-3,3′-oxindoles] formation (Scheme 2) [40].

S. Danishefsky and F. Nussbaum utilized the Mannich condensation for the synthesis of spirotryprostatin B **15** from a readily accessible tryptophan methyl ester **30** and prenyl aldehyde **32**. A mixture of diastereoisomeric spiro[pyrrolidine-3,3′-oxindoles] **33** through several synthetic pathways was then converted into spirotryprostatin B **15** (Scheme 3) [41].

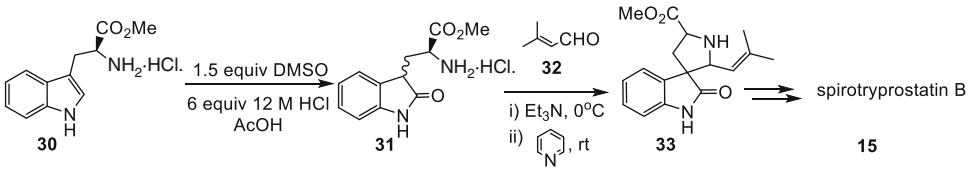
Oxidative rearrangements of tetrahydro-β-carbolines and relative systems

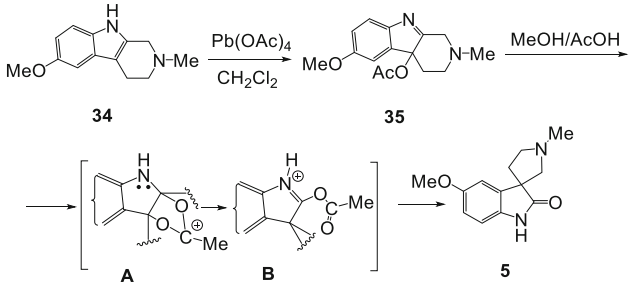
Tetrahydro-β-carbolines are useful starting materials for the construction of the spiro[pyrrolidine-3,3′-oxindoles]. The first transformation of tetrahydro-β-carboline to spirooxin-

Scheme 2 Synthesis of elacomine and isoelacomine by stereocontrolled spirocyclization of 2-halotryptamines



Scheme 3 The Mannich route to the spirotryprostatin B from tryptophan methyl ester





Scheme 4 Acid-catalyzed oxidative rearrangement in the synthesis of horsfiline

dole alkaloid (±)-horsfiline **5** was described by Bodo et al. in 1991 [8]. Thus, the reaction of tetrahydro-β-carboline **34** with $Pb(OAc)_4$ led to 4 α-acetoxyindolenine **35**, which was further converted into the intermediates **A** and **B** by an acid-catalyzed rearrangement resulting in horsfiline **5** as a racemic mixture (Scheme 4) [42].

A number of authors applied the Pictet–Spengler/oxidative rearrangement method involving a prenyl-substituted tetrahydro-β-carboline [43] and different tryptamines [44] as starting materials that lead to the spirooxindole hemiterpene alkaloids (±)-horsfilline **5**, (±)-elacomine **4** and (±)-coerulescine **6**.

Other types of the oxidative methods of convertion of indoles into spirocyclic oxindoles include the diastereospecific Sharpless osmylation process, *tert*-butyl hypochlorite, lead tetraacetate, and sodium tungstate as oxidants. Thus, A. Peterson and J. Cook described a highly diastereoselective synthesis of the spirooxindole diastereomers **41**,**42** through the conversion of N_a-methylated indoloketones **36** by utilizing the Sharpless osmylation process for an asymmetric dihydroxylation (Scheme 5) [45]. The employment of dihydroquinine 4-chlorobenzoate (DHQ-CLB) as the ligand led to the diastereoselective (94 % *de*) formation of oxindole **42a**.

The simple, convenient and stereospecific method of preparation of the spiroketooxindole **44**–**46** in high yield by utilizing *tert*-butyl hypochlorite was described by P. Yu and J. Cook [46]. The diastereomers **46** were obtained after treatment of the N_b-benzyl tetracycliceketone **43** with t-BuOCl. The same process with N_b-H or N_b-benzoyl substituted analogs finished the diastereomers **44** and **45**, respectively (Scheme 6). These derivatives are of use as templates for the total synthesis of the voachalotine-related oxindole alkaloids.

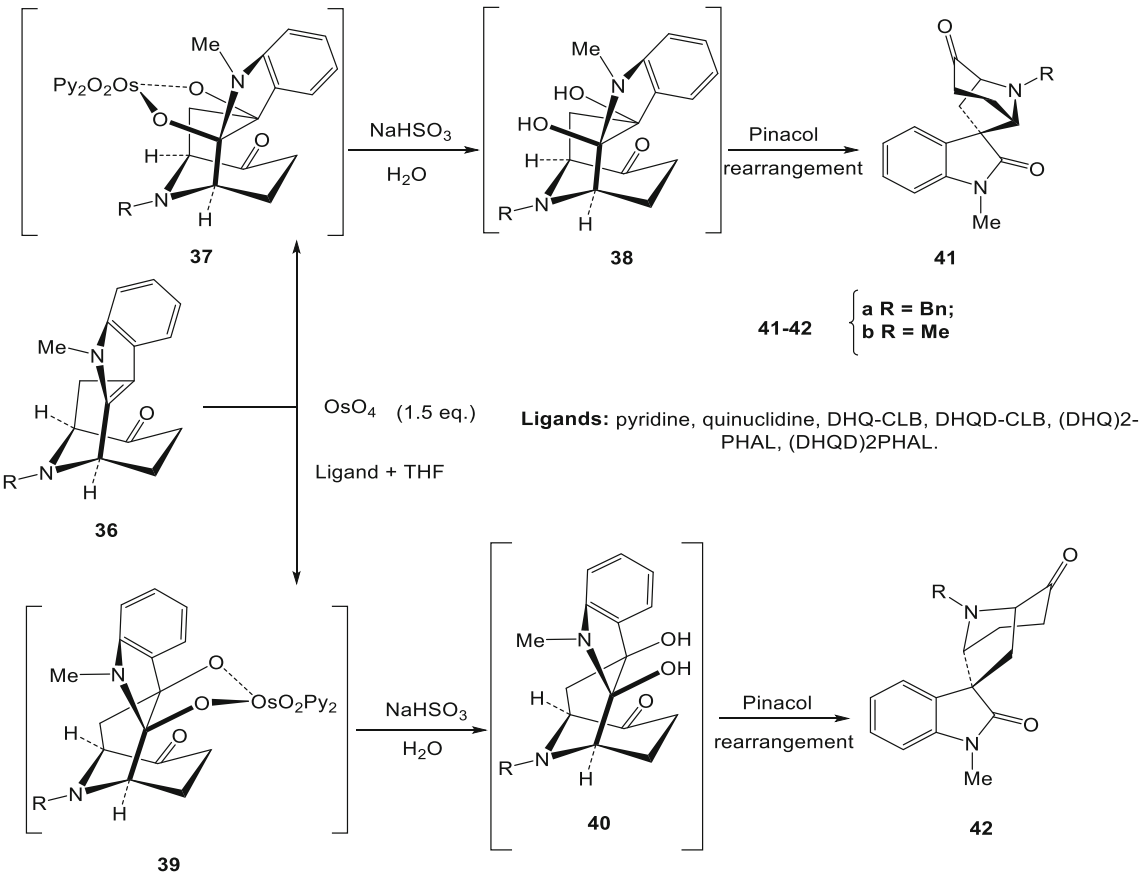
Somei et al. proposed a method for the selective hydroxylation of the nitrogen atom of indolic cycle by the oxidation of β-carbolines **34** in the presence of hydrogen peroxide and sodium tungstate [47]. The resulting 9-hydroxy-β-carboline **47** was easily converted to (-)-coerulescine **6** (Scheme 7).

Intramolecular heck reactions and similar conversions in spiro[pyrrolidine-3,3′-oxindoles] synthesis

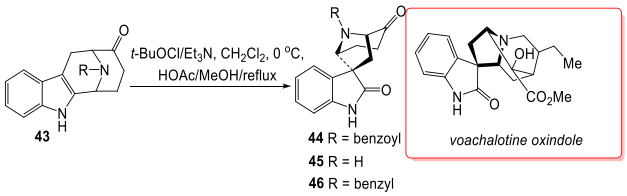
The highly esteemed Heck reaction is particularly useful for the construction of the asymmetric quaternary carbon centers as well as preparing the 3,3′-disubstituted oxindoles and other complex natural products [48].

Kamisaki et al. performed the synthesis of the spiro[pyrrolidine-3,3′-oxindole] **49** through the intramolecular domino cyclization of carbamoyl chloride **48** in the presense of catalysts, such as $Pd(OAc)_2$ with Cs_2CO_3 or Pd^0 with $Bi(OTf)_3$, in the absence of any base [49,50]. The reaction without Cs_2CO_3 took place smoothly to give the desired spirooxindole **49** as a major product. However, the Pd^0-catalyzed reaction of **48** in the presence of $Bi(OTf)_3$ (10 mol%) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF) provided spirooxindole **49** in a 52 % yield with no diene **50** contamination (Scheme 8).

L. Overman and M. Rosen achieved the total synthesis of spirotryprostatin B **15** and three stereoisomers through the stereoselective asymmetric Heck cyclization followed by the capture of the resulting η^3-allylpalladium intermediate that led to the pentacyclic system and the C3-C18 stereorelationship in a single step (Scheme 9) [51]. It was discovered that cyclization of the key intermediate **51** with 10 % $Pd_2[DBA]_3 \cdot CHCl_3$, 40 mol% $(otol)_3P$ and an excess of AcOK in THF at 70 °C readily led to the formation of a 1:1 mixture of spirooxindole **52** and its isomer. Use of the chiral



Scheme 5 Conversion of N_a-methylated indoloketones by the Sharpless osmylation process

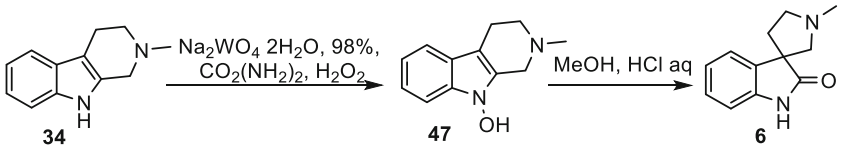


Scheme 6 Simple method to prepare spiroketooxindole by treatment with *tert*-butyl hypochlorite

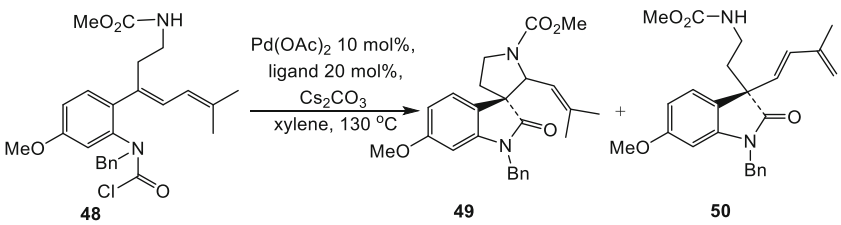
palladium catalyst ($Pd_2[DBA]_3$/(*S*)-BINAP-catalyzed) controled the stereochemical outcome of the formation of the first carbon-carbon bond. Cleavege of the SEM protecting group from **52** and chromatographic purification led to spirotryprostatin B **15.**

Recently, Zhu et al. developed an oxidative palladium-catalyzed carbo-heterofunctionalization of alkenes through a direct intramolecular aromatic C-H functionalization (Scheme 10) [52]. The conversion of simple N-aryl acrylamides **53** into acetoxylated 3,3′-spiropyrrolidinyloxindoles **54** was performed by utilizing MeCN (*c* 0.1 M) in the presence of $PdCl_2$ (0.1 equiv) and $PhI(OAc)_2$ (2 equiv) at 80 °C in 37–52 % yield. This domino carboamination process was shown to be applicable to various substrates.

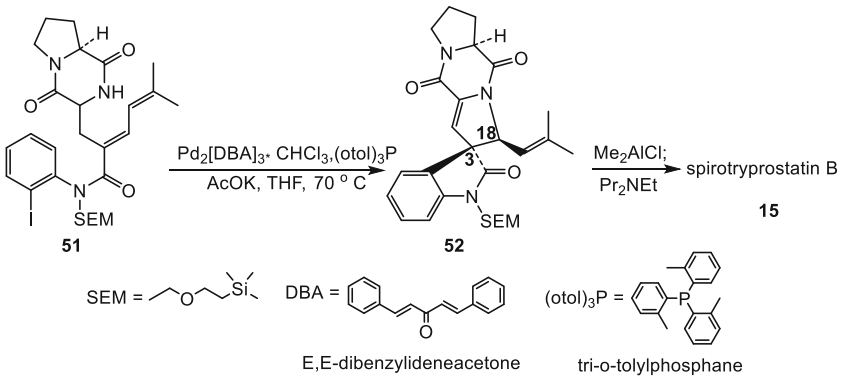
Scheme 7 Two-step oxidative rearrangement of hexahydro-β-carboline with sodium tungstate

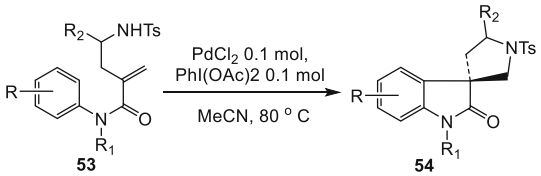


Scheme 8 Domino Pd-catalyzed spirooxindole formation



Scheme 9 Synthesis of spirotryprostatin B via Heck reaction





Scheme 10 Spirocyclization by oxidative Pd-catalyzed carbo-heterofunctionalization of N-aryl acrylamides

The biologically active spiropyrrolidine-3,3′-oxindoles **56** were synthesized via the Pd-catalyzed domino spirocyclization process from the linear anilides **55** [53]. The selection of the ligand affects the pathway of the formation of the product from amide **55** through Heck or aminopalladation processes. The 2-di-*tert*-butylphosphino-2′-methylbiphenyl was used as the most effective ligand in the key step of the *trans*-aminopalladation of the double bond (Scheme 11).

Jaegli et al. developed the intramolecular domino Heck/cyanation sequence allowing ready access to diversely functionalized 3-alkyl-3-cyanomethyl-2-oxindoles **57**, and converted them into described 3,3′-spiropyrrolidinyloxindoles **58** using methoxymethyl acetal (MOM) protected anilides **55** as common starting materials (Scheme 12) [54].

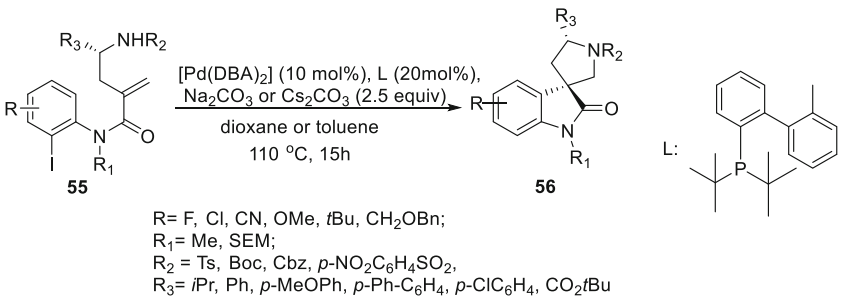
The Pd-catalyzed intramolecular R-arylation of amides **60** was applied to the synthesis of spirooxindole natural products and its derivatives. Thus, Maison et al. presented a new synthesis of horsfiline **5**, giving the natural product in only four steps from commercially available carboxybenzyl (Cbz) protected pyrollidine-2-carboxylic acid **59** (Scheme 13) [55].

1,3-Dipolar cycloaddition reactions in the synthesis of spiropyrrolidinyl-oxindole systems

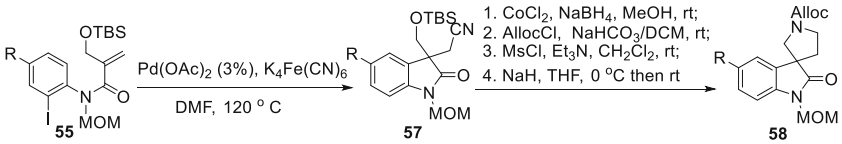
Methods for the construction of the 3,3′-spirooxindole core

The 1,3-dipolar cycloaddition reactions are regarded as one of the most useful processes in the synthesis of the five

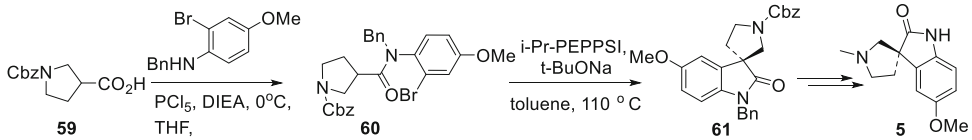
Scheme 11 Spirocyclization of substituted anilides



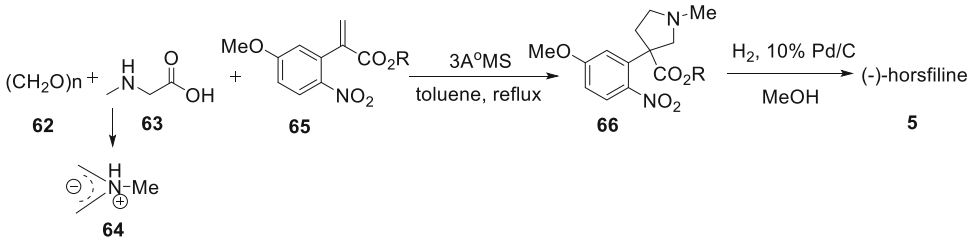
Scheme 12 3-Functionalized-3-cyanomethyl-oxindoles as precursors of 3,3′-spiropyrrolidinyl-oxindoles



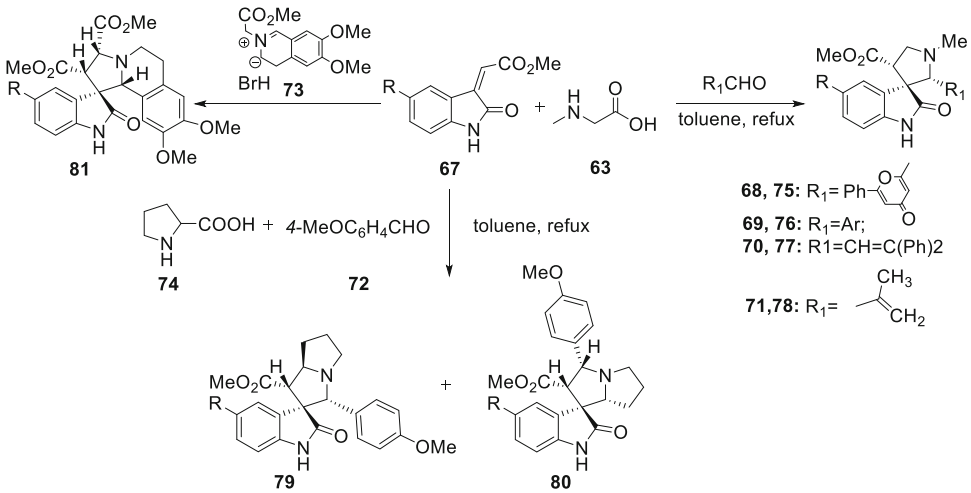
Scheme 13 Total synthesis of horsfiline **5**



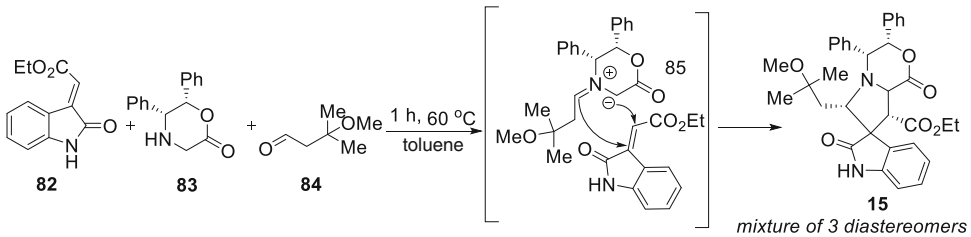
Scheme 14 Synthesis of (-)-horsfiline via 1,3-dipolar cycloaddition reaction



Scheme 15 Using oxindolylidene acetate as 2-π components in 3,3′-spirooxindole core construction



Scheme 16 Three-component reaction based on the asymmetric 1,3-dipolar cycloaddition of a chiral azomethine ylide to an ethyl oxindolylidene acetate



membered heterocyclic ring. Among the various dipoles, azomethine ylides were shown to be the most utilized in recent years in the construction of the pyrrolidine derivatives by the reaction with alkens. This method can be applied for the synthesis of spiro[pyrrolidine-3,3′-oxindoles] and spiro[pyrrolidine-3,2′-oxindole] systems. Thus, Palmisano et al. represented the synthesis of the (-)-horsfiline **5** based on the the reaction of N-methyl-azomethine ylide **64** prepared *in situ* from formaldehyde **62** and sarcosine **63** with alken **65** followed by reductive heterocyclization (Scheme 14) [56].

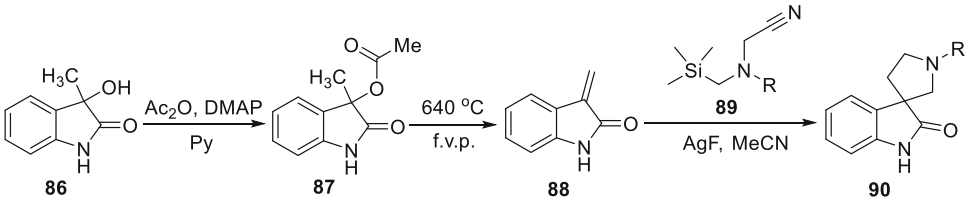
The 1,3-dipolar cycloadditions of azomethine ylides to 2-oxoindolin-3-ylidene derivatives were investigated by a number of authors [57,58]. Methyl oxindolylidene acetate **67** can be used as a 2-π component in reactions with a wide range of different azomethine ylides generated *in situ* from sarcosine **63** and the corresponding carbonyl compounds (6-phenyl-4*H*-pyran-4-one-2-carbaldehyde **68**, aldehydes **69**–**72** and isoquinolinium bromide **73**) (Scheme 15). It is noteworthy that when using the anise aldehyde **72** and *D*, *L*-proline **74** the resulting product was obtained as a mixture of isomers **79** and **80**.

Williams et al. proposed another method of spirotryprostatin B **15** synthesis based on the asymmetric 1,3-dipolar cycloaddition of a generated *in situ* chiral azomethine ylide **85** to the ethyl oxindolylidene acetate **82** (Scheme 16) [59].

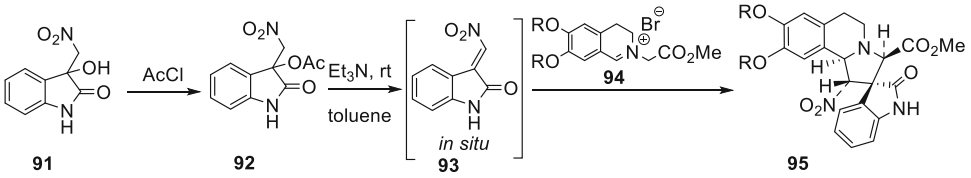
Utilization of the 3-methylideneindolin-2-one **88** and its derivatives as 1,3-dipolyarophiles in the synthesis of the natural spiro[pyrrolidine-3,3′-oxindoles] allows avoiding the step of the 5-carboxyl group removal [60,61]. This synthon can be prepared by flash vacuum pyrolysis of the ester **87** in a 60–89 % yield. Cycloaddition reactions of **88** and of the 1-(trimethylsilylmethyl)piperidine-2-carbonitrile **89** gave spirooxindoles **90** in 4–20 % yields (Scheme 17).

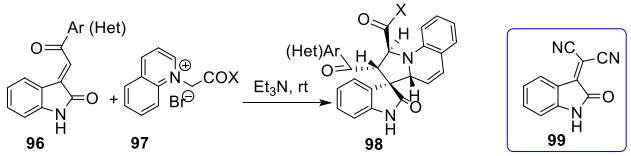
3-Nitromethyleneoxindole **93** can be also successfully used as a 1,3-dipolarophile in 1,3-dipolar cycloadditions only under neutral conditions [62]. Various 3,3′-spirooxindol compounds **95** were stereoselectively obtained in one cycloaddition step by treating the mixture of nitroderivatives

Scheme 17 Utilization of the 3-methylideneoxindole in the spiro[pyrrolidine-3,3′-oxindoles] synthesis



Scheme 18 Utilization of the 3-nitromethyleneoxindole **93** in the spiro[pyrrolidine-3,3′-oxindoles] synthesis





Scheme 19 1,3-Dipolar cycloaddition of the N-phenacyl-quinolinium ylides to ethylideneindolin-2-ones

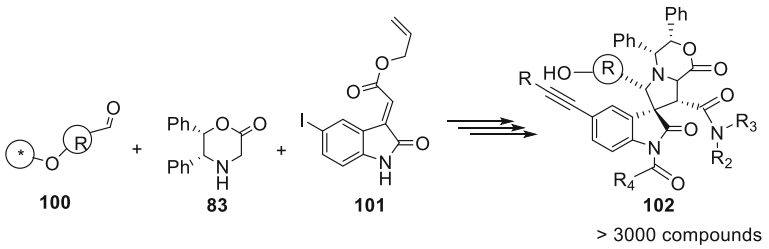
92 and isoquinolinium salt **94** with two equivalents of triethylamine in toluene at room temperature (Scheme 18).

Serov et al. synthesized a series of 3,3′-spirooxindoles **98** by the cycloaddition of the phenacyl-quinolinium ylides **97** to the 3-[(*E*)-2-aryl(hetaryl)-2-oxoethylidene]indolin-2-ones **96**. However, completely substituted activated olefin—2-oxo-(3*H*)-indole-3-ylidine-malononitrile **99** did not react with phenacyl-quinolinium ylides **96** as a dipolarophile (Scheme 19) [63].

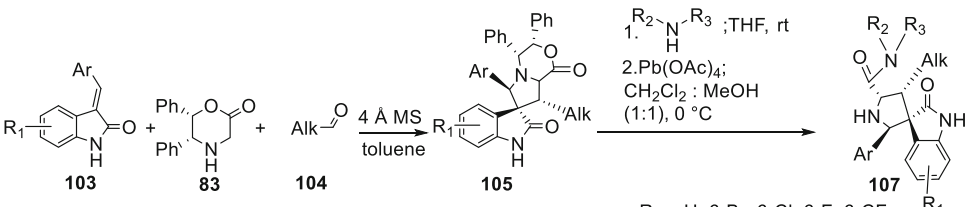
Schreiber et al. reported the split-pool synthesis of more than 3000 3, 3′-spirooxindoles **102** on the high capacity macrobeads [64]. The key reaction to assemble stereoselectively the 3, 3′-spirooxindole core is a Williams' three-component coupling of **83**, the allyl ester of 5-iodo-2-oxoindolyl-3-idene acetate **101** and the macrobead-supported aldehydes **100** in the presence of mild Lewis acids ($Mg(ClO_4)_2$) to promote the reaction (Scheme 20).

Wang et al. have used a similar Williams' approach and synthesized a series of 3,3′-spirooxindoles **107** that could act as potent, specific small-molecule inhibitors of the MDM2-p53 interaction with antitumor activity [21,65]. The the key step is an asymmetric 1,3-dipolar cycloaddition reaction of 3-arylidene-2-oxindoles **103** with morfolinone **83** and aliphatic aldehyds **104**. The amination of 3,3′-spirooxindoles **105** and mild oxidative hydrolysis leads to the target compounds **107** (Scheme 21) [67].

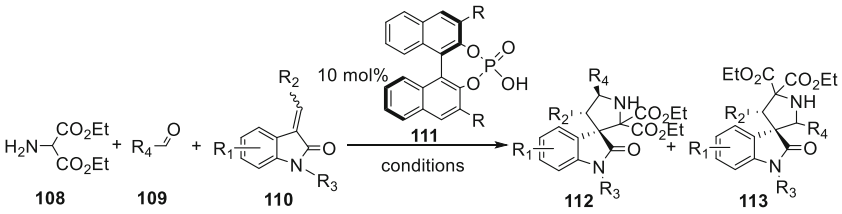
Scheme 20 The Lewis acid mediated split-pool synthesis of the library of 3,3′-spirooxindoles



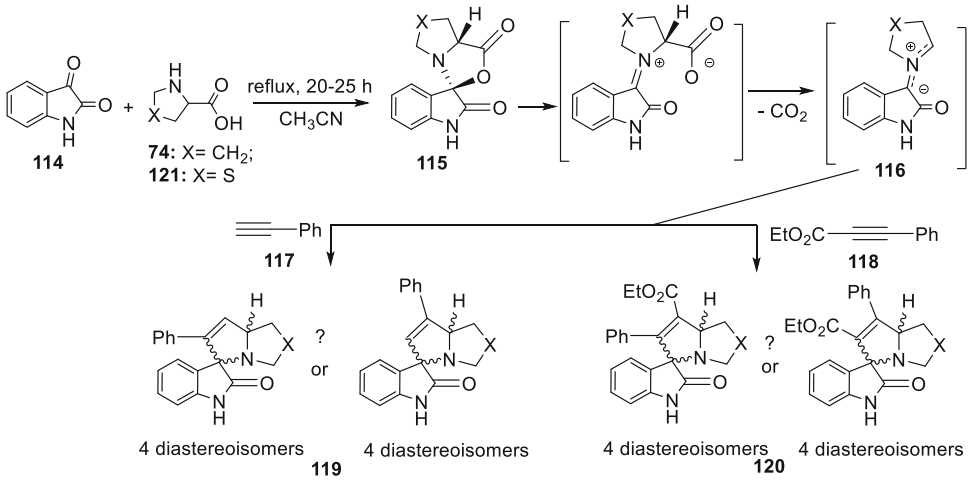
Scheme 21 Synthesis of a series of 3,3′-spirooxindoles with an antitumor activity



Scheme 22 Asymmetric cycloaddition reactions of substituted methyleneindolinones catalyzed by chiral phosphoric acids



Scheme 23 The reaction of isatin with cyclic α-aminoacids in the presence of dipolarophiles



Chen et al. described the asymmetric catalytic three-component 1,3-dipolar cycloaddition of a broad range of methyleneindolinones **110** with amino esters **108** and aldehydes **109** in the presence of chiral phosphoric acids **111**, which regioslectively led to the spirooxindols **112** and **113** in high yields under mild conditions (Scheme 22) [68].

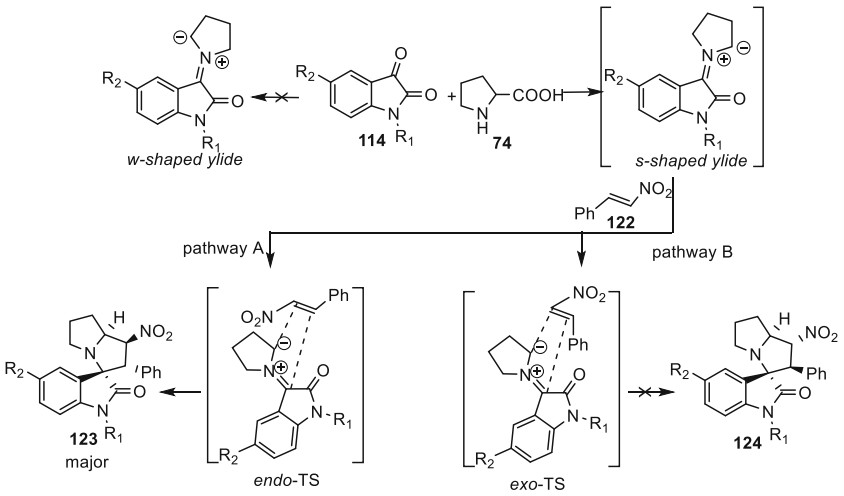
The reaction of 1,3-dipolar cycloaddition with azomethine ylides, obtained from isatin and α-amino acids for 3,2′-spirooxindole core building

The domino 1,3-dipolar cycloaddition reactions of azomethine ylides, generated *in situ* through the decarboxylative condensation of isatins and α-amino acids, with various dipolarophiles, are shown to be the most useful methodology for the regio- and stereoselective formation of a variety of complex 3,2′-spirooxindoles [69]. In 1970, Rizzi reported evidence for the formation of the nonstabilized azomethine ylide intermediate from the decarboxylative condensation between sarcosine and benzophenone. The way of generating the azomethine ylide is believed to proceed through the initial formation of the oxazolidinone, which eliminates carbon dioxide while heating [70]. In the 1990s, Grigg et al. reported on similar reactions by using proline and other α-amino acids as azomethine ylides precursors and methyl acrylate and α, β-unsaturated ketones as dipolarophiles forming spiro-pyrrolidine-oxindoles [71–73]. Recently, this substantial method has found many applications in combinatorial chemistry due its simplicity and variability [74,75].

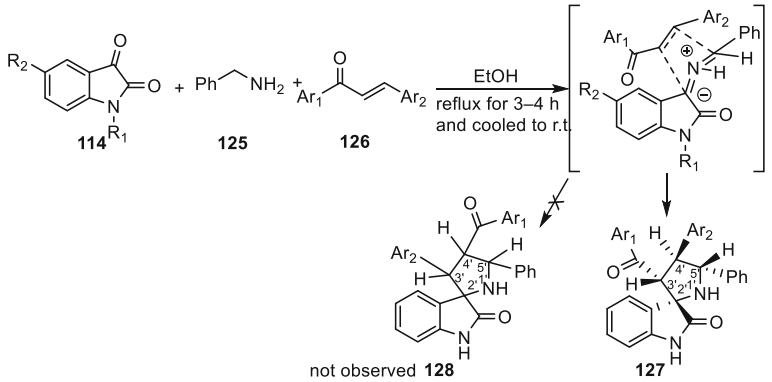
One of the interests of theoretical investigations of the regioselectivity in 1,3-dipolar cycloadditions is related to high level *ab initio* methods for the calculation of transition states and activation parameters. Thus, theoretical studies have been carried out to study the stereochemistry of the cycloadducts **119** and **120** from the interaction between the azomethine ylide **116** derived from isatin **114** with L-proline **74** or thiazolidine-4-carboxylic acid **121** and dipolarophiles **117** and **118**. Geometry optimization of azomethine ylide **116** points out on its planar structure. The planar proline ring lies in the same plane with the isatin moiety. The authors of this research described the selected products as stereoisomers **115**, **119** and **120** but they completely failed to prove their stereochemistry by the relevant methods (Scheme 23) [76].

In the past decades, the understanding of the mechanism in the 1,3-dipolar cycloaddition reactions has grown from an advantageous cooperation between theory and experiment and continues to arouse a real interest. The regio- and stereochemistry of these reactions may be affected by the appropriate dipole and dipolarophile steric and electronic effects or by using a catalyst. Thus, Sarrafi et al. reported the synthesis of spironitropyrrolizines **123** via cycloaddition of isatins **114**, proline **74** and (*E*) − β-phenyl nitroolefins **122** (Scheme 24). The theoretical investigation of all possible regio- and stereocycloaddition pathways of formation of cycloadducts **123** showed that the S-shaped ylide goes through the cycloaddition via an endo-transition state (pathway B) excluding the obtaining of the *exo*-TS cycloadduct

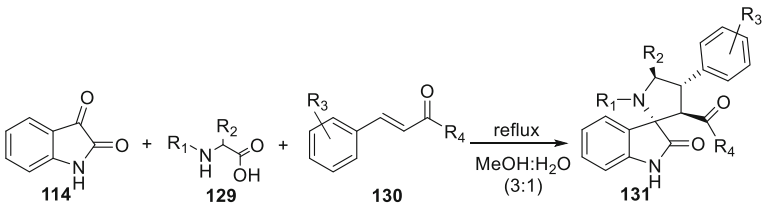
Scheme 24 Proposed mechanism for the cycloaddition of the azomethine ylides with nitrostyrene



Scheme 25 The synthesis of the spiropyrrolidine oxindoles via a multicomponent 1,3-dipolar cycloaddition reaction of isatins, benzylamine and chalcones



Scheme 26 Synthesis of the spiropyrrolidine oxindoles via a multicomponent 1,3-dipolar cycloaddition reaction of isatin, α-amino acids, and (*E*)-ß-substituted-styrenes

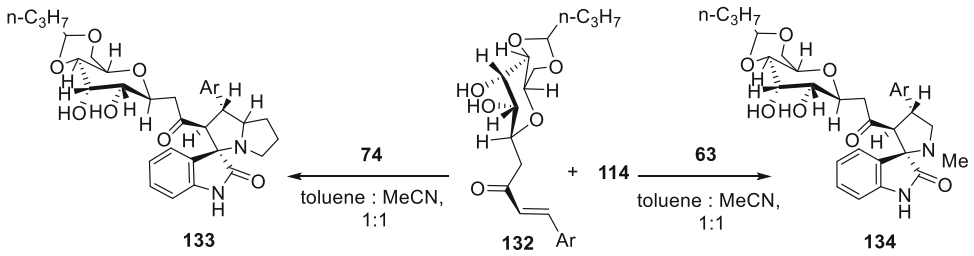


[77]. Later studies had shown that the regioselectivity of the reaction of isatin, *L*-proline, and (*E*) − β-phenyl nitroolefins **122** was affected by solvent and temperature, and was independent of the ratio of the reactants [78].

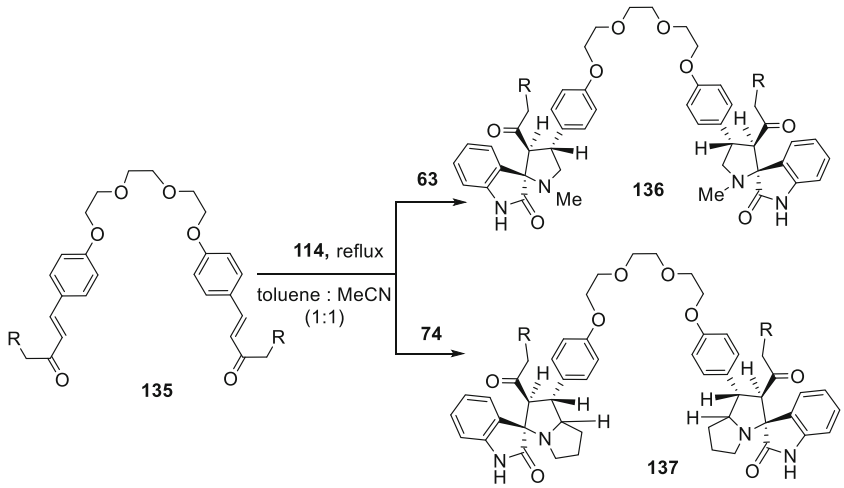
Later, this group of authors synthesized a series of spiropyrrolidine oxindoles **127** via a multicomponent 1,3-dipolar cycloaddition reaction of isatins **114**, benzylamine **125** and chalcone derivatives **126** (Scheme 25) [79]. Indeed, this way of synthesis of target spirooxindoles **127** is also attractive because the pool of primary fatty-aromatic amines is much more diverse than the α-amino acids. The possible product **128** was not observed. The calculations of the molecular mechanism of the cycloaddition showed the key role of the [1,5]-H shift in the azomethine ylide generation.

There are many reports in the literature on the formation of spiropyrrolidine oxindoles by the reaction of azomethine ylides, generated from α-aminoacids and isatins, with α, β-unsaturated ketones (chalcones). Both N-unsubstituted and N-substituted α-amino acids have been employed in the study [80]. Thus, a series of spiro[pyrrolidine-3,2′-oxindole] derivatives **131** were synthesized by 1,3-dipolar cycloaddition reaction of isatin **114**, α-amino acids, **129** and (*E*)-ß-substituted-styrenes **130** (chalcones, cinnamic esters, and amide) (Scheme 26). Bioactivity screening conducted by Chen et al. showed that compounds **131** exhibited an antitumor activity in the A549 and P388 cell lines, and several compounds were found to be active under the concentration of 10^{-4}M [81].

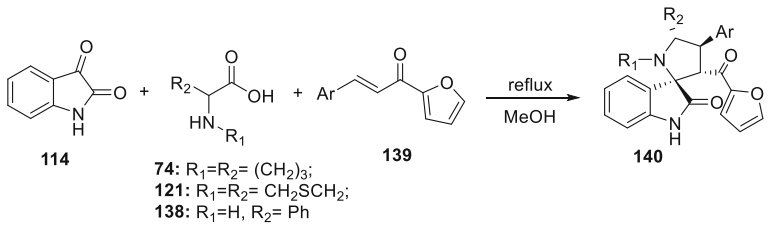
Scheme 27 Easy access to sugar-based spirooxindolepyrrolidines and -pyrrolizidines



Scheme 28 Synthesis of sugar-based ether-linked dispirooxindolopyrrolidine or -pyrrolizidines



Scheme 29 Synthesis of oxindole-fused furanyl-grafted spiropyrrolidines



Hemamalini et al. presented efficient one-pot synthesis of novel sugar-based spirooxindolopyrrolizidines **133** or -pyrrolidines **134** based on the [3+2] cycloaddition reaction with α, β-unsaturated β − *C*-glycosidic ketones as dipolarophiles (Scheme 27) [82].

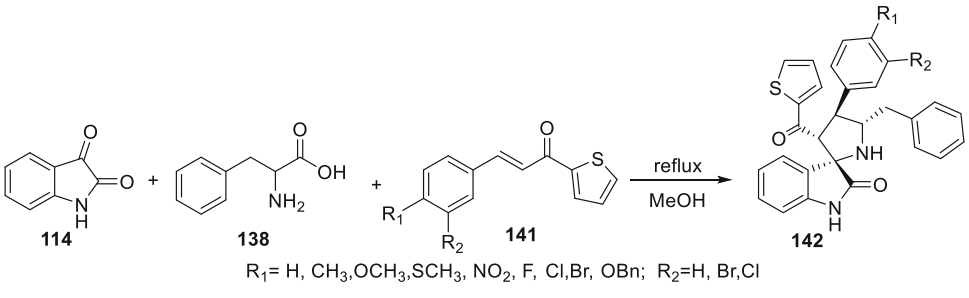
The method utilizing azomethine ylides, derived from isatin **114** and sarcosine **63** or *L*-proline **74**, with ether linked α, β-unsaturated-β − *C*-glycosidic ketones **135** (R=β − *C*-glycosidyl) as a dipolarophiles was proposed by the same authors (Scheme 28) [83].

Recently, Guansheng Wu et al. prepared a series of spirooxindolo-pyrrolidines, pyrrolizidines, and pyrrolothiazoles **140** by regioselective, three-component reactions between α, β-unsaturated ketones with furanyl substituents **139** and unstable azomethine ylides generated *in situ* from isatin **114** and different α-amino acids (*L*-proline **74**, thiazolidine-4-carboxylic acid **121**, phenylalanine **138**) (Scheme 29). The synthesized compounds were screened for their antibacterial activities against a spectrum of pathogens [84].

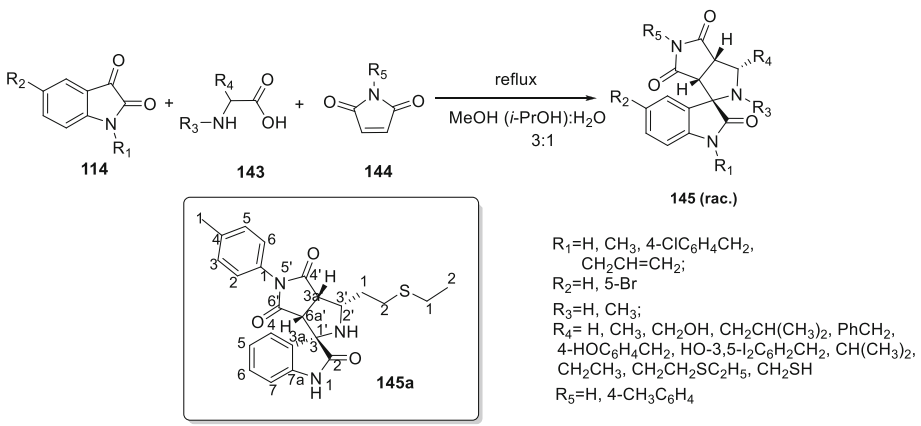
Another example represents a synthesis of spiro pyrrolidines **142** by cycloaddition reaction of azomethine ylide generated from phenylalanine **138** and isatin **114** with (E)-3-aryl-1-(thiophen-2-yl) prop-2-en-1-ones **141** for a good yield. The reaction proceeded with high regio- and stereoselectivity (Scheme 30). All the synthesized compounds have been evaluated for their anti microbial activity against *Echerichia coli*, *Enterobacter aerogens*, *Shigella flexneri*, *Salmonella typhimumium Candida albicans*, and *Aspergillus niger* using the Agar-Agar well diffusion method. The position of the substituent on the phenyl ring significantly influenced anti-microbial activity, with an activity order of p-F > p-Br > m-Br > p-Cl > m-Cl derivatives [85].

Various applications of the "classical" dipolarophiles, such as 1-aryl-1H-pyrrole-2,5-diones (N-arylmaleimides) were reported by different groups of authors. Most of the synthesized compounds revealed moderate anti-tumor properties against HCT116 (colon), MCF7 (breast), and HEPG2 (liver) human tumor cell lines [86,87]. The most recent report describes our employment of acyclic α-amino acids in these

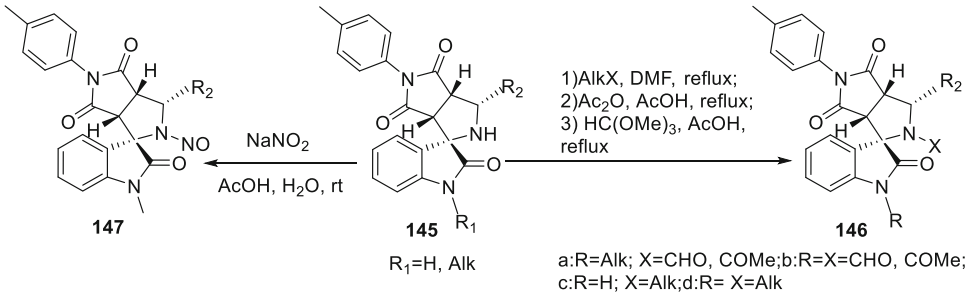
Scheme 30 Synthesis of oxindole-fused thiophenyl-grafted spiropyrrolidines



Scheme 31 N-arylmaleimides in the synthesis of spiro[indole-3,2′-pyrrolidin]-2-ones

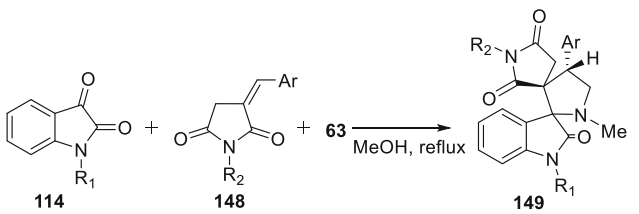


Scheme 32 Further derivatization of synthesized spiropyrrolidine oxindoles



reactions and the associated stereoselectivity problems of cycloaddition. There was established a stereochemical direction of the cycloaddition of maleimides **144** to azomethine ylides obtained from isatins **114** and acyclic α-amino acids **143**, including sulfur-containing ones (cysteine, ethionine). The resulting compounds **144** were obtained in two enantiomeric cyclic forms having a *cis* configuration of methine protons in the pyrrolo[3,4-c]pyrrole system. The clarification of the mutual disposition of the protons in the pyrrolidine ring of **145a** was carried out by using 2D NMR analysis (NOESY, COSY, HSQC, HMBC) (Scheme 31).

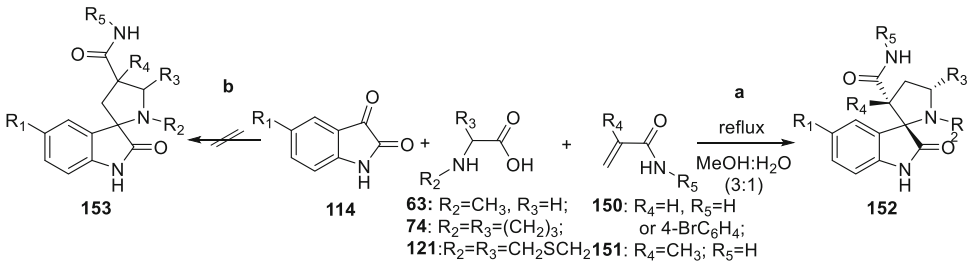
The presence of an NH group within the pyrrolidine ring of compounds **145** enabled the study of alkylation, acylation, and nitrosation reactions characteristic of secondary amines. It might be stated that the primary target of electrophilic attack was the N-2' nitrogen atom of the pyrrolidine ring while employment of K_2CO_3 enabled the alkylation to be carried out both at the N-1 and N-2' nitrogen atoms (Scheme 32) [88].



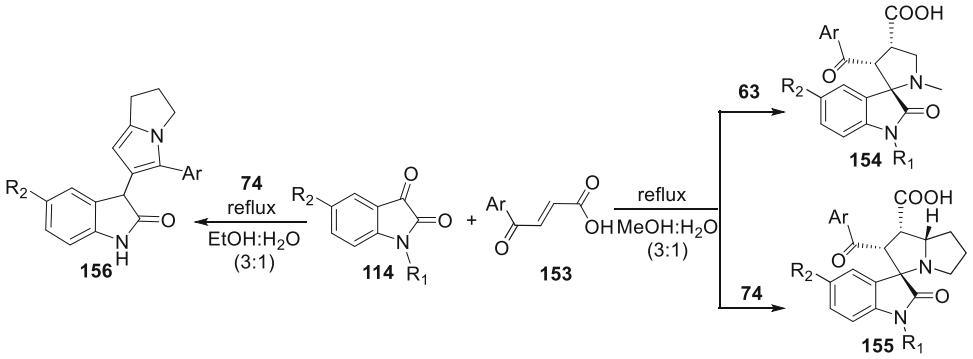
Scheme 33 Utilization of 3-benzylidene-1-alkyl-pyrrolidine-2,5-diones as dipolarophiles

Conversion of N-maleimides **144** into 3-benzylidene-1-alkyl-pyrrolidine-2,5-dions **148** enabled synthesis of series of novel dispiropyrrolidines **149** through 1,3-dipolar cycloaddition of an azomethine ylide generated from sarcosine **63** and isatins **114** (Scheme 33) [89].

Scheme 34 Utilization of unsymmetrical dipolarophiles acrylamides and methacrylamide in 1,3-dipolar cycloaddition reactions



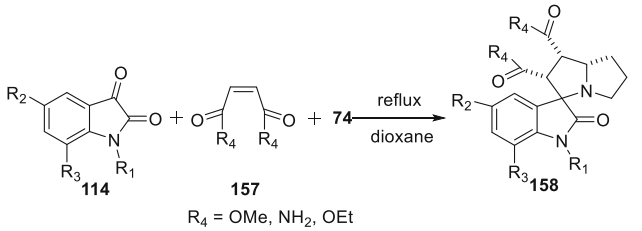
Scheme 35 The three-component reaction of isatins, sarcosine/proline and aroylacrylic acids



There are some publications on the use of esters of acrylic and cinnamic acids as dipolarophiles [72,90]. In a recent study we put previously unemployed unsymmetrical dipolarophiles acrylamides **150** and methacrylamide **151** in the cycloaddition with azomethine ylides obtained from isatin **114** and sarcosine **63** or from cyclic α-amino acids (proline **74**, thiazolidine-4-carboxylic acid **121**). The cycloaddition of azomethine ylides to acrylamides may occur along two routes (a and b) and lead to the formation of compounds **152** or **153**, respectively (Scheme 34). However, a regioselective formation of spiro[indole- 3,2′-pyrrolidin]-2-ones **152** was confirmed by ^{1}H NMR spectra [91].

Aroylacrylic acids **153** were for the first time successfully used in this three-component reaction as unsymmetrical dipolarophiles [92]. The domino-reaction of dipolarophiles **153** with isatins **114** and sarcosine **63**/proline **74** led to spiropyrrolidines **154** and spiropyrrolizidines **155** in moderate to good yields. All experiments showed the formation of only one type of regioisomer. The higher reactivity of aroylacrylic acids affects the reaction time, which is decreased to 10-15 min by refluxing in a mixture of methanol and water. Interestingly, the long-term heating of isatins **114**, aroylacrylic acids **153** , and proline **74** leads to the formation of novel rearranged products **156** (Scheme 35), which have unexpected structures as was confirmed by ^{1}H, ^{13}C and 2D NMR spectroscopy.

Liu et al. reported a three-component tandem cycloaddition reaction between substituted isatins **114**, *L*-proline **74** and various maleic acid derivatives **157** that led to the racemic spiropyrrolizidine oxindoles **158** (Scheme 36) [93].



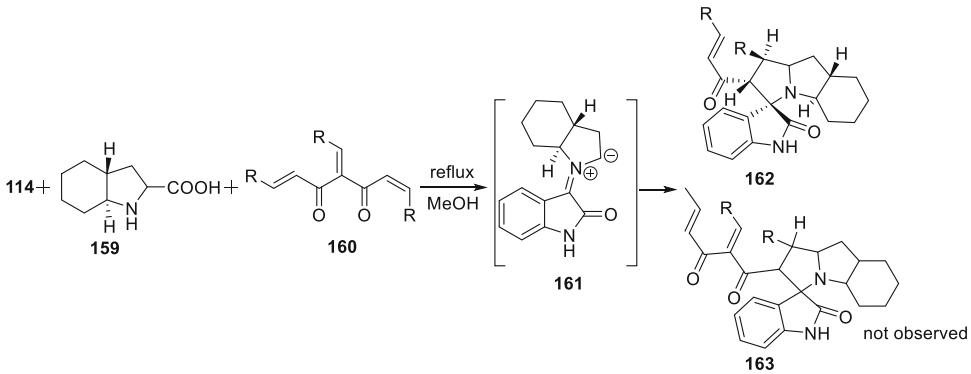
Scheme 36 Synthesis of racemic spiropyrrolizidine oxindoles

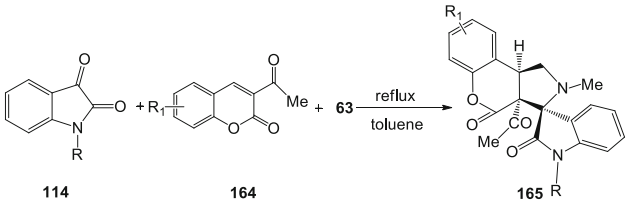
Murugan et al. reported the cycloaddition of azomethine ylides generated from the decarboxylative condensation of isatin **114** with octahydro-1*H*-indole-2-carboxylic acid **159** with triarylideneacetylacetone derivatives **160** to obtain novel spiroheterocycles **162** with high regio- and stereoselectivity. The hypothetical product **163** was not detected (Scheme 37) [94]. Presumably, the *anti*-ylide **161** is involved in the transition state. The steric repulsion between the carbonyl groups of oxindole and the octahydro-1H-indole-2-carboxylic acid ring disables the formation of *syn*-ylide. Formation of the cycloadducts was followed by the cleavage of the cinnamoyl group.

3-Acetyl-2*H*-chromen-2-ones **164** have been used as a cyclic analogs of α, β-unsaturated ketones in the synthesis of chromeno[3,4-c]spiropyrrolidine-oxindoles **165** (Scheme 38) [95].

The reactions of 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones **166** with isatin **114**, sarcosine **63** or thiazolidine-4-carboxylic acid **121** regioselectively gave spiropyrrolidines **167** or spirothiapyrrolizidines **168** (Scheme 39) [96].

Scheme 37 Utilization of bisarylideneacetones as dipolarophiles in spiropyrrolidine derivatives synthesis





Scheme 38 Synthesis of chromeno[3,4-c]spiropyrrolidine-oxindoles

Synthesis of pyrrolidinyl-spirooxindoles **171** fused to sugar lactone (Scheme 40) has been achieved by a one-pot 1,3-dipolar cycloaddition of α, β-unsaturated lactone **169**, isatins **114** and secondary α-amino acids (sarcosine **63**/*L*-proline **74**/piperidine-2-carboxylic acid **170**). The cycloaddition was found to be highly regio- and diastereoselective [97].

A number of functionalized 3-spiropyrrolidine **173** and 3-spiropyrrolizidine **174** oxindoles has been synthesized with excellent yields utilizing Baylis-Hillman adducts **172** as dipolarophiles (Scheme 41) [98].

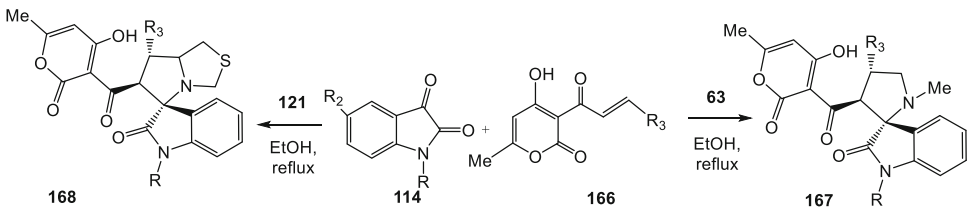
The 1,3-dipolar cycloadditions involving 1,4-naphthoquinone **178** as dipolarophile and an azomethine ylide generated from α-amino acids (*L*-proline **74**, *L*-isoleucine **175**, *L*-phenylalanine **138**, *L*-tryptophan **176**, *L*-valine **177**) and isatins **114** have been used to afford the pyrrolidine-2-spiro-3′-oxindoles **179** with moderate to excellent yields (Scheme 42) [99].

Another example of utilizing the 1,4-naphthoquinone **179** as the dipolarophile describes formation of spirooxindoles **180** followed by spontaneous dehydrogenation (Scheme 43) [100]. Oxydative processes were avoided when the reactions were carried out under nitrogen atmosphere. Synthesized compounds were evaluated for their antimicrobial and antifungal activities.

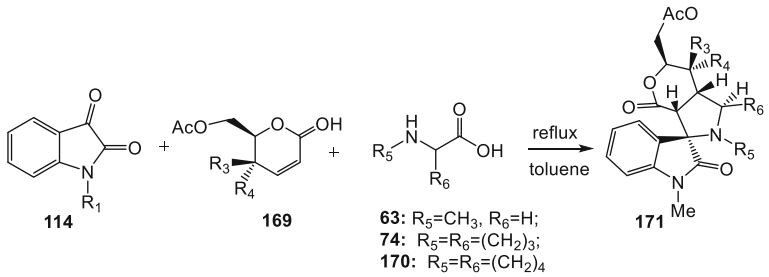
Taghizadeh et al. described a library of new chiral spirooxindolopyrrolizidines **183** from the isatin derivatives **114**, (*S*)-proline **74**, and chiral cinnamoyl oxazolidinone **182** in high to excellent yields followed by the removal of the chiral auxiliary in a non-destructive manner (Scheme 44) [101].

Spirooxindoles **185** containing tri- and tetracyclic fused pyrrolobenzo[*b*]thiophene-1,1-dioxide were obtained when a benzo[*b*]thiophene-1,1-dioxide **184** was used as dipolarophile in the three-component reaction with substituted isatins **114** and sarcosine **63** or *L*-proline **74** (Scheme 45) [102]. The methodology affords high yields of products in a short reaction time.

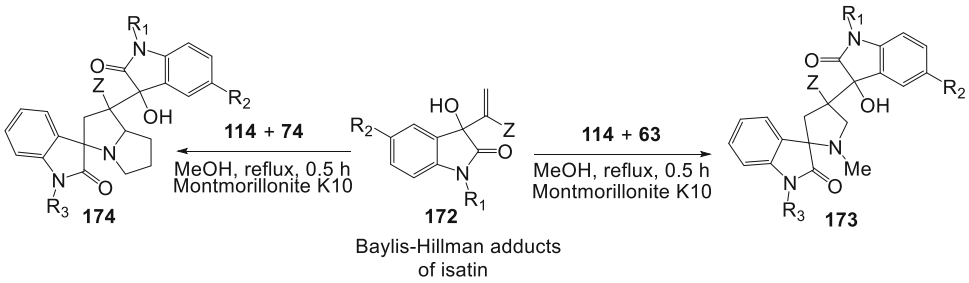
Scheme 39 Utilization of 4-hydroxy-6-methyl-3-((*E*)-3-phenylacryloyl)-2*H*-pyran-2-ones as dipolarophiles in spiropyrrolidines/spirothiapyrrolizidines synthesis



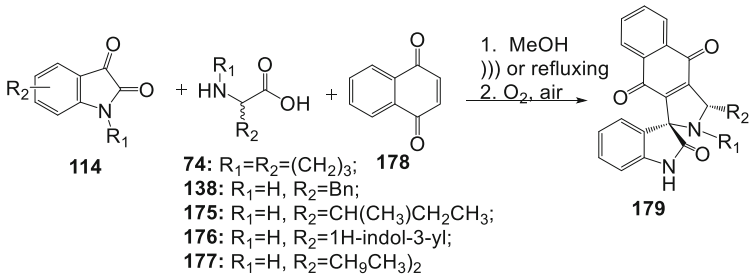
Scheme 40 Synthesis of sugar lactone-fused spiropyrrolizidine oxindoles



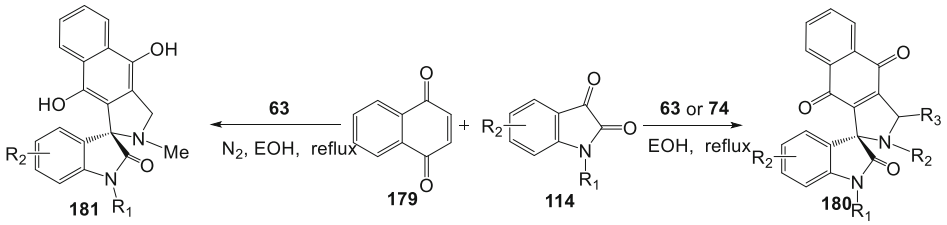
Scheme 41 Synthesis of spiropyrrolizidineoxindoles and spiro-pyrrolidineoxindoles from the Baylis-Hillman adducts of isatin



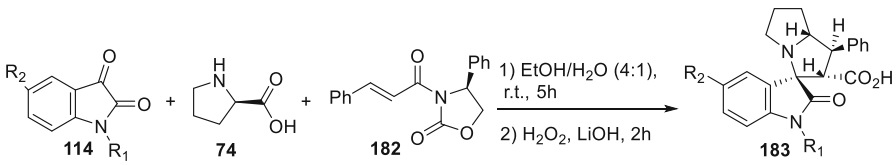
Scheme 42 1,3-Dipolar reaction of isatin, amino acids, and 1,4-naphthoquinone under ultrasound irradiation



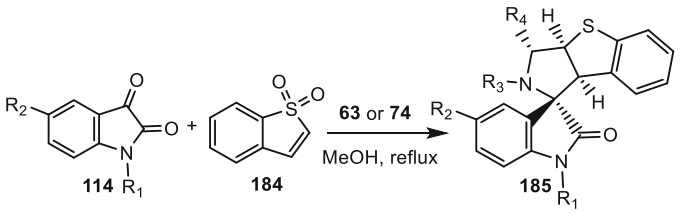
Scheme 43 Synthesis of spirooxindole derivatives from substituted isatin, *L*-proline or sarcosine and 1,4-napthoquinone



Scheme 44 Asymmetric synthesis of new chiral spirooxindolopyrrolizidines



Scheme 45 Spiro-fused pyrrolobenzo[*b*]thiophene-1,1-dioxide derivatives



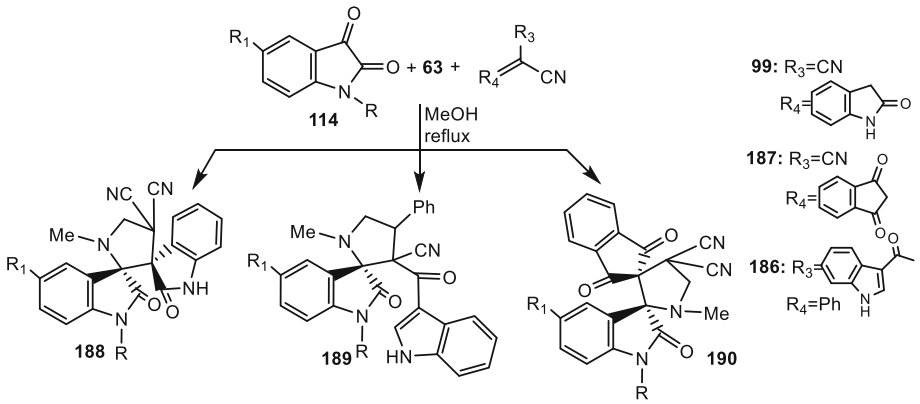
As has been noted above, 2-oxo-(3*H*)-indole-3-ylidine-malononitrile**99** does not react with phenacyl-quinolinium ylides **97** [63]. Although, spiro- and dispiropyrrolidine oxindoles **188**–**190** were synthesized using isatylidene malononitrile **99**, 2-(1*H*-indole-3-carbonyl)-3-phenyl-acrylonitrile **186** and 2-(1,3-dioxo-indan-2-ylidene)-malononitrile **187** as dipolarophiles, respectively (Scheme 46) [103]. The observed *endo*-regioisomers **188**–**190** are more favorable due to the secondary orbital interaction, which is not possible in the *exo*-transition state.

2-Oxo-(2*H*)-acenaphthylen-1-ylidene-malonodinitrile **191** and 2-fluoren-9-ylidene-malonodinitrile **192** have been investigated for the first time as dipolarophiles in the 1,3-dipolar cycloaddition reaction with the azomethine ylides generated *in situ* from N-substituted isatins **114,** and sarcosine **63** to afford novel dispiroheterocycles **193** and **194** (Scheme 47) [104].

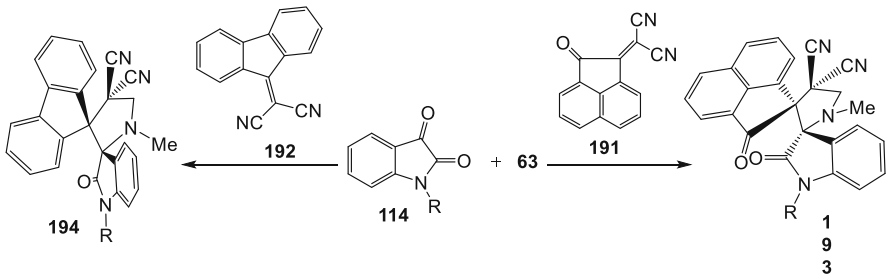
Fluorene derivatives, such as 9-arylidine-fluorene **195** can be utilized in the regioselective synthesis of novel dispiro[pyrrolo/pyrrolizidino] ring systems **196** by the cycloaddition to the azomethine ylides generated by a decarboxylative route from sarcosine **63**/*L*-proline **74** and isatin **114** using different methodologies (Scheme 48) [105]. The regioisomers **197** were not observed.

Dispirooxindoles can be obtained when α, β-unsaturated ketones, such as 3-aroylmethyleneindol-2-ones **198** are

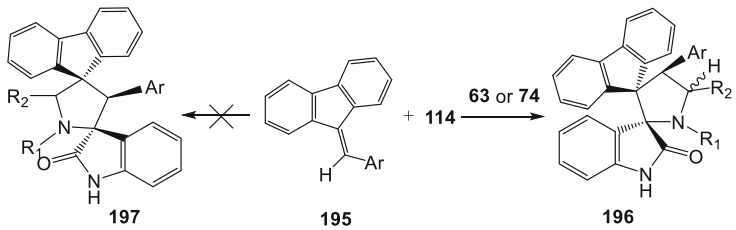
Scheme 46 1,3-Dipolar cycloaddition reaction of isatin, sarcosine, and isatylidene malononitrile



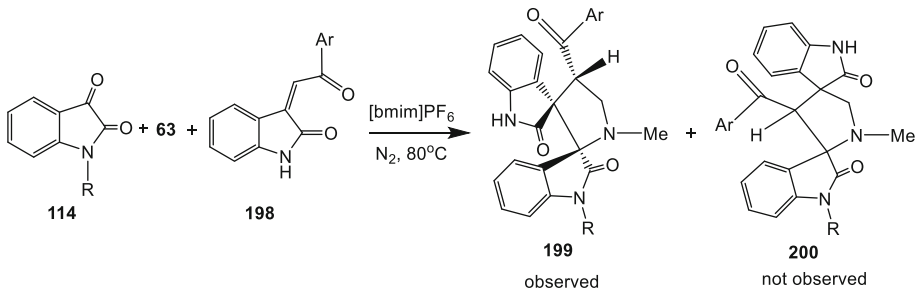
Scheme 47 Use of acenaphthylen and fluoren ylidene-malonodinitrile derivatives in 3,2′-spirooxindole synthesis



Scheme 48 Use of 9-arylidine-fluorene as a dipolarophile in spirooxindole synthesis



Scheme 49 Synthesis of dispiropyrrolidine-bisoxindole derivatives

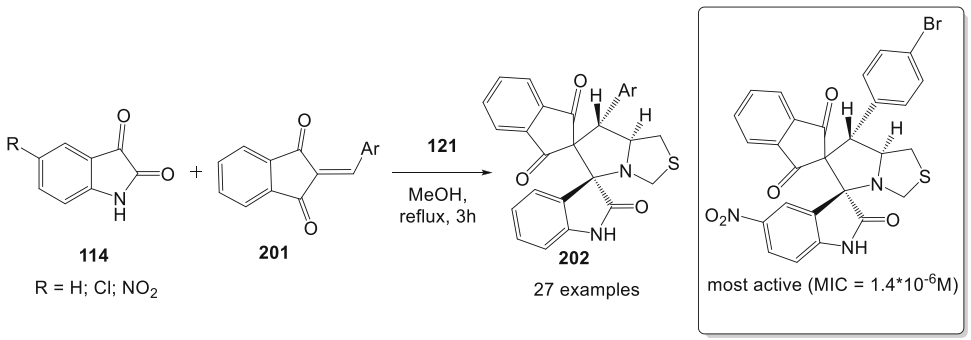


taken as dipolarophiles [106]. Recently, the synthesis of novel dispiropyrrolidine-bisoxindole derivatives **199** has been accomplished by three-component, 1,3-dipolar cycloaddition methodology by stirring the reaction mixture under nitrogen atmosphere at 80 °C in the presence of ionic liquid for the first time (Scheme 49) [107]. The secondary orbital interaction (SOI) of the carbonyl group of dipolarophile **198** with azomethine ylide affects the regiochemistry in the product formation. Hence, only one regioisomer **199** was obtained in the reaction.

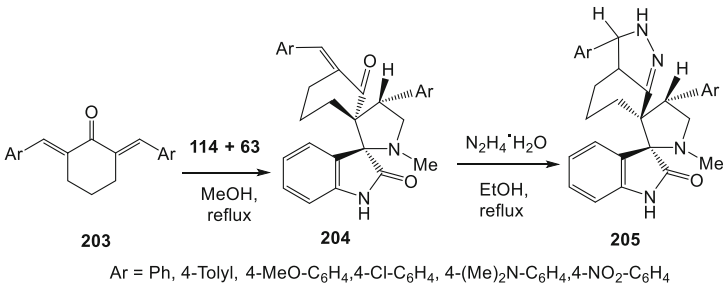
In this way, 2-arylmethylideneidene-1,3-indanediones **201** reacted with non-stabilized ylides generated *in situ* by the decarboxylative condensation of isatins **114** with 1,3-thiazoline-4-carboxylic acid **121** to afford dispiro-oxindolylpyrrolothiazoles **202** (Scheme 50). The obtained compounds possess minimum inhibitory concentration against pathogenic bacteria in the range of 1.4–55.2 μM (near to references of anti-tubercular drugs, such as ethambutol, ciprofloxacin, rifampicin and isoniazid) [108].

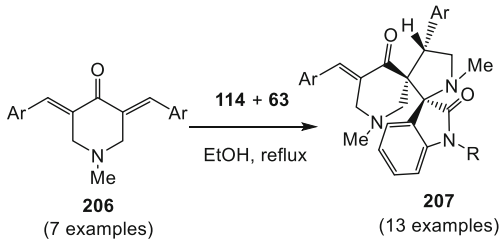
2,6-Bis(arylmethylidene)cyclohexanones **203** are of interest in the synthesis of spirooxindole derivatives [109]. Thus, a regioselective 1,3-dipolar cycloaddition reaction with the azomethine ylide derived from isatin **114** and sarcosine **63** by a decarboxylative route afforded a series of spiro[pyrrolidine-2′,3-oxindoles] **204** with no traces of the other regioisomers (Scheme 51) [110].

Scheme 50 One-pot synthesis of dispiro-oxindolylpyrrolothiazoles with antitubercular activity



Scheme 51 The 2,6-bis(arylmethylidene)cyclohexanones as electron deficient π-systems in 3,2′-spirooxindols synthesis





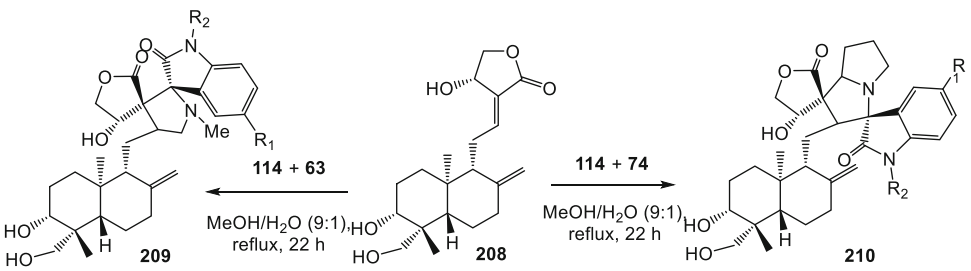
Scheme 52 3,5-Bis(arylmethyliden)-1-methyl-4-piperidinones as 1,3-dipolarophiles in 3,2′-spirooxindole synthesis

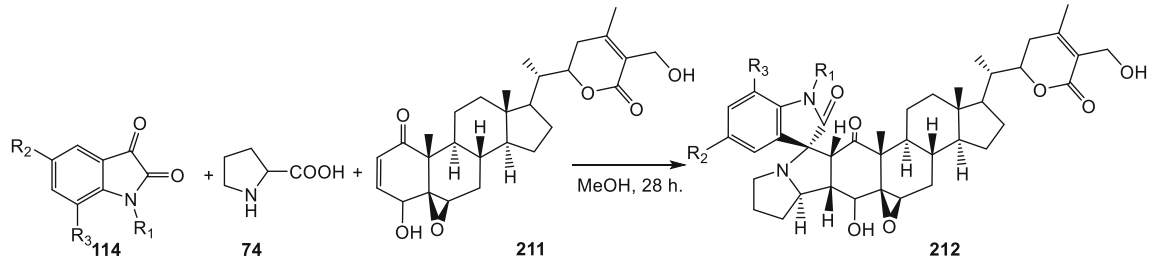
Similar results were obtained by A. Girgis when 3,5-bis(arylmethylene)-1-methyl-4-piperidinones **206** were regioselectively reacted with azomethine ylides, generated *in situ* via decarboxylative condensation of isatins **114** with sarcosine **63,** affording dispiro[3*H*-indole-3,2′-pyrrolidine-3,3-piperidine]-2(1*H*), 4″-diones **207** (13 examples) (Scheme 52) [111]. It was found that the representative examples of the synthesized compounds reflect mild activity against most of the human tumor cells.

Hazra et al. presented a facile synthesis of novel dispiro-compounds **209, 210** via 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from isatin derivatives and α-amino acids (sarcosine **63** or *L*-proline **74**) to the conjugated double bond of andrographolide **208** (the major labdane diterpene constituent of *Andrographis paniculata*) (Scheme 53) [112].

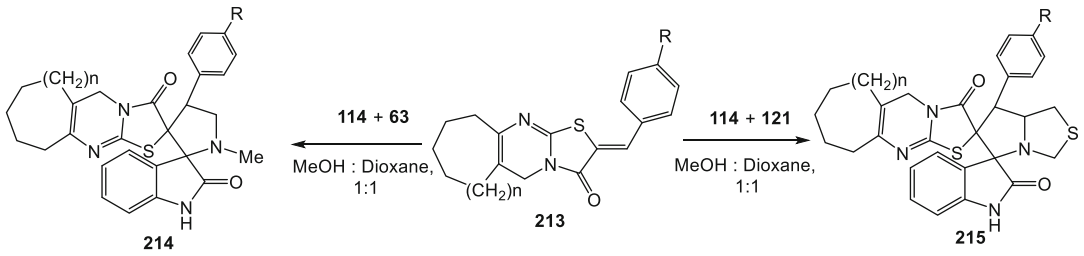
Natural products with steroidal framework have opened so many areas for medicinal and pharmacological chemistry. There was an attempt to apply steroidal dipolarophiles in the synthesis of spirooxindoles [113]. The most recent research is devoted to the facile, atomeconomic synthesis of novel spiro-pyrrolizidino-oxindole adducts **212** of withaferin-A (a polyfunctional steroidal lactone based on an ergostane framework) **211** (10 compounds) via the intermolecular cycloaddition of azomethine ylides generated *in situ* from proline **74** and isatins **114**. The reaction is highly chemo-, regio-, and stereoselective affording the *cis*-fused products with β-oriented hydrogen (Scheme 54). Bioevaluation of several representatives of adducts **212** against six cancer lines (e.g., CHO, HepG2, HeLa, HEK 293, MDCK-II, and Caco-2) identified them as promising potential anticancer compounds [114].

Scheme 53 Synthesis of dispiropyrrolizidino-oxindole andrographolide adducts

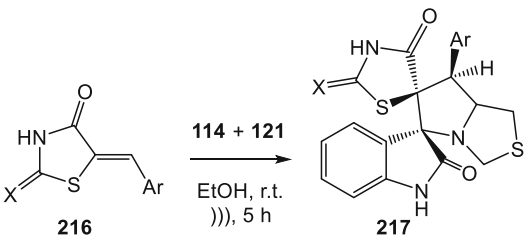




Scheme 54 Various estrone derivatives as 1,3-dipolarophiles in spirooxindole synthesis



Scheme 55 Synthesis of a new class of spirooxindolo pyrrolidines and spirooxindolo thiapyrrolizidines



Scheme 56 Synthesis of dispirooxindolecyclo[pyrrolo[1,2-c]thiazole-6,5′-thiazolidine] derivatives under ultrasonic conditions

The ylides generated from isatin **114** and sarcosine **63** or *L*-thiazolidine-4-carboxylic acid **121** were reacted with arylidene octahydro/decahydro cycloalka[*d*]thiazolo[3,2-*a*] pyrimidine-3-ones **213** to yield novel dispiropolycyclic complex heterocycles **214** and **215** (Scheme 55) [115].

The 5-arylidene-1,3-thiazolidine-2,4-dione **216** is described as dipolarophile in a series of research [116,117]. Recently, dispirooxindolecyclo[pyrrolo[1,2-c]thiazole-6,5′-thiazolidine] derivatives **217** have been regioselectively synthesized from isatin **114**, thiazolidine-4-carboxilic acide **121** and 5-benzylidene-2-thioxothiazolidin-4-one **216** (Scheme 56) [118].

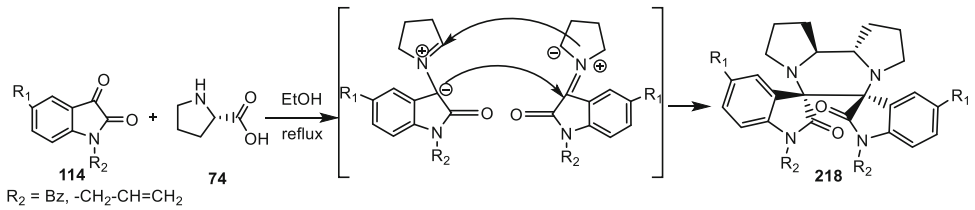
Interestingly, the condensation of 1-allyl (benzyl)-5-haloisatins **114** and *L*-proline **74** in a molar ratio of 1:1 in ethanol medium under reflux for 1–2 h leads to self-condensation dispiroadducts **218** with carbon dioxide release (Scheme 57) [119].

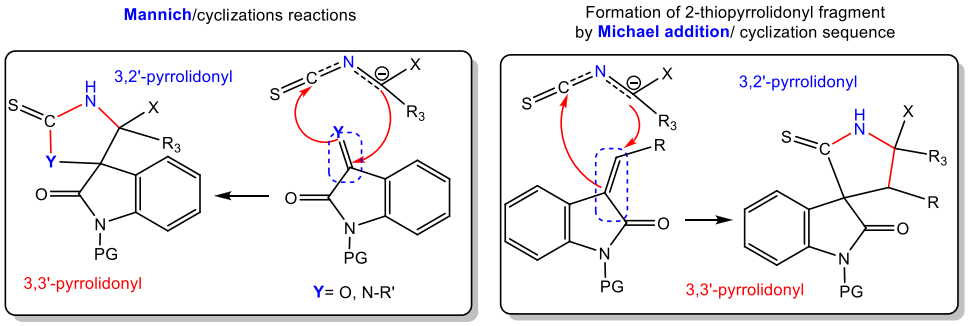
Enantioselective Michael/Cyclization reaction sequence for the 3,3′- and 3,2′-thiopyrrolidonyl spirooxindole construction

There are two principal different ways to utilize 2-oxindolic reagents in the reaction with α-isothiocyanato compounds, such as the Mannich/cyclizations reactions (discussed below) and the Michael addition/cyclization sequence. However, only the Michael addition leads to the formation of spiro-linked 2′-thiopyrrolidonyl fragments. Thus 3,3′- and 3,2′-thiopyrrolidonyl spirooxindoles can be formed depending on the structure of the 2-oxindolic core [120,121] (Scheme 58).

The enantioselective Michael addition/cyclization sequence of α-isothiocyanates **219** and methyleneindolinones **220** leads to the 3,3′-thiopyrrolidonyl spirooxindole scaffolds **222**. The methyleneindolinones **220** serve as the perfect electron-deficient olefins because of their high reactivity as Michael acceptors, as well as their unique structural characteristics (Scheme 59).

Scheme 57 Formation of dispiroadducts via the isatin ylides self-condensation process





Scheme 58 Mannich and Michael additions type reactions in 2-oxindolic core synthesis

In particular, Y. Cao group firstly reported the enantioselective Michael addition/cyclization method using an α-isothiocyanato imide and methyleneindolinones [124]. Other authors expanded the usefulness of the α-isothiocyanato nucleophiles in obtaining optically active spirooxindoles. The catalytic asymmetric Michael addition/cyclization of isothiocyanato oxindoles also leads to an enatiomerically enriched bi-spirooxindoles containing three contiguous stereocenters and two spiro-quaternary centers (Scheme 59).

The oxygen-containing heterocycles spiro-fused with the oxindole ring system

Synthesis of spirooxindoles with a spiro-fused pyran fragment

The pyrane/chromene-based heterocycles that fuse with an oxindole ring system represent a potentially promising subset of the tetrahydropyranone and pyrrolidinyl spirooxindole natural products (Fig. 5).

The first group of synthetic strategies are based on cyclization type reactions of 2-indolinone-tethered unsaturated alcohols **224** derived from regioselective addition of stabilized organoindium reagents to isatins **114** in an aqueous environment. The diversely functionalized spiro-dihydropyran-oxindoles **225** have been obtained by using different metal-mediated carbonyl-addition/cyclization reaction sequences under Grubb's ruthenium-based catalysts (Scheme 60) [125].

S. Hande et al. have developed a concise synthetic route to various spirooxindoles **228** with a tetrahydropyran cycle through a palladium-catalyzed carbosilylation of 1,3-dienes **226** and subsequent Sakurai-type cyclization (Scheme 61) [126].

The highly functionalized spirooxindole 4H-pyran-2-ones **231** with three contiguous stereogenic centers were synthesized through the N-heterocyclic carbenes and catalyzed the three-component reaction of oxindoles **229** with alkynyl aldehydes **230** (Scheme 62) [127].

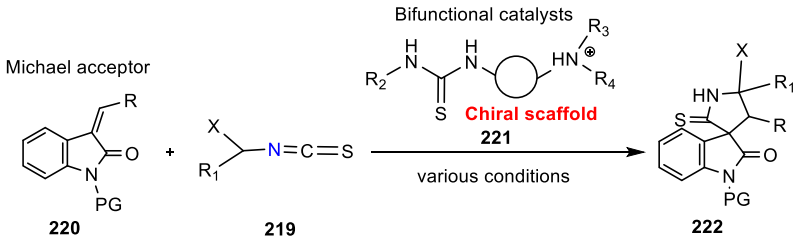
J. Porco et al., Y. Zhang and J. Panek reported the diversity-oriented stereoselective synthesis of both enantioenriched spirocyclic pyranoxindoles **234** and **235** via Lewis acid mediated Prins cyclizations (Scheme 63) [128,129]. This strategy is based on the Prins cyclization reaction of isatin dimethyl acetals **232** with enantiopure homoallylic alcohols **233** in the presence of trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a catalyst.

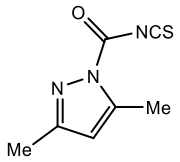
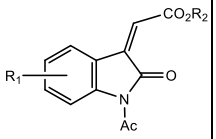
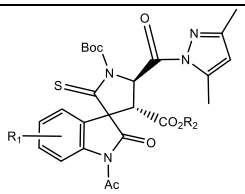
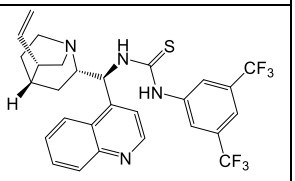
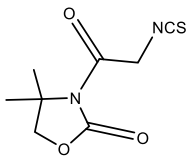
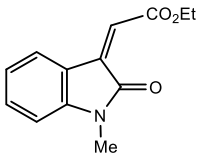
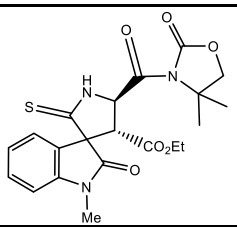
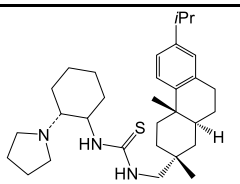
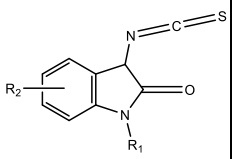
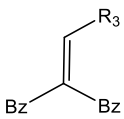
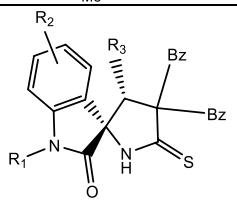
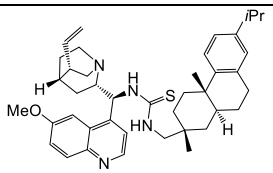
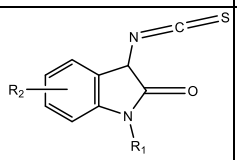
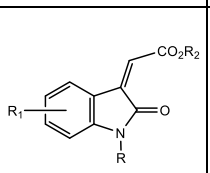
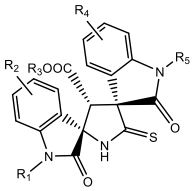
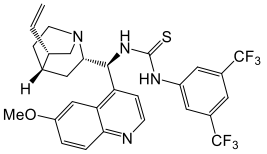
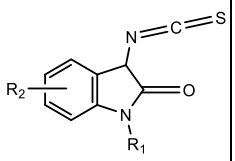
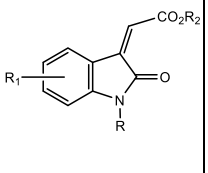
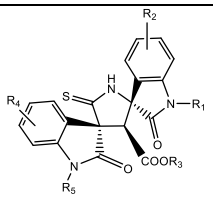
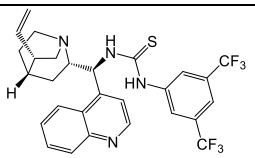
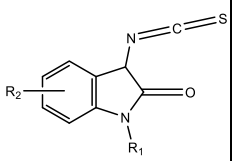
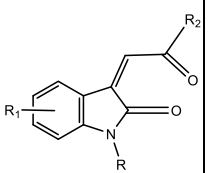
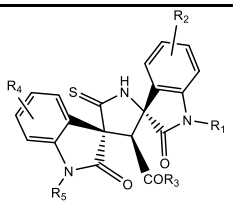
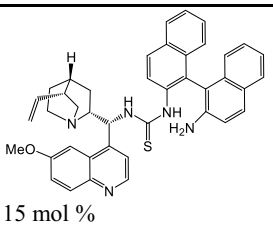
A similar approach based on a Brönsted acid-catalyzed Prins-type cyclization of isatin dimethyl acetal **232** and a β-hydroxy dioxinone fragment **236** leads to the spirooxindole pyrans **237** in high yields and excellent diastereoselectivity (Scheme 64) [130].

Recently, Zh. Lian and M. Shi disclosed a novel nitrogen- and phosphorus-containing Lewis base mediated by [4+2] and [3+2] annulations of N-protected isatins **114** with but-3-yn-2-one **238** to produce the spiro[indoline-3,2′-pyran]-2,4′(3′*H*)-diones **239** and spiro[furan-2, 3′-indoline]-2′, 4(5*H*)-diones **240**, respectively, in good yields under mild conditions [131] (Scheme 65).

In recent years the concept of fast and convenient MCRs has found various applications in the synthesis of spiro-indolones. The main synthetic method for assembling of spiro[4*H*-pyran-oxindole] compounds is based on the three-component reactions of two (usually different) 1,3-dicarbonyl compounds, or alternatively their synthetic equivalents, with isatin derivatives. We and others investigated three-component reactions of isatins **114**, malononitrile **240**, phenyl-acetonitrile **241**, methyl-, ethyl- and other cyanoacetates **242**, and various 1,3-dicarbonyl compounds **243** to afford a series of spiroindolones **244** (Scheme 66) [132–136].

As can be seen from the literature, MCRs procedures use different catalysts, such as tris(2–hydroxyethyl)amine [137], *L*-proline [138], sodium stearate [139], [BMIm]BF_4 [140] as catalysts in an alcoholic or aqueous medium for the activation of these processes, as well as non-catalyst and solvent-free conditions [141–143]. The most recent research described a silica-bonded 5-*n*-propyloctahydropyrimido[1,2-*a*]azepinium chloride (SB-DBU)Cl as the heterogeneous silica-supported ionic liquid catalyst used for the efficient synthesis of spiro[4*H*-pyran-oxindoles] **244** [144].



Reference	α-Isothiocyanato nucleophiles **219**	Michael acceptor **220**	Products **222**	Bifunctional catalysts **221**
[126]				 10 mol %
[129]				 10 mol %
[122]				 15 mol %
[127]				 15 mol %
[123]				 15 mo l%
[128]				 15 mol %

Scheme 59 Construction of spirooxindoles through an organocatalytic cascade Michael–cyclization sequence

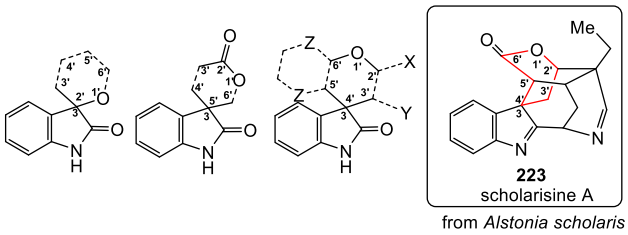


Fig. 5 Spirooxindoles types containing spiro-fused pyran or chromene fragments

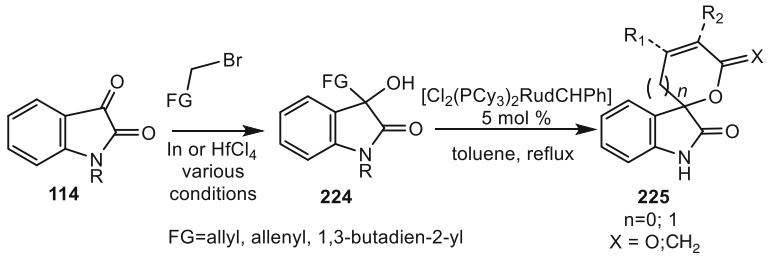
Several approaches were made for the synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazoles] **246** in the presence of basic catalysts in an alcoholic medium as well as solvent-free reaction of isatins **114**, 3-Methyl-5-pyrazolone **245** and methylene active nitriles **240** and **242** in the presence of $NaHCO_3$ under grinding [141–143,145]. A plausible mechanism for this process may probably involve the formation of arylidenemalononitriles **A** via Knoevenagel condensation reaction of isatins methylene active nitriles **240** using various bases. The following Michael addition of the nucleophile 1-aryl-3-methyl-5-pyrazolone **245** to arylidenemalononitriles **A** gives compound **B**. After that, the intramolecular nucleophilic addition reaction between the hydroxyl group and the cyano group in compound **C** leads to the imine **D** followed by formation of the spiro compounds **246** (Scheme 67).

Recently, D. Shi et al. described the one-pot synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives **246** by the four-component reaction of hydrazine **247**, β-keto ester **248**, isatins **114**, and methylene active nitriles **240** and **242** catalyzed by piperidine under ultrasound irradiation (Scheme 68) [146].

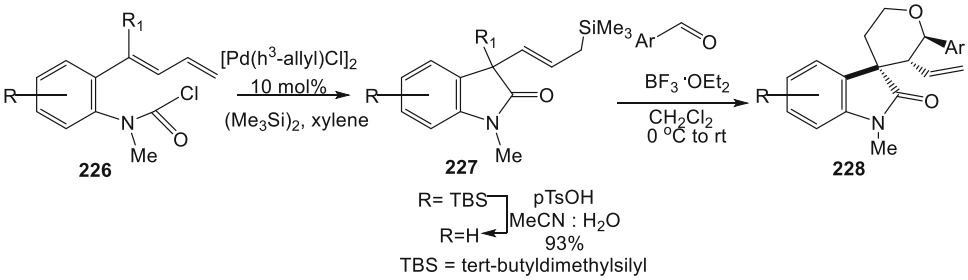
Our experience in this reactions has shown that the utilization of the 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinolines **249** (aza-analogs of 4-hydroxycoumarin) leads to similar spirocompounds **250** (Scheme 69) [147].

3-Hydroxy-1*H*-phenalen-1-one **251** is a very interesting enol-neuclophilic component in similar three-component reactions. Thus, A. Bazgir et al. described the synthesis of

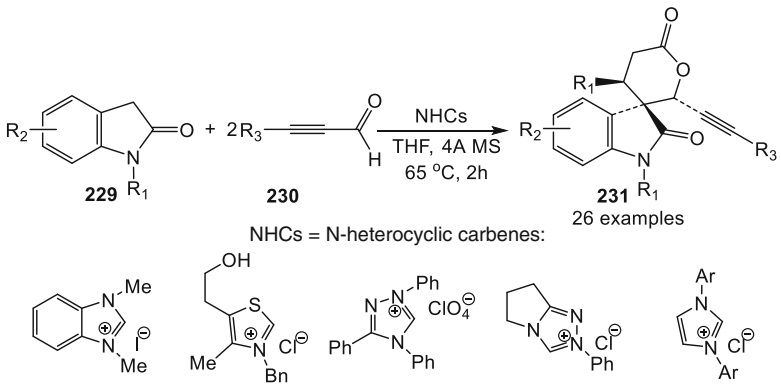
Scheme 60 Synthesis of spiro-oxolanes based on an intramolecular cyclization type reaction



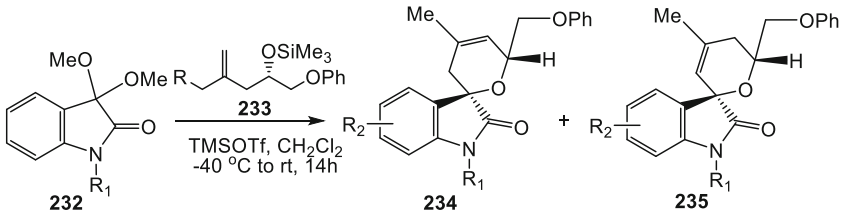
Scheme 61 Synthesis of spirooxindoles fused with a tetrahydropyran ring

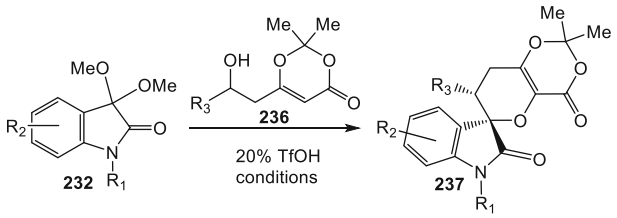


Scheme 62 Stereoselective synthetic approach to spirooxindole 4*H*-pyran-2-one derivatives



Scheme 63 The Prins-type 2-oxindole spiro-annulation





Scheme 64 The Prins-Type spiro-annulation catalyzed by Brönsted acid

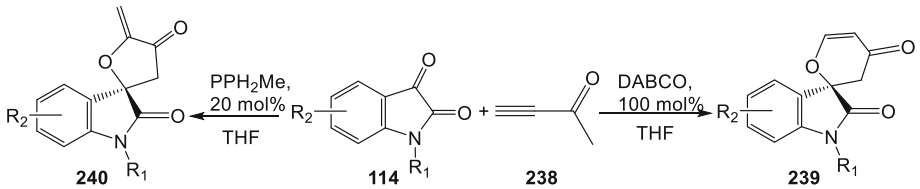
spiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitriles **252** from 3-hydroxy-1*H*-phenalen-1-one **251**, malononitrile **240** and isatin **114** in aqueous media in the presence of *p*-TSA (Scheme 70) [148].

The Michael addition of isatinilidenemalonodinitriles **99** with ketones **253** with a cinchona-based chiral primary amine **A** and *L*-camphorsulfonic acid **B** as catalysts gave the optically active adducts **254** in high yields with excellent enantioselectivity (95 to >99 % *ee*). Lately, the Michael adducts **254** were used in a cascade reduction/cyclization process for the synthesis of the spiro[2*H*-pyran-3,4′-indoline] derivatives **255** in moderate to good yields with 90–99 % *ee* (Scheme 71) [149].

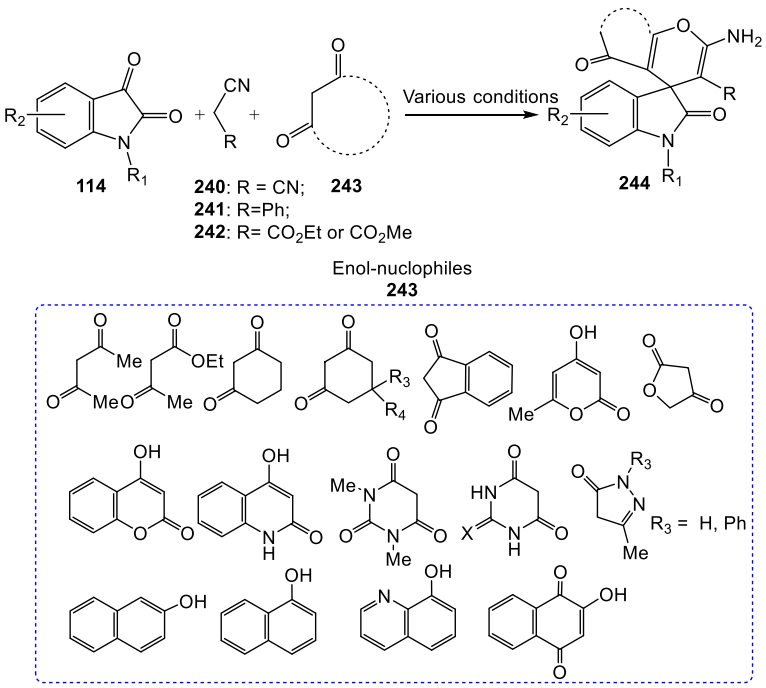
The selective Rh(I)-catalyzed condensation of *N*-methylisatin **114** with two molecules of 1,3-cyclohexanedione **256** or 4-hydroxy-6-methyl-2-pyrone **257** gives spirooxindoles **258** and **259** with 46 and 36 % yield (*dr* = 5:1), respectively (Scheme 72) [150]).

The cyclocondensation reaction of isatins **114**, 1,3-cyclohexadiones **256**, and 2-methylpyrimidine-4,6-diol **260** or 3-methyl-1-phenyl-1*H*-pyrazol-5-ol **261** in aqueous media

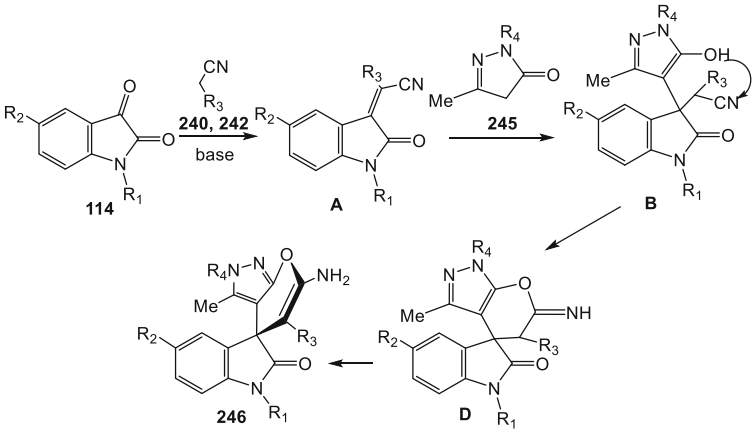
Scheme 65 Nitrogen- and phosphorus-containing Lewis base catalyzed with [4+2] and [3+2] annulations



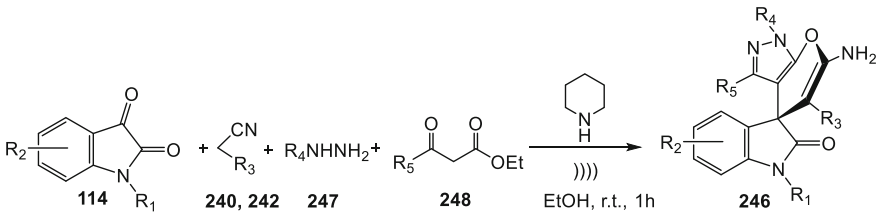
Scheme 66 MCRs of isatins and 1,3-dicarbonyl compounds



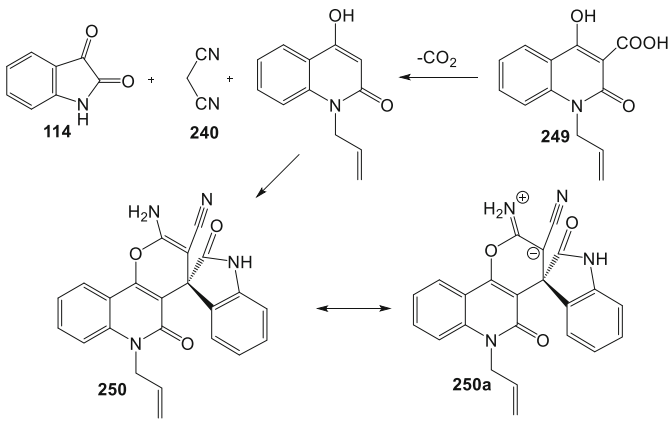
Scheme 67 Mechanism for the formation of spiro[indoline-3,4′-pyrano[2,3-c]pyrazoles]



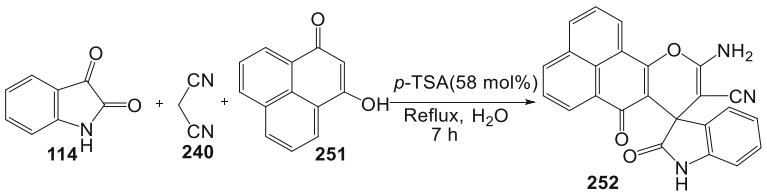
Scheme 68 Four-component synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives



Scheme 69 Synthesis spirocyclic[indole-3,4′-pyrano[3,2-c]quinolines]



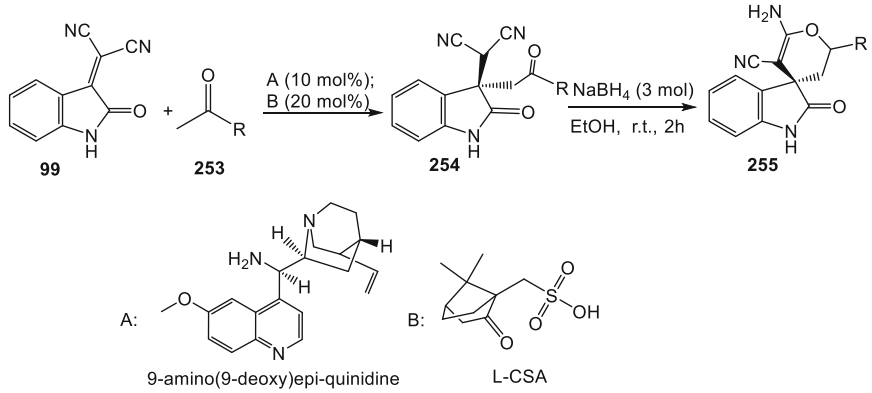
Scheme 70 *p*-TSA catalyzed synthesis of spiro[benzo[*g*]chromene-4,3′-indoline]-3-carbonitriles



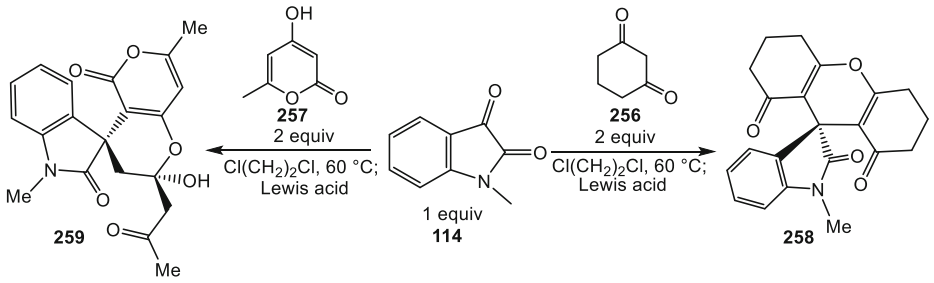
under *p*-TSA catalysis gives the spiro[chromeno[2,3-d] pyrimidine-5,3′-indoline]-2′,6(7*H*)-diones **262** and spiro [chromeno[2,3-c]pyrazole-4,3′-indoline]-2′,5(6*H*)-diones **263** (Scheme 73) [151].

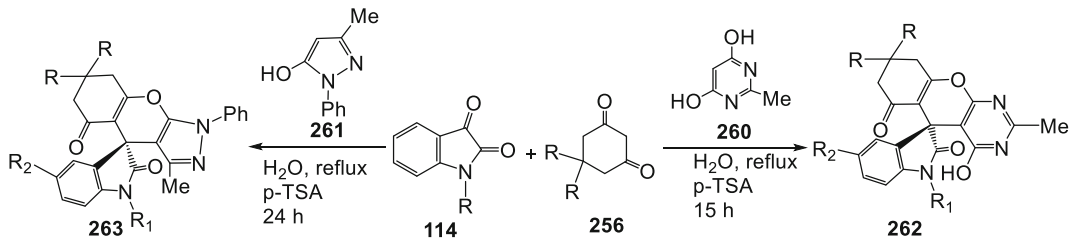
In recent years there has been considerable interest in the utilization of barbituric acid **264** in the construction of spiro compounds. Several approaches have been made for developing of new selective and environmentally friendly methodologies in the synthesis of spirooxindole heterocycles containing chromenopyrimidine ring fragments **265**. Thus, the procedures used water as a solvent in the presence of *p*-TSA as a catalyst [152]. Recently, two groups of authors identified dodecyl benzenesulfonic acid (DDBSA) functionalized by silica-coated magnetic nanoparticles ($\gamma - Fe_2O_3$@SiO_2-DDBSA) [153] and $KAl(SO_4)_2 \cdot 12H_2O$ in [Bmim]PF_6 [154] as an efficient catalysts for the synthesis of a library

Scheme 71 Asymmetric cascade Michael/reduction/cyclization reaction for the synthesis spiro[2*H*-pyran-3,4′-indoline] derivatives



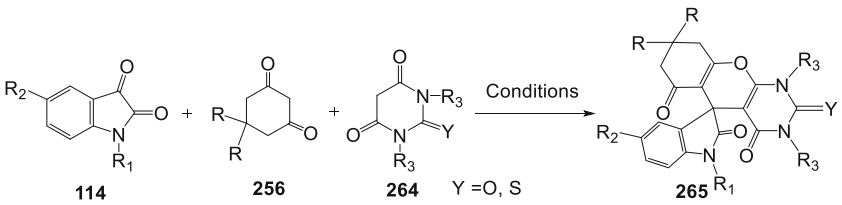
Scheme 72 Reactions of *N*-methylisatin and various 1,3-dicarbonyls





Scheme 73 Synthesis of spiro-fused chromeno[2,3-*c*]pyrazoles and chromeno[2,3-*d*]pyrimidines

Scheme 74 Synthesis of spiro[chromeno[2,3-*d*]pyrimidine-5,3′-indoline]tetraones

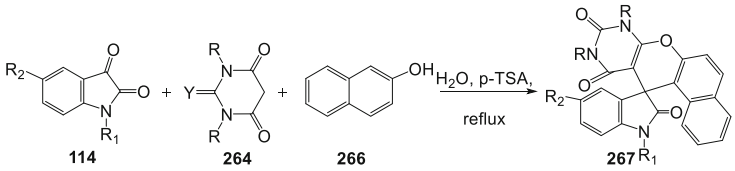


of similar spirooxindole-chromeno[2,3-*d*]pyrimidine derivatives **265** by reaction of isatins **114**, cyclohexane-1,3-diones **256**, and barbituric acids **264** (Scheme 74).

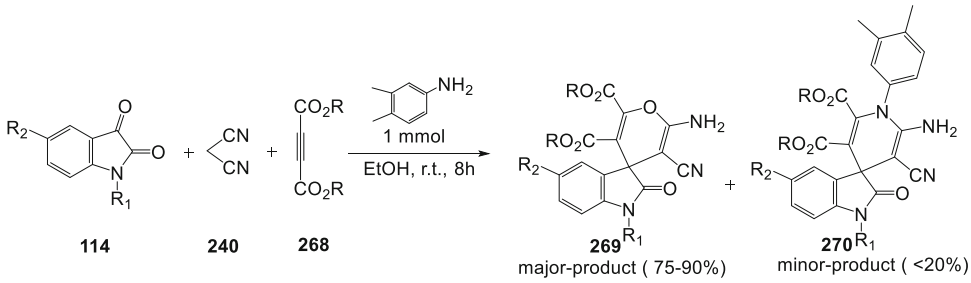
It was shown that refluxing of a mixture of barbituric acid **264**, β-naphthol **266**, and isatin **114** in water in the presence of catalytic *p*-TSA afforded the spironaphthopyranopyrimidine-indolines **267** in good yields (Scheme 75) [155].

Recently, A.Bazgir et al. presented a practical, simple, and efficient method for the synthesis of pyrano-fused spirooxindoles **269** and **270** via an organocatalytic reaction of isatins **114**, malononitrile **240**, and dialkyl acetylenedicarboxylate **268** in the presence of 3,4-dimethylaniline as a catalyst in ethanol (Scheme 76) [156].

Scheme 75 One-pot procedure for the spironaphthopyranopyrimidine-indolines synthesis



Scheme 76 Synthesis of polyfunctionalized pyrano-fused spirooxindoles



Synthesis of 3-spiroindolinones spiro-fused with piperidine moieties

Organic compounds incorporating the spiro[indoline-3,4′-piperidine] scaffold have been considered as "privileged structures" for drug research [157]. For example, Ibutamoren (MK-677, L-163,191) is a potent, orally active growth hormone secretagogue that mimics the stimulating action of the endogenous hormone ghrelin [158,159]. Some spiro[indoline-3,4′-piperidines] have been identified as vesicular acetylcholine transporters (Fig. 6) and as novel targets for insecticide action against major agricultural pest species with low mammalian toxicity [160].

The synthetic strategies for the formation of the spiro[indoline-3,4′-piperidine] skeleton are based on a large variety of classical synthetic methods [161,162]. Thus, an intramolecular Heck reaction of a tetrasubstituted alkene **271** was used in the total synthesis of the marine fungal alkaloid (±)-communesin F **273** [163] (Scheme 77).

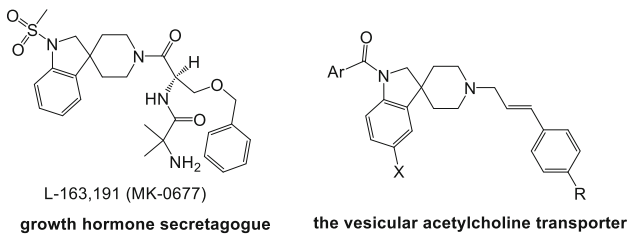


Fig. 6 Biologically active spiro[indoline-3,4′-piperidines]

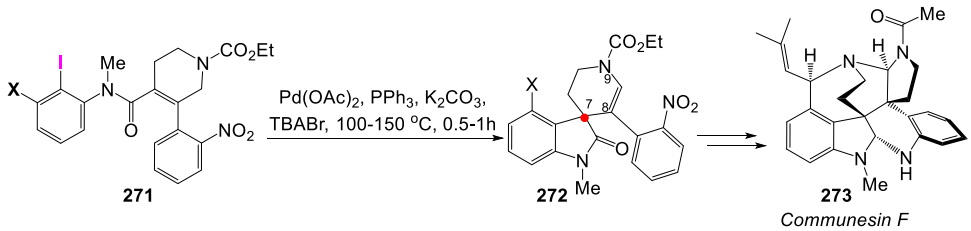
A novel synthetic strategy was realized for the formation of the chiral spiropiperidineoxindole system **276** from a ring closing metathesis of an enantiopure quaternary 3-aminooxindole **274** in the presence of a 2nd generation Grubbs catalyst (Scheme 78) [164].

Later, the synthesis of spirooxindoles **281** and **282** with the same stereochemistry as the core structure of tabernoxidine was accomplished by a Sakurai type reaction (Scheme 79) [130]. In the first step, a Mitsunobu reaction of alcohol **227** with glutarimide **277** or succinimide **278** was followed by reduction to give compounds **279** or **280**, respectively. The followed Sakurai-type cyclization with $BF_3 \cdot 3OEt_2$ proceeded diastereoselectively and gave compounds **281** or **282** in excellent yields.

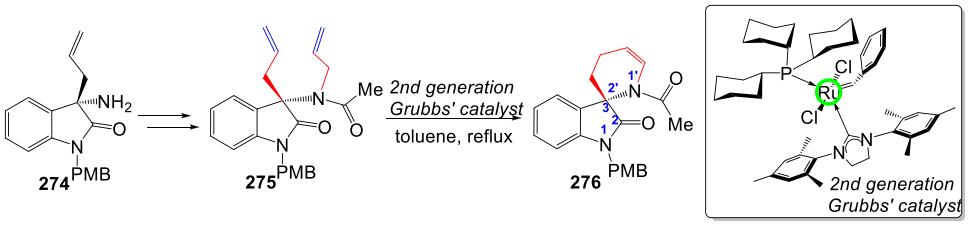
Recently, an efficient $FeCl_3$-catalyzed stereoselective intramolecular tandem 1,5-hydride transfer/ring closure reaction was developed by Han et al. (Scheme 80) [165]. This method allows obtaining structurally diverse spirooxindole tetrahydroquinolines **284** in high yields (up to 98 %) with good to excellent levels of diastereoselectivity (up to 99:1 *dr*).

MCRs have been also widely used in the synthesis of spiro[indoline-3,4′-piperidines]. A novel efficient route for the synthesis of spiro dihydropyridines **287** was developed through a four-component reaction of isatin **114**, malononi-

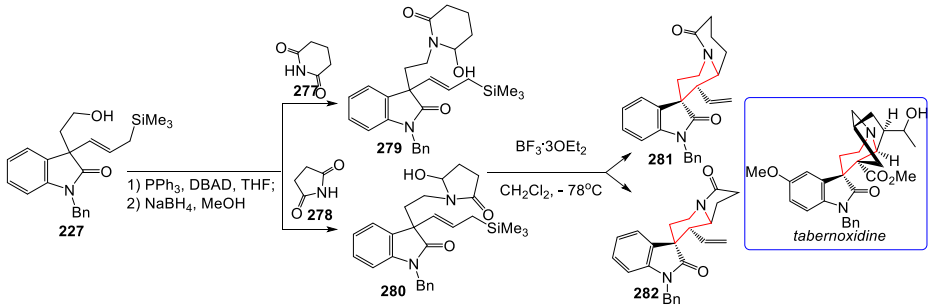
Scheme 77 The application of an intramolecular Heck reaction for the spiro[indoline-3,4′-piperidine] scaffold construction

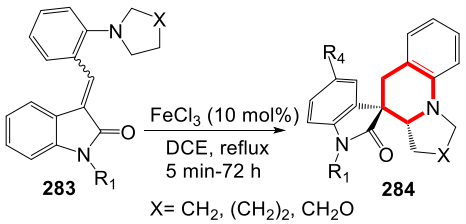


Scheme 78 Key ring-closing metathesis reaction in the presence of the 2nd generation Grubbs catalyst in spiropiperidine-3,2′-oxindoles synthesis



Scheme 79 Synthesis of spirooxindoles fused with a piperidine ring





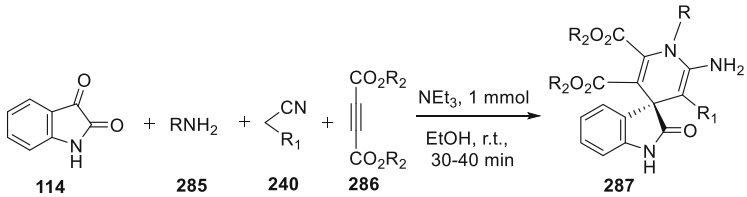
Scheme 80 Intramolecular 1,5-hydride transfer/ring closure reaction of methyleneindolinones

trile **240**, primary amines **285** and acetylenic esters **286** with high yields and a simple experimental procedure (Scheme 81) [166].

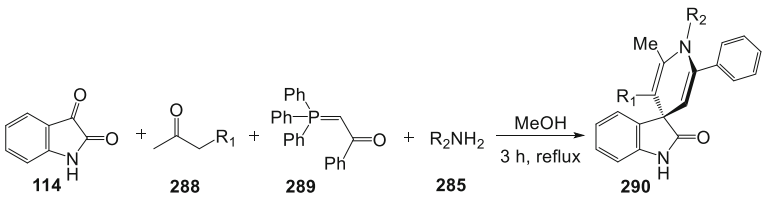
Another four-component reaction of isatin **114**, 1,3-dicarbonyl compounds **288**, 1-phenyl-2-(1,1,1-triphenyl- λ^5-phosphanylidene)-1-ethanone **289** and amine **285** under refluxing in dry methanol afforded a series of spirooxindole derivatives **290** containing indoline-3,4′-pyridine-3′-carboxylate fragments in 74–85 % yields (Scheme 82) [167].

The reactions of isatin with aromatic amines and suitable CH-acids proceed very easily and can be done even in the absence of solvents, for example, under mechanical activation. For instance, it was suggested a simple synthesis of spiro[diindenopyridine-indoline]triones could be done **292** via the reaction of 1,3-indandione **291**, aromatic amines **285** and isatins **114** based on a "Grindstone Chemistry" method in the presence of a catalytic amount of *p*-TSA (Scheme 83) [168]. Compounds **292** are potent anticancer agents, which have cytotoxic and apoptosis inducing potencies that compare favorably with the clinical anticancer agent etoposide [169].

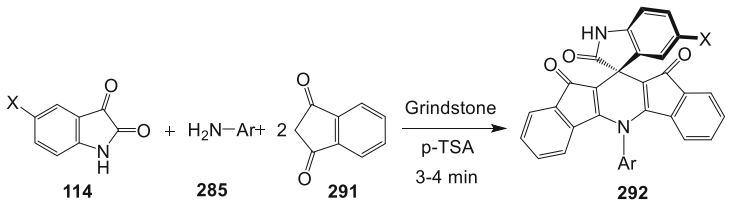
Scheme 81 Synthesis of spiro[indole-3,4′-(1′,4′-dihydropyridine)] derivatives



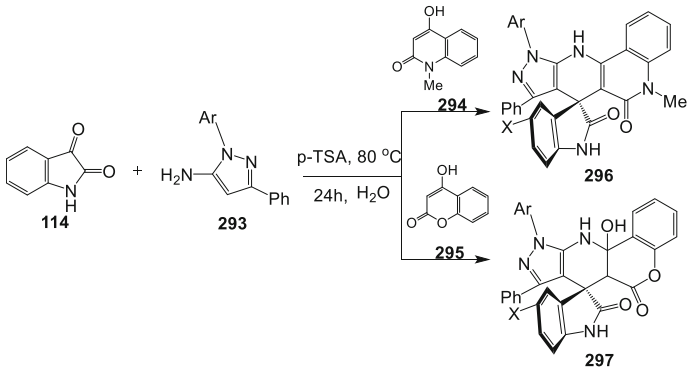
Scheme 82 One-pot four-component approach to spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives



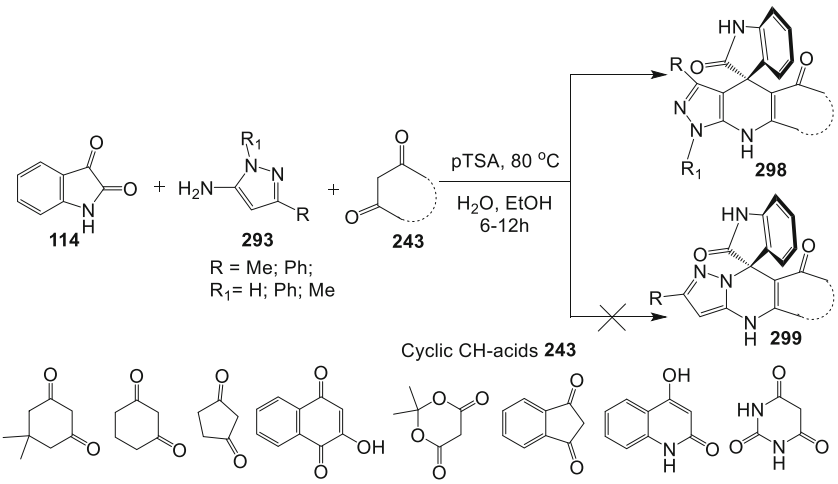
Scheme 83 One-pot synthesis of spiropyridine-indolines with 4-azafluorenone pharmacophore



Scheme 84 Three-component synthesis of spirooxindoles fused with benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridine and chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine systems



Scheme 85 Utilization of cyclic CH-acids for spiro-pyrazolo[3,4-*b*]pyridines synthesis



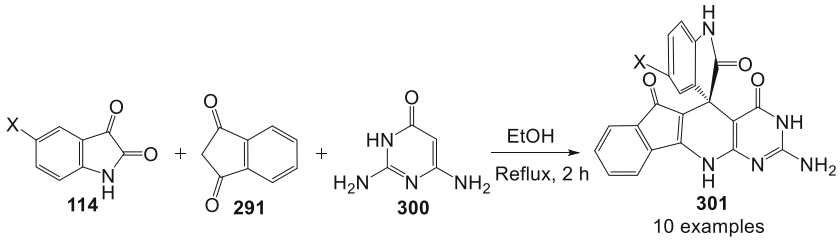
Among the first, S. Ahadi et al. reported the synthesis of spiro[benzo[*h*]pyrazolo[3,4-*b*][1,6]naphthyridine-7,3′-indoline]-2′,6(5*H*)-diones **296** and spiro[chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridine-7,3′-indoline]-2′,6(6*aH*,10*H*)-diones **297** from the reactions of CH-acids (4-hydroxy-1-methylquinolin-2(1*H*)-one **294** or 4-hydroxycoumarin **295**) with isatins **114** and 1*H*-pyrazol-5-amines **293** in water catalysed by *p*-TSA [170]. It is noteworthy that the product **297** does not eliminate water even under prolonged refluxing (Scheme 84).

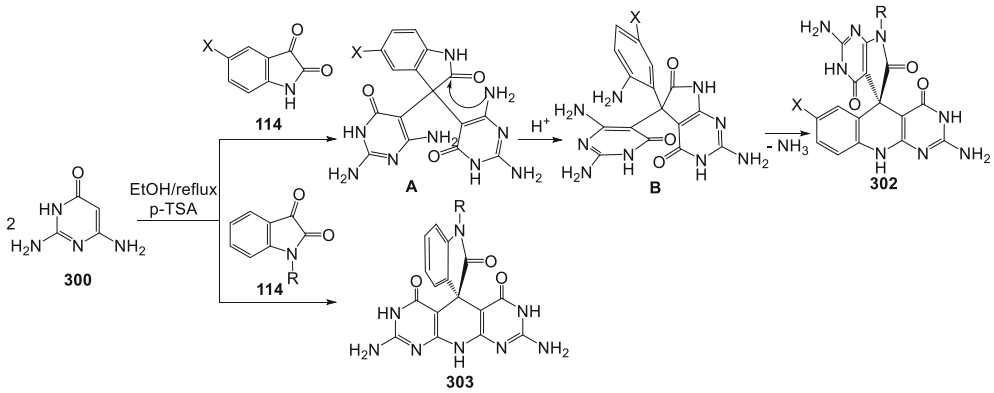
A few years later, it was described the interactions between 5-amino-3-methyl-1-phenylpyrazoles **293**, β-diketones **243** and isatin **114** in aqueous media with *p*-TSA as a catalyst, leading to the formation of several spiro-pyrazolo[3,4-*b*]pyridine derivatives **298** (Scheme 85). The alternative products **299** were not observed [171,172].

At the same time, G. Shakibaei et al. presented a catalyst-free synthesis of 2-amino-1*H*-spiro[indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indoline]-2′,4,6(11*H*)-triones **301** by the similar MCRs of isatins **114** with 1,3-indandione **291** and 2,6-diaminopyrimidin-4(3*H*)-one **300** in refluxing ethanol with 73–82 % yields (Scheme 86) [173].

Isatins with various substituents react differently with 2,6-diaminopyrimidin-4(3*H*)-one **300** [174]. It was found that a mixture of 2,6-diaminopyrimidin-4(3H)-one **300** and N-unsubstituted isatins **114** in the presence of a catalytic amount of *p*-TSA afforded the spiro[pyrimido[4,5-*b*]quinoline-5,5′-pyrrolo[2,3-*d*]pyrimidine]-triones **302** in a 85 % yield after refluxing in ethanol for 8 h. This reaction may have proceeded through the intermediate **A**, formed *in situ* by interreaction of isatins **114** with 2,6-diaminopyrimidin-4(3*H*)-one **300**, and converted into the intermediate **B** followed by forma-

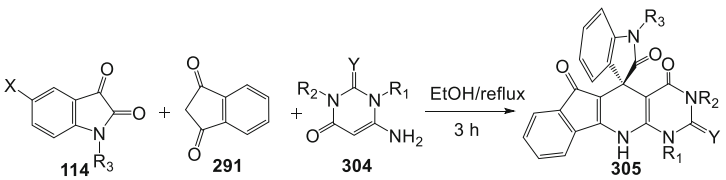
Scheme 86 Catalyst-free synthesis of 2-amino-1*H*-spiro[indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indoline]-2′,4,6(11*H*)-triones



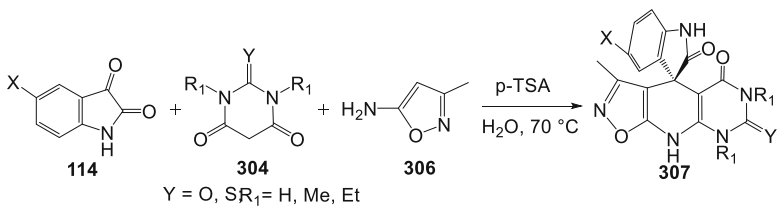


Scheme 87 Variants of interaction of isatins with 2,6-diaminopyrimidin-4(3*H*)-one

Scheme 88 Synthesis of spiroindeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines



Scheme 89 Spiro[indoline-isoxazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine] derivatives synthesis



tion of cyclized product **302** and ammonia. Although, when using *N*-alkylisatins **114** under similar conditions, different products 2′, 8′-diamino-spiro[indoline-3,5′-pyrido[2,3-*d*:6,5-*d*′]dipyrimidine]-2, 4′, 6′(3′*H*, 7′*H*, 10′*H*)-triones **303** were formed in 78–87 % yields (Scheme 87).

Aminouraciles have also found application in the synthesis of spirooxindoles. Thus, the refluxing of 1,3-indandione **291** with amino uracils **304**, and isatins **114** without any catalyst in ethanol for 3 h afforded spiroindeno[1,2-b]pyrido[2,3-d]pyrimidine-5,3′-indolines **305** in good yields (Scheme 88). It should be noted, that when the reaction of aminouraciles **304** and isatin **140** was carried out with other cyclic diketones, such as dimedone **256** or barbituric acid **264** in the same conditions, the reaction mixture showed a combination of starting materials and other numerous products [175].

When isoxazole **306** was used instead of 2,6-diaminopyrimidin-4(3*H*)-one **300** or 1,3-diaryl-pyrazol-5-amines **293** in the reactions with isatins **114** and barbituric acids **304**, the spiro[indoline-isoxazolo[4′,3′:5,6] pyrido[2,3-d] pyrimidine] derivatives **307** were obtained in high yields (Scheme 89) [176].

Synthesis of 3-spirooxindoles fused with cycloalkyl radicals

Methods of spiro[cyclohexane-1′,3-indoline]-2-one framework construction

The synthesis of the spiro[cyclohexane-1′,3-indoline]-2-one scaffold is of general interest due to its connection with

a gelsemine group of alkaloids (Fig. 1). For example, this nucleus is presented in the highly potent and selective vasopressin V_2-receptor antagonist **SR121463A** [177]. The spiro-oxindole **308** [178] is a potent inhibitor of the MDM2–p53 interaction in the discovery of anticancer agents. The novel bichromophoric spirocyclic indolones **309** possess bright fluorescence and high quantum yield (Fig. 7) [179].

The spiro[cyclohexane-1,3′-indolin]-2′,4-dione ring can be prepared either from a preexisting 4-oxo protected cyclohexyl derivative or from an oxindole. Thus, methyleneindolinones **310** were used as starting materials in the synthesis of spirocyclohexenindolone derivatives **312** via the Diels-Alder cycloaddition with several dienes, for example, Danishefsky's diene **311** (Scheme 90) [180,181].

Various*ortho*-iodo anilides were successfully used in the synthesis of spiro[cyclohexane-1′,3-indoline]-2-ones [182]. Th. Müller et al. applied another approach based on the insertion-coupling-isomerization-Diels-Alder domino reaction for a search of new luminescent bichromophoric spirocyclic indolones **309** [178]. The reaction with alkynyl *ortho*-iodo anilides **313** and 1-phenylpropargyl prenyl ethers **314** as substrates and $[PdCl_2(PPh_3)_2]$ and CuI as a catalytic system under 130 °C for 16 h led to formation of spirocyclic indolones **315** in moderate yields (Scheme 91).

Y-C. Chen and co-workers found that interaction of 2,4-hexadienal **317** with the diphenylprolinolsilyl ether **318** and *o*-fluorobenzoic acid (OFBA) leads to reactive trienamine intermediates **A** which undergo Diels-Alder reactions with 3-olefinic oxindoles **316** (Scheme 92). This method offers a facile entry to highly complex molecular frameworks with excellent stereocontrol [183].

An example of a highly efficient organocatalytic Diels-Alder reaction is presented by the synthesis of carbazole-spirooxindole derivatives **322** from methyleneindolininones **316** and 3-vinylindoles **320** (Scheme 93). A simple bis-thiourea **321** was used as the organocatalyst, that provided the products in excellent yields and stereoselectivity (>99:1 *dr*, up to 99 % *ee*) [184].

Methyleneindolinones have also been used in bifunctional organocatalytic asymmetric [4+2] cycloaddition reactions for the construction of spiro[4-cyclohexanone-1,3′-oxindoline] derivatives [185]. Recently, cyclobutenones **323**

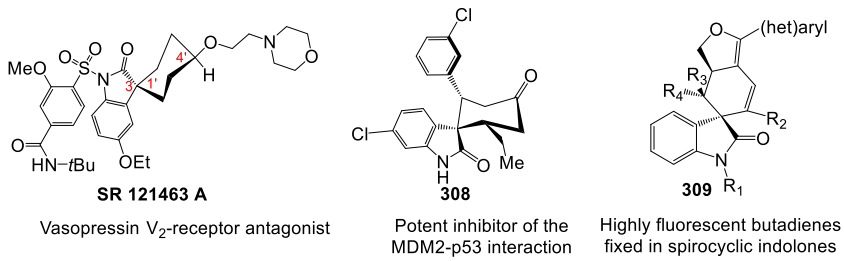
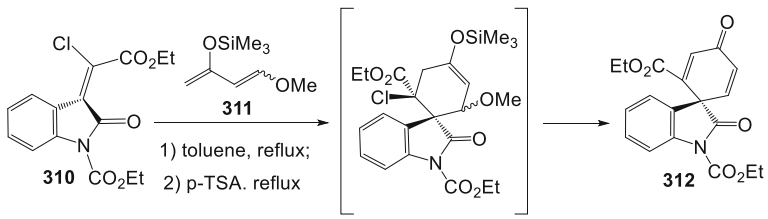
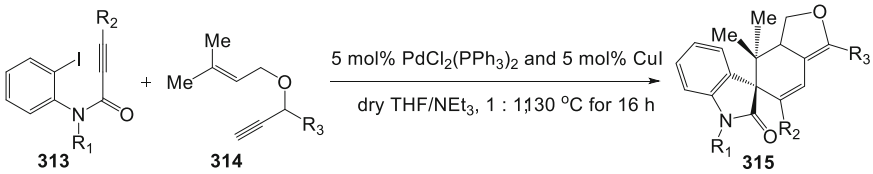


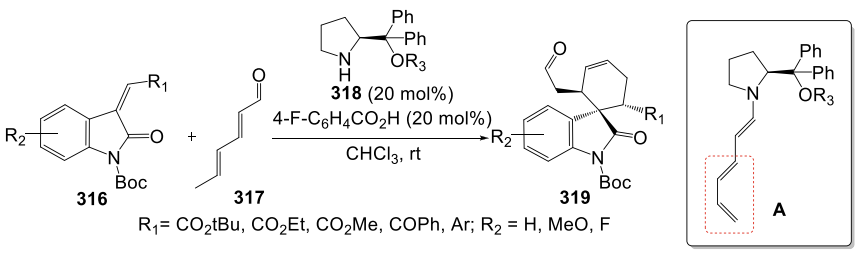
Fig. 7 Various applications of spiro[cyclohexane-1′,3-indoline]-2-ones



Scheme 90 Cycloaddition reaction of 3-chloromethylene-2-indolones dienes

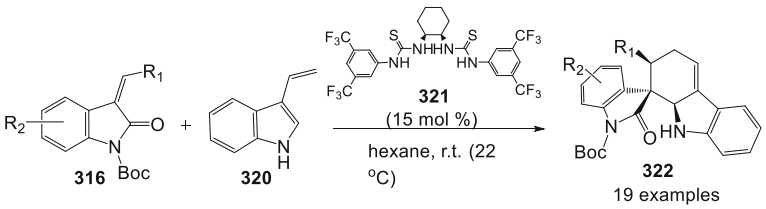


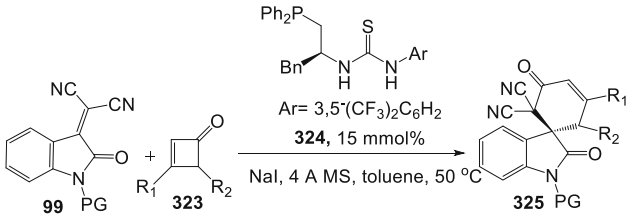
Scheme 91 Synthesis of luminescent bichromophoric spiroindolones



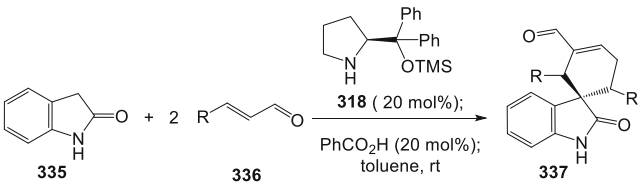
Scheme 92 Diels-Alder reaction of 2,4-hexadienal with 3-olefinic oxindoles

Scheme 93 Stereocontrolled Diels–Alder reaction of 3-vinylindoles with methyleneindolinones





Scheme 94 1,4-Dipolar cycloadditions of cyclobutenones with isatylidenemalononitrile



Scheme 97 Synthesis of spiro[cyclohexane-1′,3-indoline]-2-one via a Michael–Michael-aldol reaction

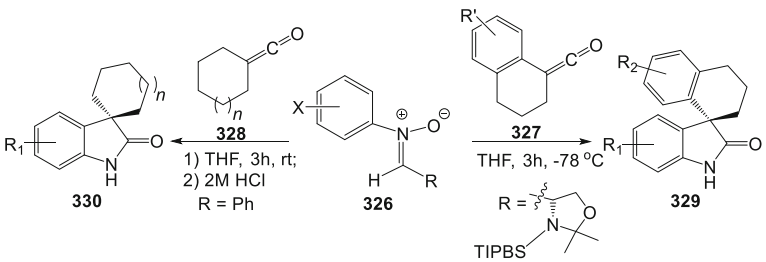
have been used in the asymmetric intermolecular 1,4-dipolar spiroannulation with isatylidenemalononitrile **99** in the presence catalyst **324** followed by formation of 3-spirocyclohexenone 2-oxindoles **325** in good yield with up to 87 % *ee* (Scheme 94) [186].

Recently, chiral *N*-arylnitrones **327** and **328** were used with carbocyclic alkylarylketenes **326** in a pericyclic cascade comprising [3+2]-cycloaddition followed by a [3,3]-sigmatropic rearrangement process to generate spirocyclic oxindoles **329** and **330** in good yields and with excellent levels of enantioselectivity (90–99 % *ee*) (Scheme 95) [187].

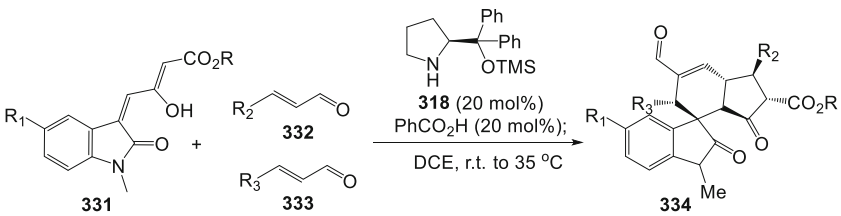
The organo-catalyzed Michael/Michael/aldol condensation sequences allow the direct, one-step synthesis of complex spirooxindolic cyclohexane derivatives starting from simple precursors [188]. In 2010, Y-C. Chen's group offered the one-pot method for the synthesis of methyleneoxindoles **331** with two molecules of α, β-unsaturated aldehyde **332** and **333** under quadruple iminium/enamine/iminium/enamine catalysis that led to spirooxindoles **334** bearing six contiguous stereocenters in excellent stereoselectivities (96 to 99 % *ee*, >99 % *dr*). A chiral amine α, α-diphenylprolinol *O*-TMS ether **318** served as a catalyst in this unique tripleMichael/aldol process (Scheme 96) [189]. Subsequently, a tandem reaction of aliphatic aldehydes with electron-deficient olefinic oxindoles could be supplemented with various activated olefins or imines to afford spirocyclic oxindoles with miscellaneous molecular complexity [190,191].

Later, it was disclosed that oxindoles **335** could react with unsaturated aldehydes **336** via a Michael–Michael-aldol reaction to give the desired spirocyclic compounds **337** in the presence of the catalyst **318** (20 %) and benzoic acid (20 %) in toluene. The final products were obtained in good yields and in a total stereocontrolled fashion in most of the examples (Scheme 97) [192].

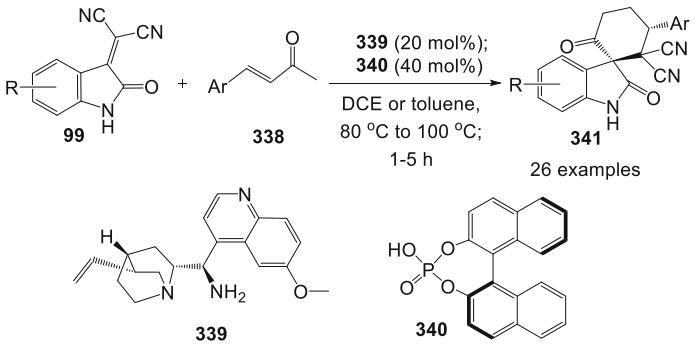
Scheme 95 One-pot pericyclic cascade approach to asymmetric spirocyclic oxindoles



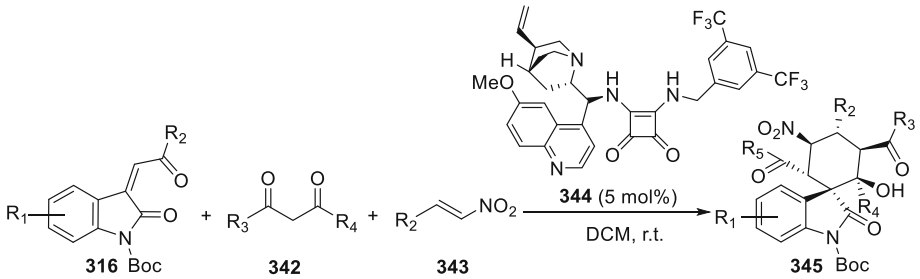
Scheme 96 Asymmetric quadruple domino reactions catalyzed by 2-(diphenyl(trimethylsilyl)oxy)-methyl)pyrrolidine



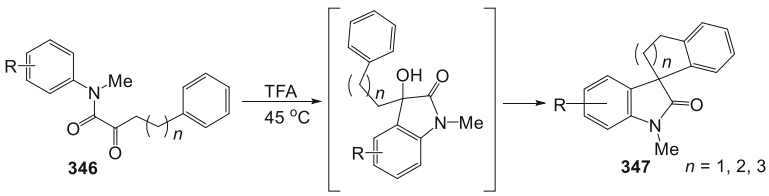
Scheme 98 Double Michael addition of isatylinidene malononitriles with arylideneacetones



Scheme 99 Asymmetric organocatalytic cascade strategy for privileged spirocyclohexane oxindoles



Scheme 100 Synthesis of spirooxindoles by double intramolecular arylation of R-ketoanilides



The optically pure spiro[cyclohexane-1,3′-indoline]-2′,3-diones **341** could be efficiently synthesized in high yields (88–99%) with excellent diastereo- and enantioselectivity (94:6–99:1 *dr*, 95–99 % *ee*) through the cascade Michael additions of isatylidene malononitriles **99** with (R)-β-unsaturated ketones **338** via the catalysis of a cinchona alkaloidderived primary amine **339** together with an BINOL-phosphoric acid **340** (Scheme 98) [193].

The most recent report devoted to a Michael–Michael–aldol cascade sequence represents an interaction between 1,3-dicarbonyl compounds **342**, nitroalkenes **343**, and methyleneindolinones **316** in the presence of 5 mol% chiral squaramide **344**. The reactions led to a series of enantioenriched spirocyclohexane oxindoles **345** bearing six contiguous stereocenters in good yields (up to 85 %) and with excellent stereoselectivity (>20:1 *dr*, >99 % *ee*) (Scheme 99) [194].

There have been described interesting examples of the intramolecular Friedel-Crafts reaction for the synthesis of diversely functionalized spirooxindoles [195,196]. In the latter case, compounds **347** can be derived from readily accessible α-keto-*N*-arylacetamides **346** bearing alkyl side chain residues in the presence of trifluoroacetic acid (TFA) at room temperature or at 45 °C. This method could be applied for the synthesis of spirooxindoles fused with cyclopentyl-, cyclohexyl and cycloheptyl rings (Scheme 100).

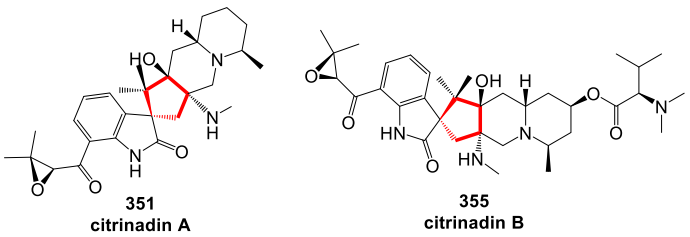
Spirocyclopentaneoxindoles synthesis

A number of natural alkaloids (Fig. 8) and synthetic drug candidates include the 3-spirocyclopentane-2-oxindoles as a main motif of their scaffolds [197,198]. The direct catalytic enantioselective synthesis of these compounds is fraught with challenges in chiral substrate-controlled methods.

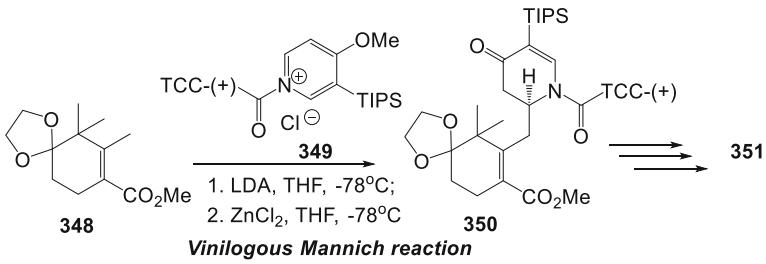
Zhiguo Bian et al. have achieved the first total synthesis of (–)-citrinadin A **348** through this methodology, which takes 20 stages. The key step has a vinylogous Mannich reaction of the dienolate derived from **348** with the chiral pyridinium salt **349** followed by formation of the first stereogenic center of compound **350**. The chirality at this center served as a control point when introducing other stereocenters in the pentacyclic core (Scheme 101). Citrinadin A has shown to exhibit cytotoxicity against murine leukemia L1210 (IC_{50} 6.2 mg/mL) and human epidermoid carcinoma KB cells (IC_{50} 10mg/mL) [199,200].

Several attempts were made to provide the stereocontrolled synthesis of the citrinadin B core **354** [201]. Recently,

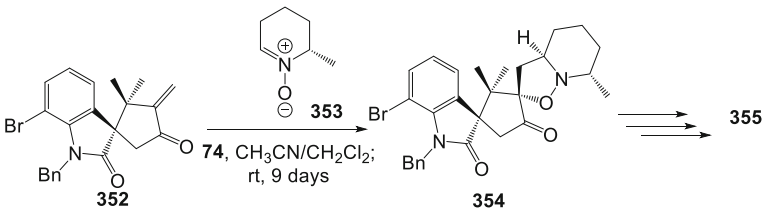
Fig. 8 Naturally occurring spirocyclopentaneoxindoles



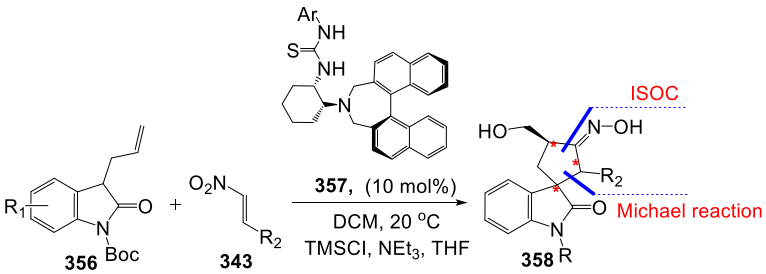
Scheme 101 Vinylogous Mannich reaction in the first total synthesis of (–)-citrinadin A



Scheme 102 Intermolecular nitrone cyloaddition reaction as a key step in the total synthesis of the citrinadin B **355**



Scheme 103 Organocatalytic asymmetric synthesis of spirocyclopentaneoxindoles by Michael addition/ISOC/fragmentation

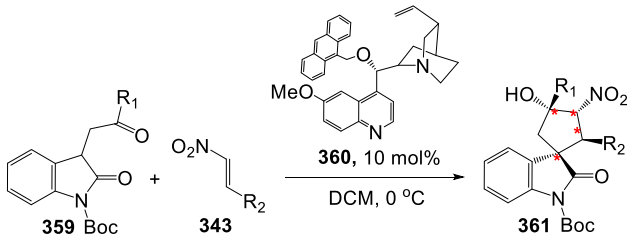


Li et al. have developed a convergent synthetic strategy that employs enone **352**, which was serving as the dipolarophile in the stereoselective intermolecular nitrone **353** cyloaddition reactions as a key step (Scheme 102) [202].

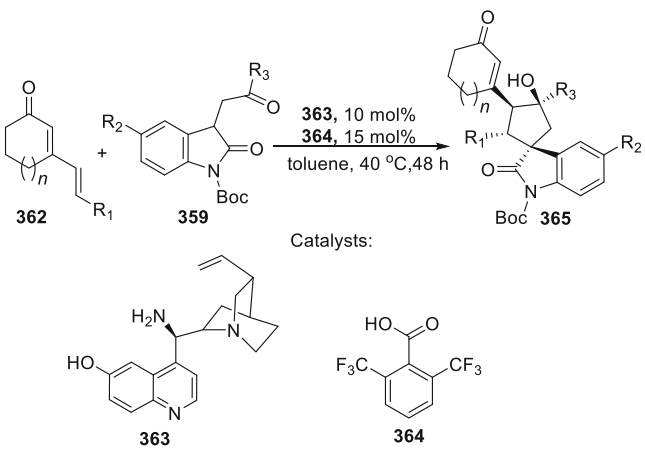
The asymmetric organocatalytic multistep one-pot reactions have appeared as a powerful tool for efficient construction of complex molecules from readily available simple starting materials. Li et al. have described organocatalyzed Michael addition/intramolecular silyl nitronate-olefin cycloaddition (ISOC)/fragmentation reaction of 3-allyl-substituted oxindoles **356** and nitroolefines **343**, which gave diastereoselective (up to > 30:1 *dr*) and enantioselective (up to > 99 % *ee*) spirocyclopentaneoxindoles **358** with the oxime functional group and including one spiroquaternary stereocenter in good yields (Scheme 103) [203].

Later, the Michael-Henry cascade reactions provided spirooxindoles **361** in high yields and excellent enantioselectivity in a single step from various oxindole derivatives **359** and nitroolefines **343** as starting materials in the presence of a chiral tertiary amine catalyst **360** in DCM at 0 °C for 2 h (Scheme 104) [204].

In recent years, organocatalytic enantioselective domino/cascade reactions have been employed for the synthesis of spirocyclopenteneoxindoles by various groups of authors [205–208]. Later, the cinchona-based primary amine **363** organocascade catalysis was used to access a variety of complex highly optically pure spirocompounds **365** with four contiguous stereocenters when reacting with the cyclic dienones **362** and the 3-substituted oxindoles **359** (Scheme 105) [209].



Scheme 104 Construction of spirocyclooxindoles via a Michael-Henry cascade reaction



Scheme 105 Vinylogous cascade catalysis in the synthesis of spirocyclopentane oxindoles

Recently, a novel iminium–enamine tandem process was established to construct densely substituted spirocyclopentaneoxindole core units **367** from 3-substituted bifunctional oxindoles **366** and readily available α, β-unsaturated aldehydes **336** catalyzed by a chiral secondary amine **318** with excellent stereoselectivity (up to 99 % *ee*) (Scheme 106) [210].

Several approaches were made for the construction of spirocyclic oxindolic cyclopentanes via [3+2] cycloaddition reactions. Asymmetric variants of these reactions have been implemented by using chiral catalysts [211,212]. High interest is represented in the annulation reactions of Morita-Baylis-Hillman carbonates and olefins with phosphine catalysts. Thus, a novel organocatalytic asymmetric [3+2] cycloaddition reaction between methyleneindolinones **368** and allylic compounds **369** leads to complex spirocyclopentaneoxindoles **371** with a chiral phosphine **370** as a nucleophilic organocatalyst (Scheme 107) [213].

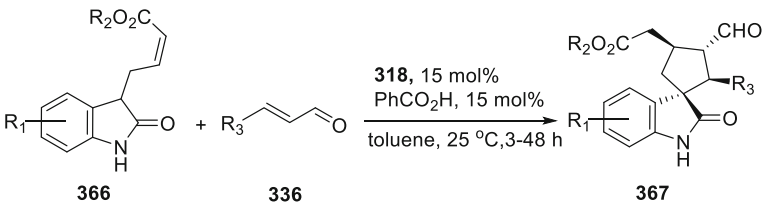
Another example of a chemo- and enantioselective [3+2] annulation of Morita–Baylis–Hillman carbonates of isatins **372** by propargyl sulfone **373** and catalyzed by β-isocupreidine (β-ICD) *O*-MOM ether **374**, describes a synthesis of spirocyclic 2-oxindoles **375** bearing an unusual cyclopentadiene motif in outstanding *ee* values (up to >99 %) (Scheme 108) [214].

Electrophiles, such as *N*-phenylmaleimide, have been also utilized to deliver complex spirocyclic 2-oxindoles with good results. Thus, an efficient asymmetric [3+2] cycloaddition reaction between Morita–Baylis–Hillman carbonates of isatins **372** and *N*-phenylmaleimide **144** catalyzed by Me-DuPhos **376** afforded spirocyclopentaneoxindoles **377** in good yields (up to 84 %) with excellent diastereo- and enantioselectivity (up to 99 % *ee*) (Scheme 109) [215].

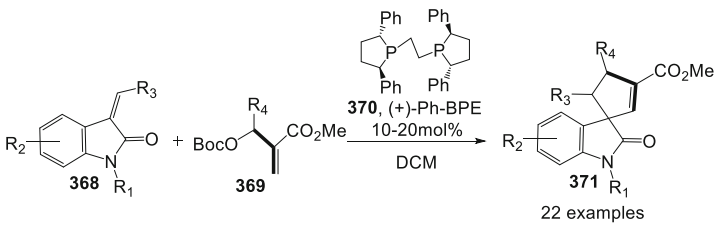
Synthesis of spiro[indoline-3,1′-cyclopropan]-2-ones

The Synthesis of spirocyclopropanes is of great interest and especially challenging due to the presence of three consecutive stereogenic centers in the highly strained three-membered ring of their molecules. The spiro[indoline-3,1′-cyclopropan]-2-ones are important semi-products for the alternate bond construction strategy for spiro[pyrrolidine-3,3′-oxindole] ring systems, relying on a cyclopropane-opening/ring-expansion reaction [32]. Spirocyclopropane-1,3-oxindole **378** acts as a kinase inhibitor and **379** is a potent

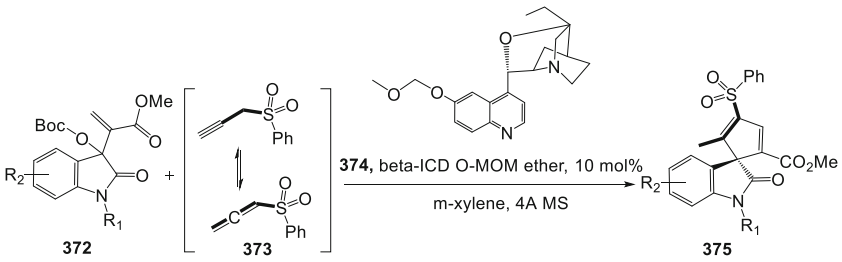
Scheme 106 Reaction of 3-substituted oxindoles with α, β-unsaturated aldehydes

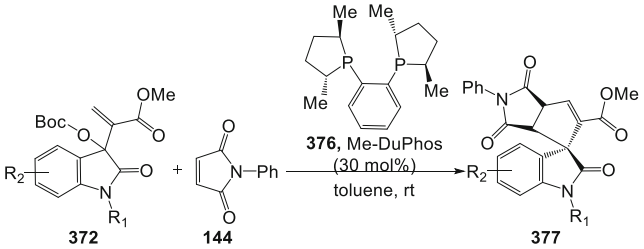


Scheme 107 Phosphine-catalyzed [3+2] cycloaddition reaction



Scheme 108 Annulation of Morita-Baylis-Hillman carbonates of isatins by propargyl phenyl sulfone





Scheme 109 Me-DuPhos-catalyzed 1,3-dipolar cycloaddition of Morita–Baylis–Hillman carbonates of isatins to *N*-phenylmaleimide

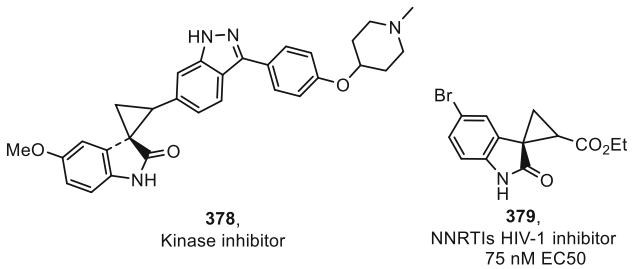


Fig. 9 The spirocyclopropyl oxindole motif in biologically active compounds

HIV-1 non-nucleoside reverse transcriptase inhibitor (Fig. 9) [216,217].

Xiaowei Dou et al. developed the first direct organocatalytic asymmetric cyclopropanation reaction of oxindoles. In this strategy, oxindoles **380** were employed as a dinucleophilic C_1 synthons and bromonitroolefins **381** with a dielectrophilic center were used as a C_2 synthon (Scheme 110). An amino acid-based multifunctional catalyst **383** promoted the [2+1] reaction, gave the products **384** and **385** in high yields and excellent enantioselectivity. By using 1,4-diazabicyclo[2.2.2]octane (DABCO) as a nucleophilic catalyst, a stereochemically retentive conversion of different diastereomers of cyclopropyl spirooxindoles was discovered [218].

The cyclopropanation formation spirooxindoles has been usually performed in the presence of toxic metal catalysts [219]. Further, spirocyclopropanes have also been reported from diazo compounds and alkenes in the presence of expensive transition metals, such as $Rh_2(OAc)_4$, CuOTf, $Hg(OTf)_2$ or Au(I)-complexes [220,221]. The disadvantage of the metal-catalyzed process is that heteroatom containing alkenes could bind tightly to a transition metal present in the catalyst, resulting in loss of their catalytic activity. Recently, there was discovered a highly efficient diastereoselective method to synthesize spiro[cyclopropane-1,3-oxindoles] **389** and **390** from thermal decomposition of 3-diazooxindoles **386** and mono-substituted **387** or 1,2-disubstituted **388** alkenes under solvent- and transition metal-free conditions in excellent yields (Scheme 111) [222].

A new asymmetric organocatalytic synthesis of *trans*-substituted spirocyclopropane oxindoles **393** based on the Michael addition of *N*-Boc-protected 3-chlorooxindole **390** to unsaturated 1,4-dicarbonyl compounds **391** running with an amino acid-based multifunctional catalyst **392** has been developed by Oseka et al. This methodology provides products **393** with two identically substituted tertiary stereocenters in moderate yields and with very high diastereo- and enantioselectivity (Scheme 112) [223].

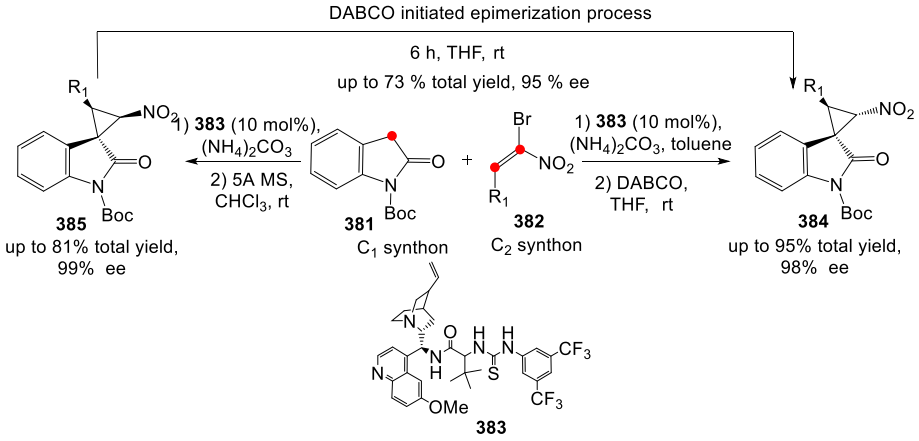
Synthesis of 3-spirooxindoles containing different two heteroatoms-substituted hetherocycles

The 3-heteroatom-substituted spirooxindoles, especially sulfur-containing phytoalexins, were firstly isolated from the plants of the family *Cruciferae* (syn. *Brassicaceae*) [224,225]. As it was pointed out earlier, spirobrassinin **21** and its related analogues (Figs. 4, 10) posess a potent antimicrobial, antitumor, and oviposition stimulant for biological activities and are of great interest in the applying of novel methodologies for their synthesis [226–228].

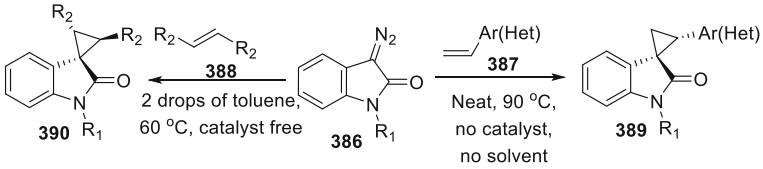
The Mannich/cyclizations reactions represent one of the ways of utilisation of 2-oxindols in the synthesis of the spiroindoline[3,4']oxazolines. Thus, Yuan et al. firstly reported the organocatalytic direct asymmetric synthesis of a library of enantioenriched spirocyclic oxindoles **396** through the aldol reactions of 3-isothiocyanato oxindoles **219** with ketones **394** and bifunctional thiourea-tertiary amines **395** as catalysts (Scheme 113) [228].

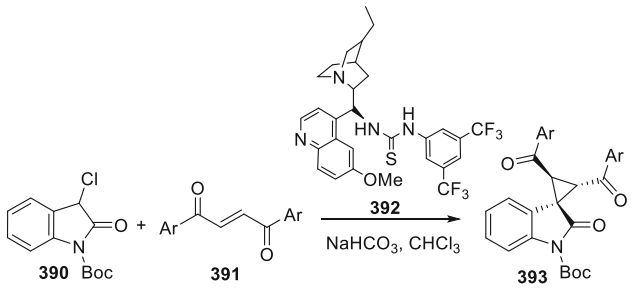
Later, Han et al. developed a method for highly efficient and diastereoselective construction of structurally diverse dispiro[oxazolidine-2-thione]bisoxindoles **396** in excellent yields (up to 97 %) and diastereoselectivity (up to 99:1) by the reaction of 3-isothiocyanato oxindoles **219** with isatins

Scheme 110 Direct organocatalytic asymmetric cyclopropanation reaction of oxindole



Scheme 111 Metal-free synthesis of spirocyclopropanes from diazocarbonyl compounds





Scheme 112 Asymmetric organocatalytic synthesis of spirocyclopropane oxindoles

114 in the presence of 1 mol% Et_3N under mild reaction conditions (Scheme 114). The following methylation of **396** led to spirobrassinin's spiroindoline[3,4′]oxasoline analogs **397** [230].

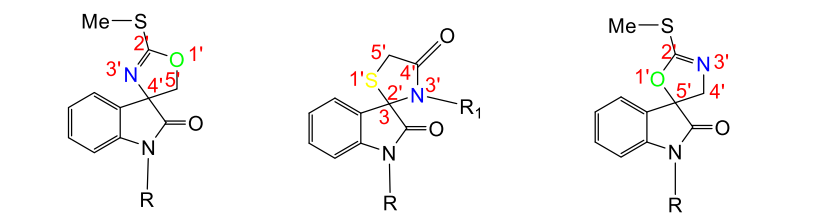
Jiang et al. developed a highly efficient and convenient strategy of the construction of unique spiroindoline[3,5′] oxasolines **400** and **401** through the organocatalyzed asymmetric aldol reaction of the N-substituted isatins **114** with isothiocyanates **398** and **399** (Scheme 115). Preliminary biological evaluation of several representatives of spirooxazolines revealed promising antipyretic activity [231].

Badillo et al. described a method for the synthesis of a new class of spirocyclic oxindole oxazolines **403** and **404** by the addition of 5-alkoxy-2-aryloxazoles **402** to isatin **114** by adding the catalytic amounts of titanium (IV) chloride (10 or 20 mol%). Utilizing the substitution at the 4-position of the oxazole enabled access to either the 2- oxazoline **403** or 3-oxazoline **404** spirocycles with excellent regiocontrol (*dr* >99:1) (Scheme 116) [232].

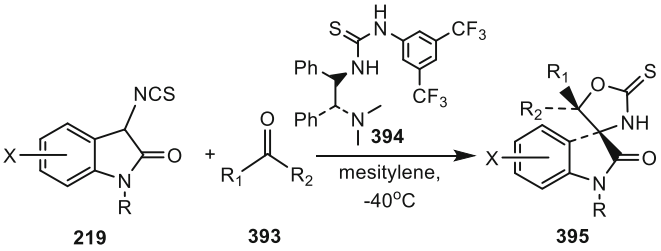
The spirocyclic isoxazolines represent another type of 3-heterocyclic spirooxindoles. The most common way for their synthesis is the 1,3-dipolar cycloaddition of alkene dipolarophiles and nitrile oxides [233]. Thus, the nitrile oxide **406** was generated *in situ* by dehydrochlorination of hydroximoyl chloride **405**. The following cycloaddition of 3-methylene oxindoles **407** gave the product **408** as a single regioisomer, albeit in low yield (Scheme 117) [234].

A similar approach to the synthesis of spiro[indole-dioxazoline-1,3,4] compounds **410** was applied by 1,3-dipolar cycloaddition reaction of isatins **114** with the aryl

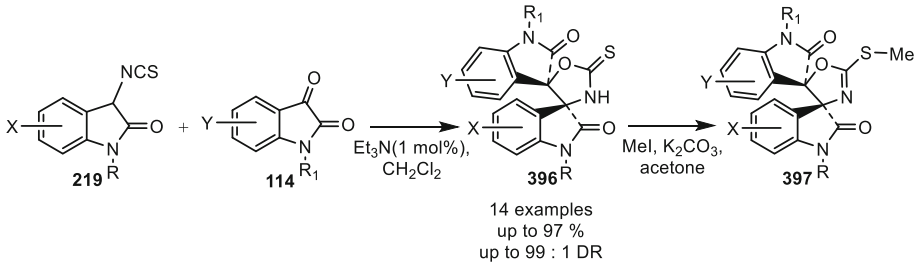
Fig. 10 Spirooxindole phytoalexins analogs



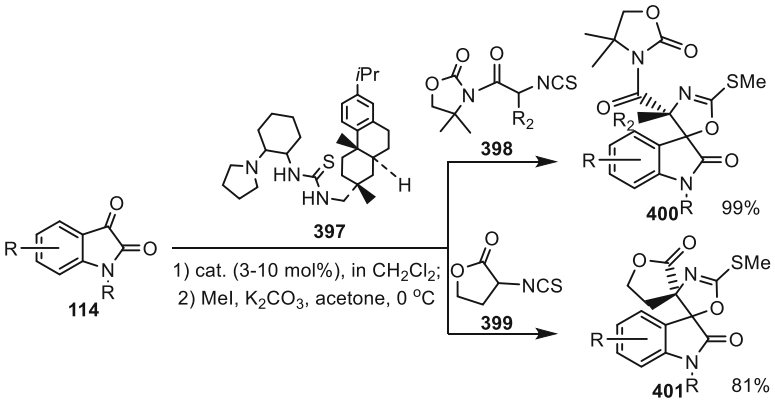
Scheme 113 Asymmetric aldol reaction of 3-isothiocyanato 2-oxindoles with simple ketones under chiral thiourea catalysis



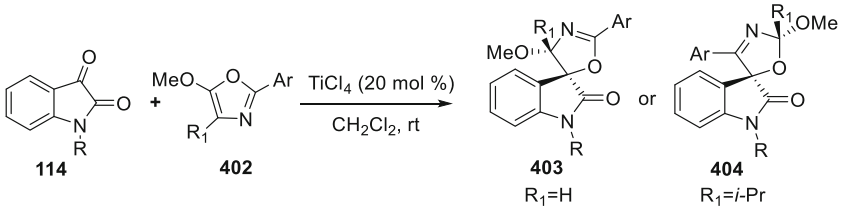
Scheme 114 Synthesis of dispiro[oxazolidine-2-thione]bisoxindoles



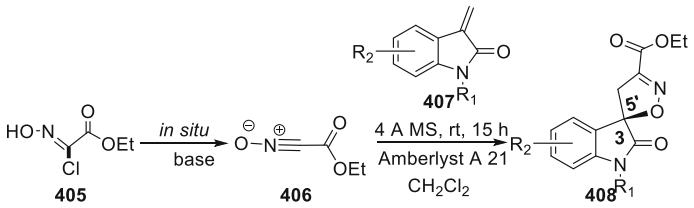
Scheme 115 Synthesis of spirobrassinin spiroindoline[3,5′]oxasoline analogs with antipyretic activity



Scheme 116 A regio- and stereoselective spirocyclization between isatins and 5-methoxyoxazoles

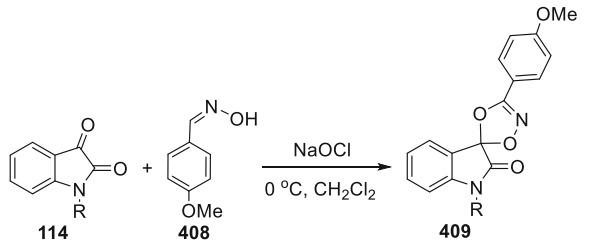


Scheme 117 Regioselective synthesis of spiro[indoline[3,5′]isoxazolidine

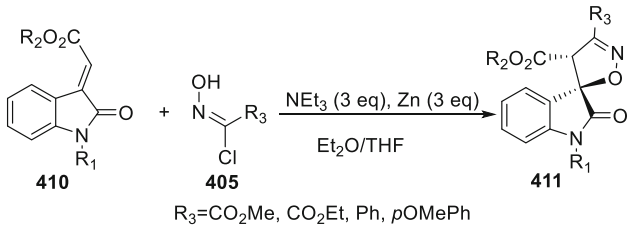


nitrile oxide generated *in situ* from 4-methoxybenzaldoxime **409** and sodium hypochloride (Scheme 118) [235].

Carlos et al. described utilization of zinc as a dehydrochlorinating agent for chlorooximes **405** with an aryl or ester side chains in the 1,3-dipolar cycloaddition reactions with 3-methylene indolin-2-ones **410**. This method can proceed without an addition of base and leads to spiroisoxazoline oxindoles **411** containing ester groups at position 4′ and aro-



Scheme 118 1,3-Dipolar cycloaddition reaction of N-alkylisatins and 4-methoxybenzaldoxime



Scheme 119 Regioselective synthesis of spiroisoxazoline oxindoles

matic or ester groups at position 3′ of the isoxazoline ring (Scheme 119) [236].

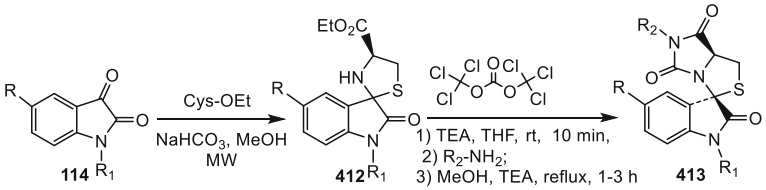
Gomez-Monterrey et al. reported the direct spirocondensation of isatins **114** and cysteine ethyl ester that led to spiro(oxoindolethiazolidine) ethyl esters **412**. The following intramolecular cyclization of these derivatives was performed in refluxing methanol in the presence of TEA and gave the novel highly antitumor potential spiro[imidazo[1,5-*c*]thiazole-3,3′-indoline]-2′,5,7-trione derivatives **413** with 39–56 % overall yields as simple isomer (Scheme 120) [237].

Vintonyak et al. established the synthesis of spirothiazolidinones **416** through the cyclisation of the isatin-3-imines **414** with mercaptoacetic acid **415**. The following oxidation of sulfides **416** with *meta*-chloroperbenzoic acid (mCPBA) led to a library of 200 indolin-2-on-3-spirothiazolidinones **417** (Scheme 121). All tested compounds of **417** are potent inhibitors of the pathophysiologically relevant title protein MptpB (*Mycobacterium tuberculosis* protein tyrosine phosphatases B) [238].

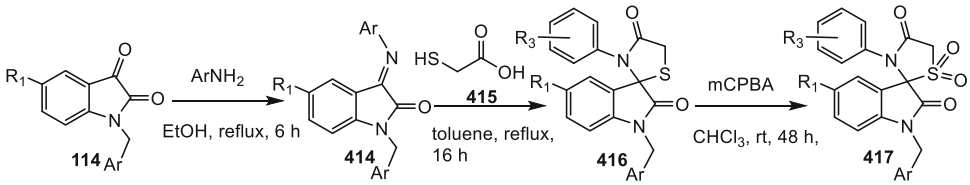
The similar approach to spiro[indole-thiazolidinones] **419** was made by R. Lesyk et al. through the one-pot three-component reaction of isatins **114**, primary aromatic amines **418**, and a mercaptoacetic acid **415** in anhydrous benzene. The following synthesis of 5-ylidene-4-thiazolidinones **421** was realized in a Knoevenagel reaction of **419** with aldehydes **420** in 2-propanol with potassium *tert*-butylate as catalyst. The reaction of isatins **114** with mercaptoacetic acid **415** and amino acids esters **422** under microwave assistance led to compounds **423** with significant antitumor activity (Scheme 122) [239].

However, novel heptacyclic spiro[indoline-3,4′-pyrazolo[3,4-*e*][1,4]thiazepine]diones **425** were obtained when amines **418** were replaced by 5-amino-3-methylpyrazoles **293** in a facile one-pot reaction with isatins **114** and mercaptoacetic acid **415** due to the formation of of 3-(5-aminopyrazol-3-yl)-3-hydroxy 2-oxindolines **424** as intermediates (Scheme 123) [240].

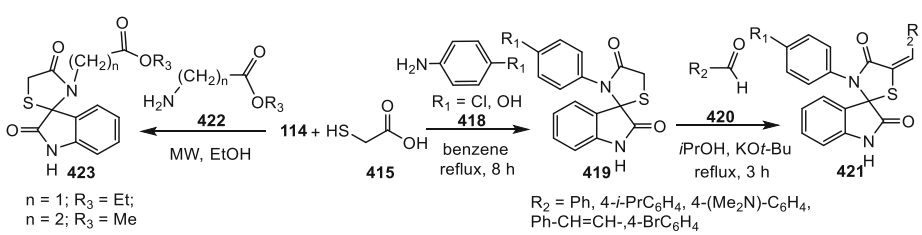
Scheme 120 Synthesis of antitumor spiro[imidazo[1,5-*c*]-thiazole-3,3′-indoline] derivatives



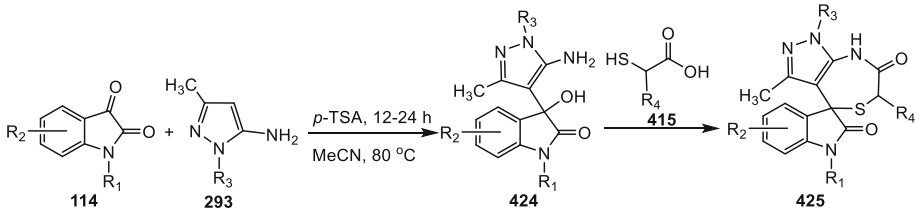
Scheme 121 Synthesis of indolin-2-on-3-spirothiazolidinones with antitubercular properties



Scheme 122 Three-component approach to spiro[indole-thiazolidinones] with antitumor activity



Scheme 123 Efficient multi-component tandem reaction giving spiro[indoline-thiazepines]



Conclusion

This review is devoted to the recent advances in the strategies of the enantioselective synthesis of various spirooxindoles that can possess significant biological activity. However, the evolution of the methodologies for the construction of spirooxindoles has increased through the past decade and is expected to have important employment for the development of complex natural compounds as well as in drug design.

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