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REVIEW

# Recent Strategies in the Synthesis of Spiroindole and Spirooxindole Scaffolds

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## Abstract

Spiroindole and spirooxindole scaffolds are very important spiro-heterocyclic compounds in drug design processes. Significant attention has been directed at obtaining molecules based on spiroindole and spirooxindole derivatives that have bioactivity against cancer cells, microbes, and different types of disease affecting the human body. Due to their inherent three-dimensional nature and ability to project functionalities in all three dimensions, they have become biological targets. Considering reports on spiroindole and spirooxindole-containing scaffolds in the past decades, introducing novel synthetic procedures has been an active research field of organic chemistry for well over a century and will be useful in creating new therapeutic agents. This review summarizes the pharmacological significance of spiroindole and spirooxindole scaffolds and highlights the latest strategies for their synthesis, focusing particularly on the past 2 years with typical examples. The spiroindole and spirooxindoles in this review are divided by the type and ring size of the spirocycle that is fused to indole or oxindole. Summarizing these procedures will be very beneficial for discovering novel therapeutic candidate molecules.

**Keywords** Heterocycles · Multicomponent reaction · Spiroindole · Spirooxindole · Spiroheterocycle

## 1 Introduction

Spiroindole and spirooxindoles, which containing a spirocycle fused at the C2 or C3 of the oxindole moiety, are a known subset of indole and also form the core building blocks of highly functionalized organic structures. These important scaffolds are known as the central skeletons of many alkaloids with potential pharmaceutical activity, such as Horsfiline **1**, Mitraphylline **2**, Marefortine **3**, Welwitindolinone A **4**,

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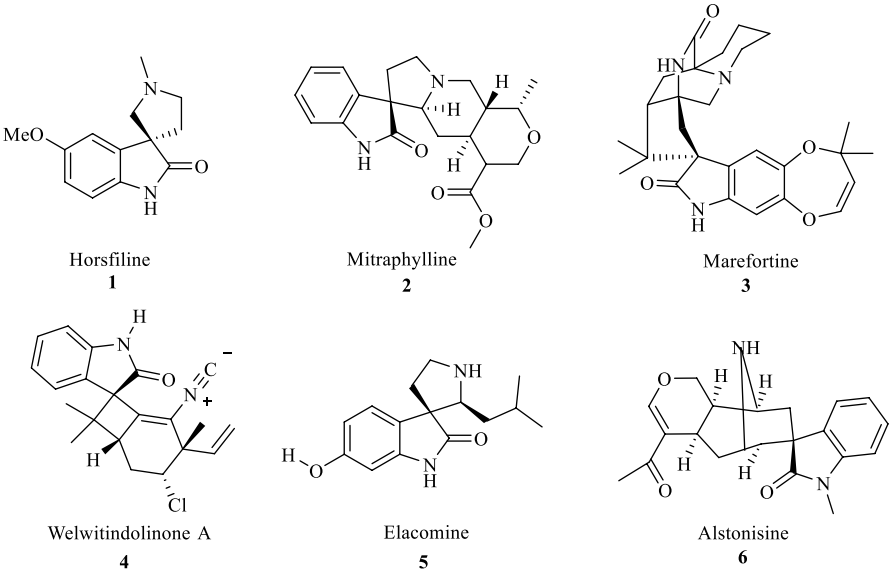



**Fig. 1** Biologically active spiroheterocyclic compounds

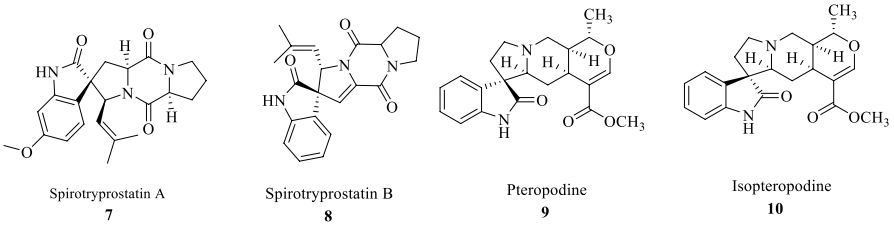



**Fig. 2** Selected pharmaceutical structures containing a spirooxindole scaffolds

Elacomine **5**, and Alstonisine **6** (Fig. 1) [1–4]. The inherent three-dimensional (3D) nature and rigidity of these spirocyclic systems leads to their good affinity to 3D proteins, thus converting these scaffolds into attractive synthetic targets in organic chemistry and drug discovery projects that have a broad spectrum of biological properties, including antimicrobial, antitumor, antidiabetic, anticonvulsant, potential antileukemic, local anesthetic, and antiviral activities. Spirocyclic systems can also be used as synthetic precursors for the production of various types of medicines. For instance, Spirotryprostatin A **7** and Spirotryprostatin B **8** show microtubule assembly inhibition, and Pteropodine **9** and Isopteropodine **10** dampen the operation of muscarinic serotonin receptors (Fig. 2) [5, 6].

Therefore, the study of new and highly efficient procedures for the synthesis of compounds containing spirocarbocycles or spiroheterocycle scaffolds at the C-2 or C-3 position of the indole core has attracted growing attention from numerous researchers around the world. Obviously, among the various synthetic procedures,

multicomponent reactions (MCRs) are preferable. For the synthesis of spirooxindole derivatives, the three-component reaction of isatin, amino acids, and 1,3-dipolarophils, Michael–Michael–aldol cascades, Heck reactions, and numerous other domino condensations have been introduced [7, 8].

Due to their considerable pharmaceutical importance and structurally uniqueness, these interesting scaffolds have been introduced as attractive synthetic targets and many review articles have been published on the formation of spiroindole and spirooxindoles. In 2014, Xia et al. [9] reviewed development of the synthesis of spirooxindole compounds produced from isatin. In 2012, Franz et al. [10] surveyed efficient procedures for the enantioselective formation of spirooxindoles, focusing on articles between 2010 and 2011. In 2018, Van der Eycken et al. reviewed recent progress towards achieving highly functionalized spiroindolines and spiroindoles to motivate additional research to discover novel and efficient procedures for achievement of new spiroindolines and spiroindoles, focusing on articles in 2016 and 2017 [11]. In 2016, Pavlovska et al. focused on the diverse methods available for the enantioselective synthesis of spirooxindoles, with an emphasis on articles published over the last decade [7]. In 2018, Shi and Mei [1] outlined recent developments in the catalytic asymmetric synthesis of spirooxindoles before 2018. In 2020, Youseftabar Miri et al. reviewed recent applications of isatin in the synthesis of spirooxindoles published by Iranian groups in the last 15 years [12].

Considering their biological importance, and the introduction of various synthetic methods for the synthesis of spiroindolines and spiroindoles, there is a need to collect the new methods introduced into this field. The procedures to obtain various spiroindolines and spiroindoles reported in the literature can be sorted into categories based on the type and size of the spirocycle that is fused to indole or oxindole such as 3-, 4-, 5-, or 6-membered rings, including different heteroatoms as illustrated in Fig. 3.

## 2 Synthetic Approaches Towards Spiroindole and Spirooxindole Scaffolds

This section lists numerous reactions, often using isatin as raw material, for the synthesis of spirooxaindole compounds, which often proceeds through MCRs as described in the following sections.

### 2.1 Fused with Carbocyclic Containing Spiro-cyclic Compounds

#### 2.1.1 Five-Membered Ring

Larhed and coworkers have described a procedure for the formation of new spirooxindoles via high regio- and stereoselective intramolecular Mizoroki–Heck 5-exocyclization of aryl iodides [4]. Electron-rich and electron-deficient aryl iodide raw materials were selectively cyclized with high stereoselectivity and good efficiencies. The selection of reaction conditions results in the

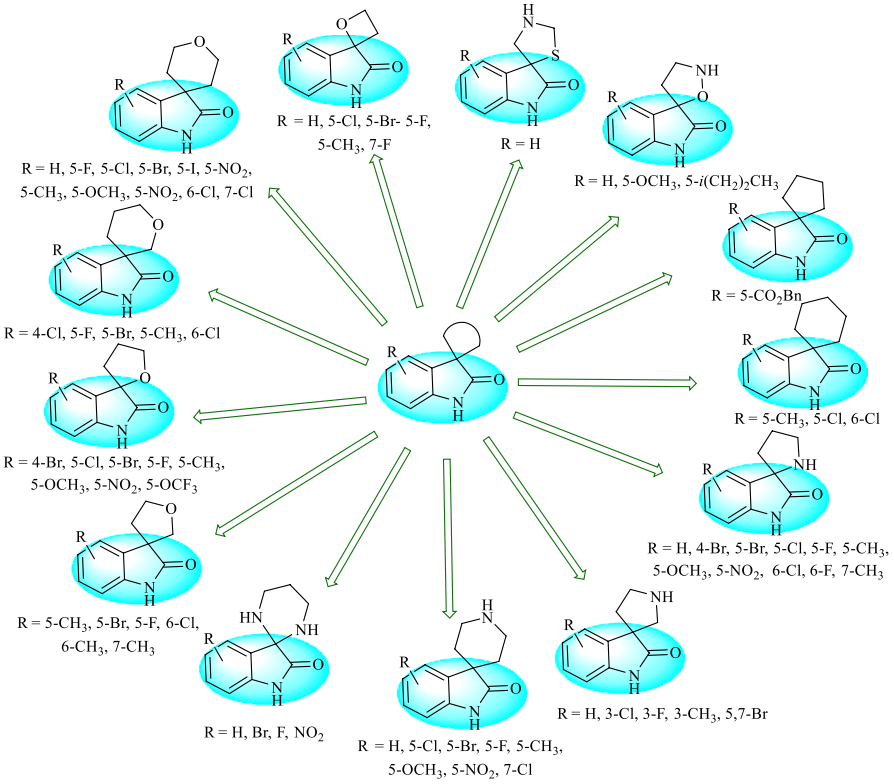
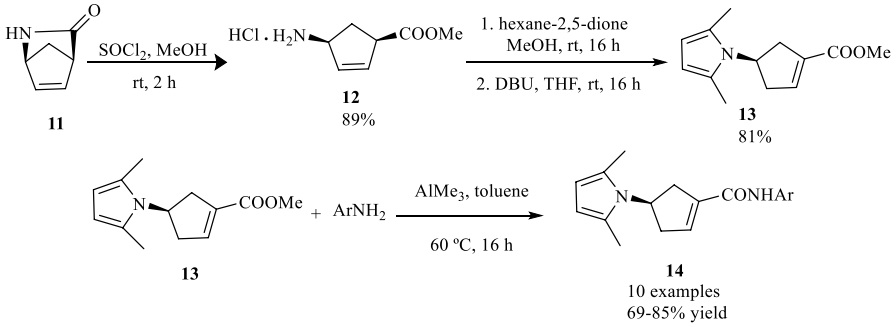



**Fig. 3** Different spirocycles fused to oxindole

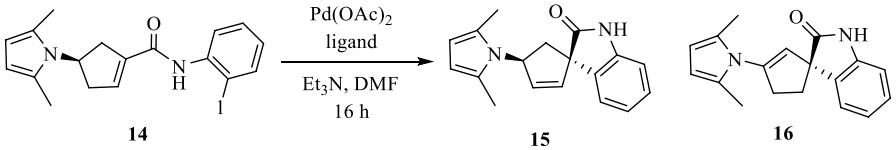
careful control of the double-bond location in the cyclopentene moiety. These new spiro products were subsequently functionalized to rigidified unnatural amino acid compounds by a consecutive gas-free Pd(0)-catalyzed alkoxycarbonylation, followed by selective *O*- and *N*-deprotection [4].

In this synthetic route, enantiomerically pure (+)-Vince lactam **11**, was changed into the related methyl ester **12** as illustrated in Scheme 1 [13]. In the next step, the free amine in **12** was protected as 2,5-dimethylpyrrole, followed by double-bond isomerization to produce the more stable form **13**. The protected ester **13** was coupled with numerous iodoanilines using trimethylaluminum to produce amide precursors **14** with high efficiency. Anilines containing electron-rich as well as electron-poor groups were formed with good efficiencies without any specified additional reactions, contrary to aryl iodide functionality (Scheme 1).

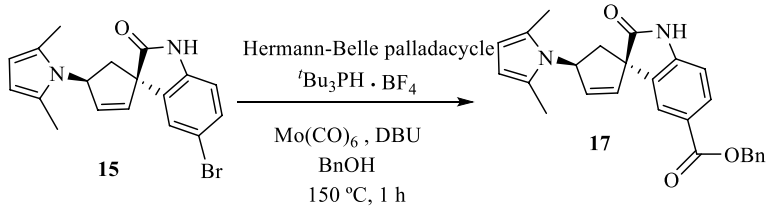
Subsequently, excellent regio- and stereoselective intramolecular Mizoroki–Heck 5-exocyclization of aryl iodides **14** directs formation of the new spirooxindoles **15** and **16** (Scheme 2). The palladium(0)-catalyzed Mizoroki–Heck reaction is one of the most important ways of generating carbon–carbon bonds [14]. Intramolecular Mizoroki–Heck cyclization also provides good control over ring size, while requiring less reactive precursors [15].




**Scheme 1** Synthesis of double-protected amino acid scaffolds **13** and Mizoroki–Heck cyclization precursors **14**




**Scheme 2** Regioselective Mizoroki–Heck cyclization for the synthesis of spirooxindoles **15** and **16**

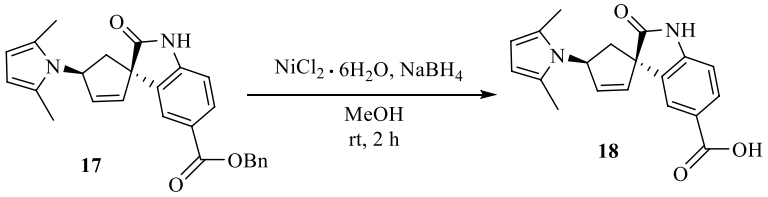



**Scheme 3** Carbonylation of **15** to produce protected unnatural amino acid **17**

Due to the biological importance of spirooxindole compounds in designing new drugs, many attempts to introduce novel procedures to synthesize the spiro nucleus structures are still necessary.

Functionalization of spirooxindole **15** was attempted by considering previous methods based on palladium-catalyzed carbonylation conditions, as shown in Scheme 3. The procedure was designed based on utilization of the Herrmann–Beller palladacycle as the palladium source, with tri-tert-butyl phosphine tetrafluoride borate as pre-ligand. Molybdenum hexacarbonyl was used as a solid CO source, and benzyl alcohol was used as the nucleophile. The reaction was performed with microwave (MW) heating of a sealed reaction vial, and **17** was acquired completely.

The free carboxylic acid **18** was synthesized with 74% yield from chemoselective deprotection of the benzyl ester **17** employing nickel hexahydrate and sodium borohydride (Scheme 4).




**Scheme 4** Synthesis of free acid **18** using deprotection process of benzyl carboxylate **17**

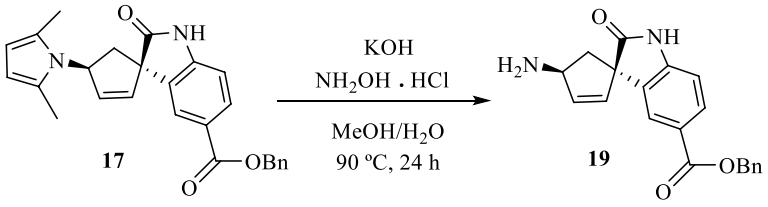
Benzyl ester **17** was also selectively *N*-deprotected to its free amine **19** in the presence of an excess of *N*-hydroxylamine hydrochloride and potassium hydroxide in a mixture of methanol/water (3:1) as reaction medium as illustrated in Scheme 5 [4].

### 2.1.2 Six-Membered Ring

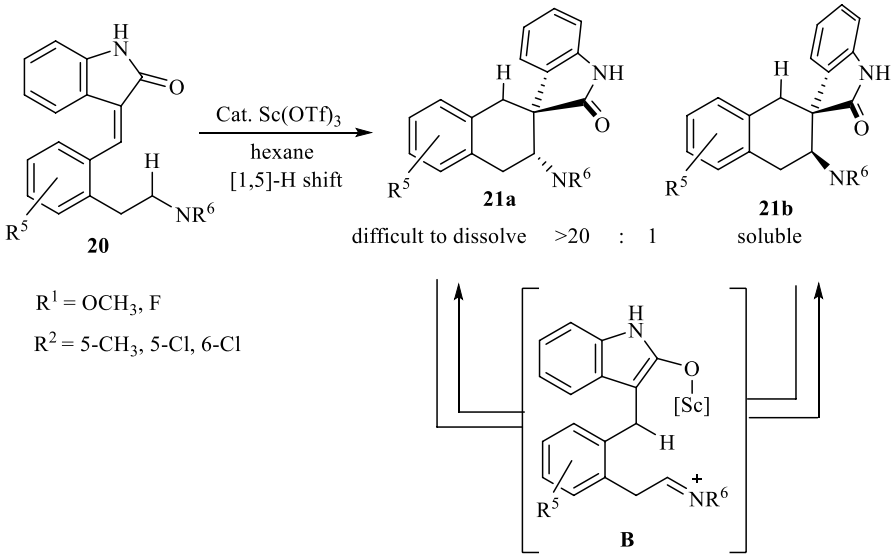
Mori and Machida [16] described the diastereoselective formation of tetralin-fused spirooxindole products **21a** and **21b** using Lewis acid-catalyzed C($sp^3$)–H bond functionalization. A catalytic amount of $Sc(OTf)_3$ was used to activate the benzylidene oxindoles **20** in hexane and reflux conditions to create the target structures **21** in good efficiencies with excellent diastereoselectivity (up to 5 > 20:1) (Scheme 6). Two parameters were necessary to reach high diastereoselectivity: (1) the internal transformation of two diastereomers, and (2) a large difference in the solubility of the two isomers in the solvent. Based on the observations obtained, the high diastereoselectivity of the conversion was justified as shown in Scheme 6. The two diastereomers **21a** and **21b** transformed to each other easily using $Sc(OTf)_3$ catalyzed ring-opening and ring-closing procedures via **B**, and only a low thermodynamic bias exists between these diastereomers [16].

## 2.2 Fusions with Nitrogen-Heterocycle Containing Spiro-cyclic Compounds

Spirooxindoles fused with *N*-heterocycles have been introduced as medicinal agents with various activities such as anti-breast cancer agents, antiviral agent, antimalarial agents, MDM2 inhibitiors, antimicrobial agents, Dengue virus inhibitor, and antitumor agents [17–20].



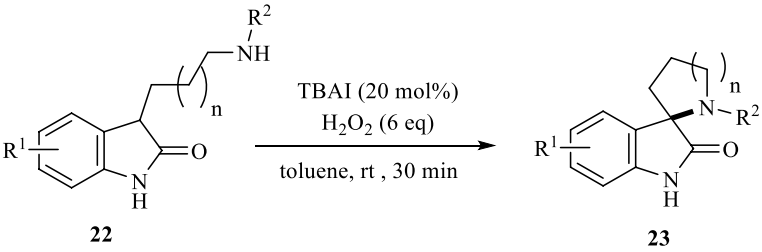

**Scheme 5** Synthesis of free amine **19** via selective *N*-deprotection of **17**



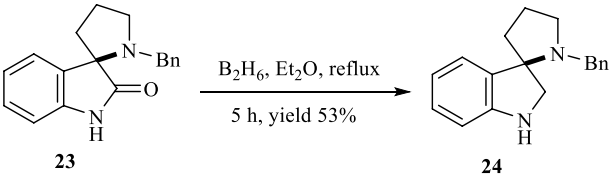

**Scheme 6** Formation of tetralin-fused spirooxindoles via Lewis acid-catalyzed C($sp^3$)–H bond functionalization with excellent diastereoselectivity

### 2.2.1 Five-Membered Ring

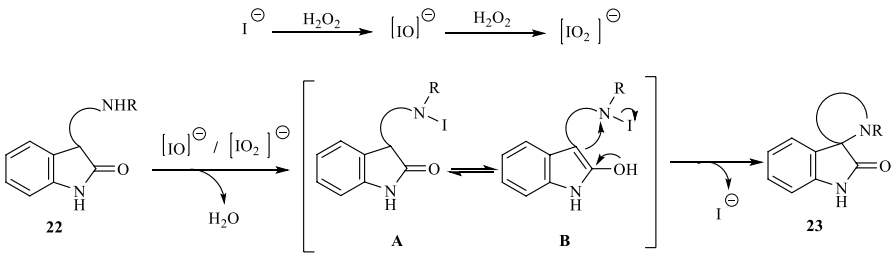
Cheng et al. have introduced a novel strategy for the formation of different 3,2′-pyrrolidinyl-spirooxindoles and its 6-/7-membered analogs using an intramolecular cyclization via an oxidative C–H/N–H bond coupling procedure in the presence of an iodide/$H_2O_2$ as a catalytic system. This method was carried out using conversion of [3-(benzylamino)propyl]-2-oxin **22** to the final compound 1′-benzylspiro[indoline-3,2-pyrrolidin]-2-one **23** in the presence of tetrabutylammonium iodide (TBAI) as an ideal iodide source and $H_2O_2$ as a final oxidant (Scheme 7) [21].




**Scheme 7** Formation of diverse 3,2′-pyrrolidinyl-spirooxindoles **23** through an intramolecular cyclization procedure




**Scheme 8** Selective reduction of amide **23** to produce spiro[indoline-3,2′-pyrrolidine] **24**




**Scheme 9** Proposed mechanism to produce 3,2′-pyrrolidinyl-spirooxindoles **23** through an intramolecular reaction

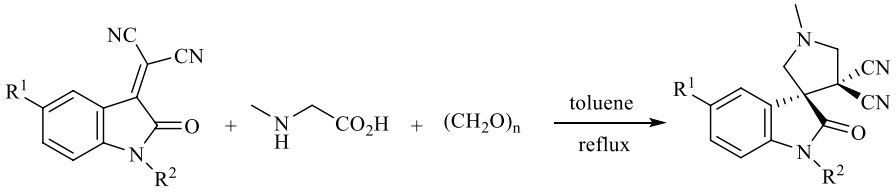
In order to show the synthetic application of this method, the selective reduction of amide **23** using borane was subsequently carried out. The synthesized spiro[indoline-3,2′-pyrrolidine] **24**, is an important scaffold found in many natural compounds and medicinal agents (Scheme 8).

Based on the experimental conclusions and recent studies, Li et al. [22] proposed a potential stepwise mechanism (Scheme 9). Firstly, two hypervalent iodine forms, i.e., $IO^-$ and $IO_2^-$ likely form by oxidation of iodide with $H_2O_2$. Those hypervalent iodines are then involved with aminoalkyl 2-oxindoles **22** to produce an iodoamino intermediate **A**, which is in equivalence with its enolate **B**. The second step readily undergoes an intramolecular cyclization to acquire the final product **23**, and the removed iodide undergoes subsequent oxidation, reproducing the active hypervalent iodine forms [21].

Yan and colleagues [23] reported the easy synthesis of a class of new functionalized spirooxindole-pyrrolidine derivatives **28** via 1,3-dipolar cycloaddition of azomethine ylide acquired from sarcosine **26** and paraformaldehyde **27** with several 2-(1-benzyl-5-chloro-2-oxoindolin-3-ylidene)malononitriles **25** (Scheme 10). This MCR yielded functionalized spirooxindoles in good efficiencies with excellent regio- and stereoselectivity. The skeleton of synthesized spiro[indoline-3,3′-pyrrolidines] **28** was well confirmed by obtaining single-crystal structures [23].

To prove the synthetic importance of this method, they also used another series of 3-methyleneoxindoles named 3-(2-oxo-2-phenylethylidene)indolin-2-ones **29** instead of **25**. If the three-component reaction was performed in toluene under reflux condition, reactions proceeded in a smooth way to obtain spiro[indoline-3,3′-pyrrolidines] **30** (Scheme 11).

Yan's group proposed that the reaction proceeds via a rational mechanism as illustrated in Scheme 12 for the formation of spiro[indoline-3,3′-pyrrolidines] **32a**

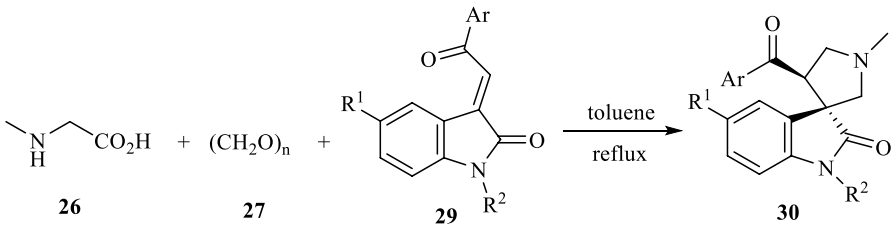



25 26 27 28

$R^1$ = Cl, F, $CH_3$

$R^2$ = Bn, $CH_3$, $C_4H_9$, $C_3H_7$, Boc

**Scheme 10** Three-component reaction for the formation spiro[indoline-3,3′-pyrrolidines] **28**




26 27 29 30

$R^1$ = Cl, F, $CH_3$

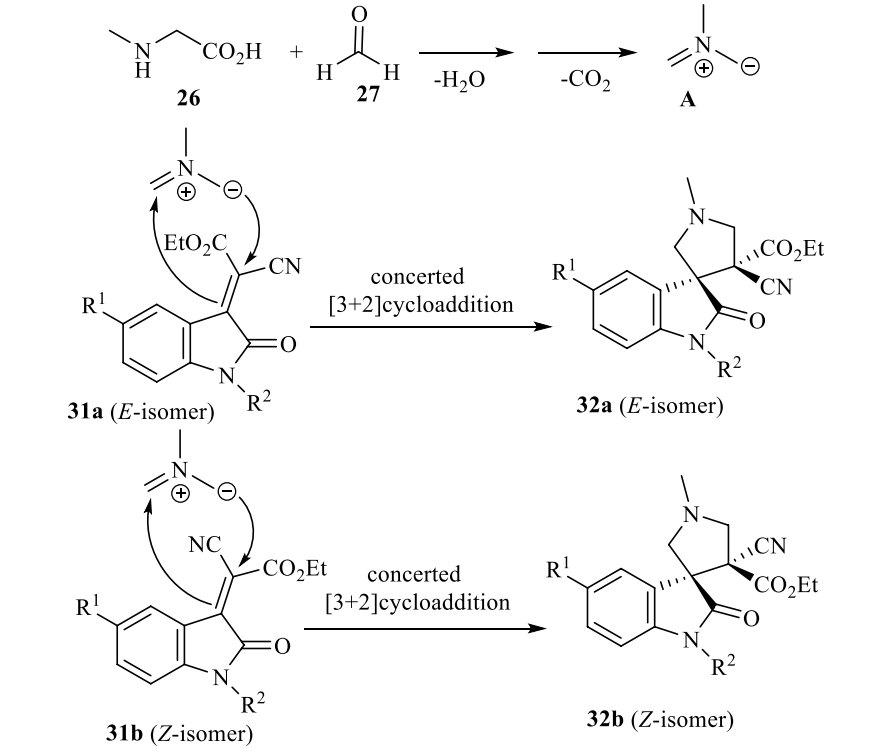
$R^2$ = Bn, $C_4H_9$

**Scheme 11** Three-component reaction for the synthesis of spiro[indoline-3,3′-pyrrolidines **30**

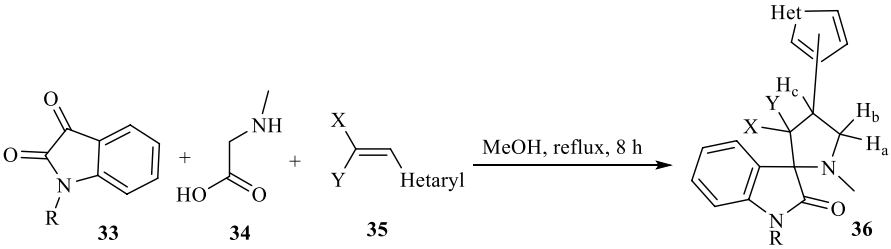
and **32b** (*Z/E* isomers) using 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **31a** and **31b** (*Z/E* isomers) as raw materials. Initially, the thermal depolymerization of paraformaldehyde obtained formaldehyde, which subsequently became involved with sarcosine to form the expected azomethine **A** by removing $H_2O$ and $CO_2$. The precursor 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **31** has two *Z/E* isomers in distinct proportions. Afterwards, the [3 + 2] cycloaddition of azomethine with 2-cyano-2-(2-oxoindolin-3-ylidene)acetate **31** led to the spiro[indoline-3,3′-pyrrolidines] **32** with two major *E*-isomers **32a** and minor *Z*-isomers **32b** [23].

Deepthi and colleagues have developed the synthesis of a library of spiro(oxindole-3,2′-pyrrolidine) attached to heteroaromatics in the pyrrolidine unit **36** applying the 1,3-dipolar cycloaddition reaction of azomethine ylide with heterocyclic ylidenes using isatin **33**, sarcosine **34**, and thiophene-3-ylidene **35** as starting materials (Scheme 13). The method shows a two-phase functionalization of thiophene/furan with spiropyrrolidine oxindoles in the second/third positions. The reactions of the heterocyclic ylidenes were also carried out applying other $\alpha$-amino acids **37**, named L-proline, thioproline, and phenylalanine. Under the same reaction conditions, azomethine ylide was produced by reaction of isatin with $\alpha$-amino acid with removal of carboxyl from the intermediate, which, under [3 + 2] cycloaddition with ylidene ,formed the related spirooxindoles [24].

Muthusubramanian and colleagues [27] introduced the formation of novel benzosuberone-tethered spirooxindoles **38**, which proceeded via a 1,3-dipolar



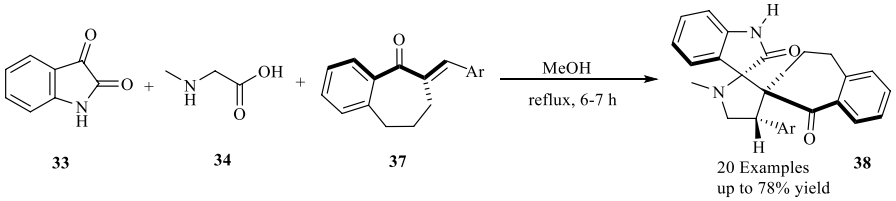

**Scheme 12** A rational mechanism to produce spiro[indoline-3,3′-pyrrolidines] with *Z*/*E* isomers



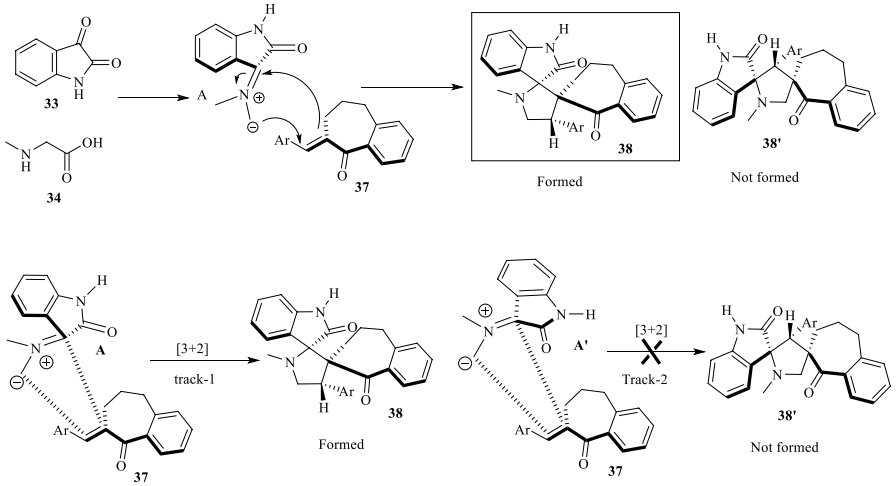

**Scheme 13** Synthesis of spiro(oxindole-3,2′-pyrrolidine) attached to heteroaromatics in pyrrolidine unit **36**

cycloaddition reaction of azomethine ylide (produced in situ using isatin **33** and sarcosine **34**) with arylidene benzosuberone **37** in refluxing methanol (Scheme 14). The 1,3-dipolar cycloaddition reaction creates an important means of forming compounds with complex structures with high regio- and stereoselectivities [25, 26].

A rational mechanism for the synthesis of benzosuberone-tethered spirooxindoles **38** is displayed in Scheme 15. In the first step, the azomethine ylide is



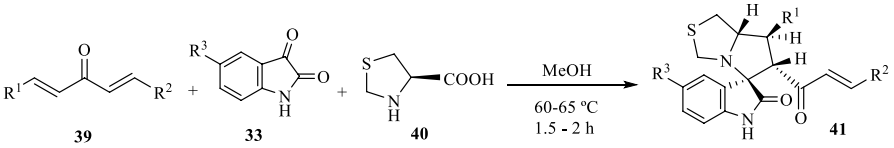

**Scheme 14** Synthesis approach towards novel benzosuberone-tethered spirooxindoles **38**




**Scheme 15** Proposed mechanism for the formation of **38**

produced by the reaction between isatin **33** and sarcosine **34** via the removal of carboxyl. Subsequently, dipole **A** and dipolarophile **37** form a single diastereomer via cycloaddition. To justify the diastereoselectivity despite the presence of three stereocenters, the most plausible reason is illustrated in Scheme 15. Probably, the cycloaddition prefers track 1 to track 2. In track 1, the pyrrolidine moiety and carbonyl of the benzosuberone structure are trans to each other to prevent steric strain. In a similar way, to escape electrostatic repulsion, two carbonyls of the compounds are placed in a trans position relative to each other [27].

Barakat et al. [28] have designed an easy and smooth procedure for the formation of spirooxindoles derivatives named spiro[indoline-3,5′-pyrrolo[1,2-*c*] thiazol]-2-one **41** having four stereogeneric centers as potent MDM2 inhibitors with an asymmetric 1,3-dipolar cycloaddition as the main stage. This method contains the one-pot multi-component condensation of $\alpha,\beta$-unsaturated dienone derivatives **39**, with the dicarbonyl compound (isatin derivatives **33**), and amino acid derivatives **40** (*L*-4-thiazolidinecarboxylic acid), which was heated in methanol to produce the final spirooxindole series **41** (Scheme 16). The structural




$R^1$ and $R^2$ = 4-ClBn, 4-BrBn, 4-FBn, 4-$CH_3$Bn, 4-$OCH_3$Bn, 4-$CF_3$Bn

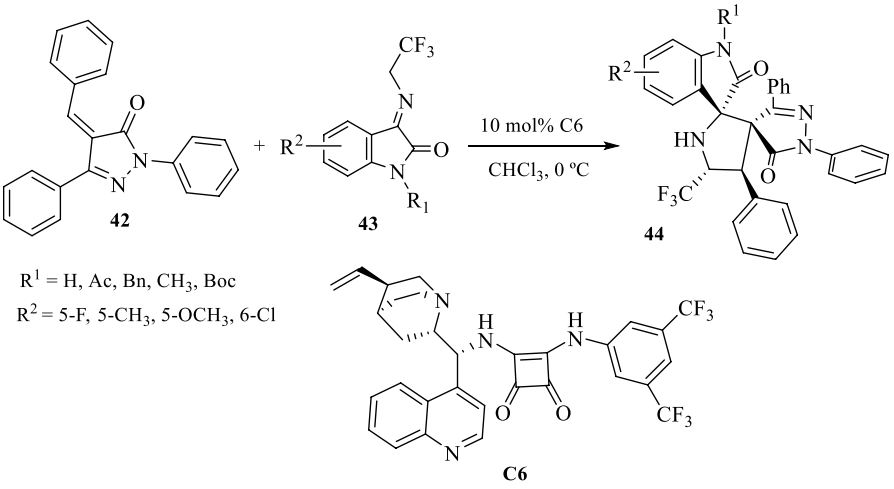
$R^3$ = H, Cl, Br

**Scheme 16** Synthesis of substituted spirooxindoles named spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazol]-2-one **41** with four stereogeneric centers

complexity and the certain stereochemistry of final compounds were certified by X-ray crystallographic analysis [28].

Yan's group have described a novel procedure for the formation of a pharmaceutical important hybrid molecule named $CF_3$-containing spirooxindole-pyrrolidine-pyrazolone compounds **44** via the organocatalytic [3 + 2] cycloaddition reaction. This reaction involves the cycloaddition of *α*,*β*-unsaturated pyrazolones **42** with *N*-2,2,2-trifluoroethylisatin ketimines **43** in dichloromethane at ambient temperature in the presence of a cinchonine-derived squaramide catalyst to produce a spiro-pyrrolidine-attached oxindole and pyrazolone product **44** with four adjacent stereocenters and two adjacent spiroquaternary chiral centers, in high efficiencies and stereoselectivities (Scheme 17) [29].

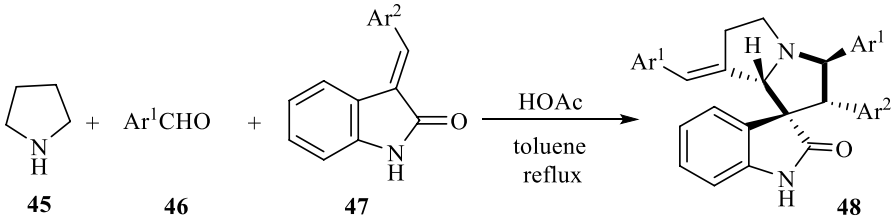
Yan and colleagues described a three-component reaction between pyrrolidine **45**, aromatic aldehydes **46**, and 3-arylideneoxindolin-2-ones **47** catalyzed by acetic acid in refluxing toluene for the synthesis of functionalized 7′-arylidenespiro[indoline-3,1′-pyrrolizines] **48** in good efficiency with excellent diastereoselectivity (Scheme 18), although the reaction with 3-phenacylideneoxindoles **49** led to a




$R^1$ = H, Ac, Bn, $CH_3$, Boc

$R^2$ = 5-F, 5-$CH_3$, 5-$OCH_3$, 6-Cl

**Scheme 17** Formation of spiro-pyrrolidine–pyrazoline oxindoles **44**

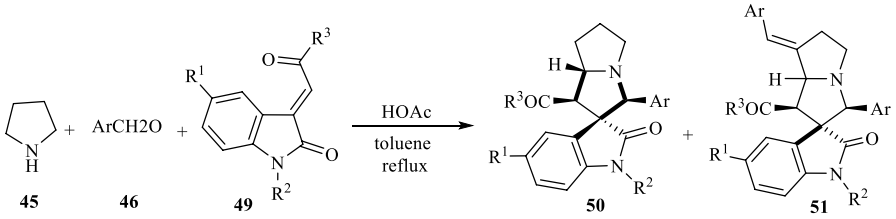



**Scheme 18** Synthesis of 7′-benzylidene-spiro[indoline-3,1′-pyrrolizines] **48**

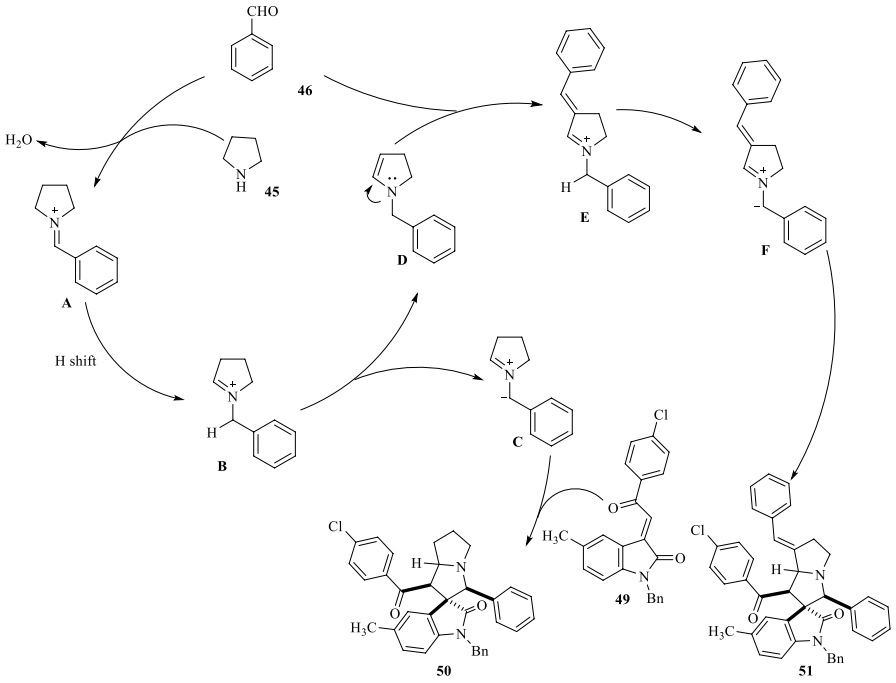
mixture of spiro[indoline-3,1′-pyrrolizines] **50** and 7′-arylidene-substituted spirooxindoles **51** in moderate efficiencies (Scheme 19). The synthesis of spiroheterocyclic products proceeds by [3 + 2] cycloaddition of the in situ formed azomethine ylides with three cyclic 1,3-dipolarophiles [30].

The reaction mechanism proceeds via the formation of azomethine ylides, $\beta$-C − H functionalization of pyrrolidine, and subsequent [3 + 2] cycloaddition (Scheme 20). Benzaldehyde **46** is involved with pyrrolidine **45** to obtain iminium ion **A**. The related iminium ion **B** would be acquired by a [1,3]-H shift step. In the following, deprotonation of **B** would produce normal azomethine ylide **C**, which, after a 1,3-dipolar cycloaddition with 3-phenacylideneoxindole **49**, synthesized the spiro compound **50**. In another route, enamine intermediate **D** would be produced via deprotonation of **B**. After an aldol-type reaction of **D** with a second molecular benzaldehyde **46**, and following dehydration, the iminium ion **E** was acquired, which would be deprotonated to obtain a conjugated azomethine ylide **F**. In the following, [3 + 2] reaction of **F** with 3-phenacylidneoxindole **49** produced the spiro product **51**. As a result, both normal azomethine ylide and conjugated azomethine ylide could be produced in situ and involved 1,3-dipolarophiles. The reaction with 2-arylidene-1,3-indanedione or 3-arylideneindolin-2-one was carried out mainly with the [3 + 2] cycloaddition of the conjugated azomethine ylide, while the reaction with 3-phenacylideneoxindole contains both [3 + 2] cycloaddition reactions of normal azomethine and conjugated azomethine ylide [30].

Dai and coworkers have developed a Rh(III)-catalyzed domino annulation of *N*-(pivaloyloxy)acrylamide **52** as a simple olefin with diazooxindole **53**

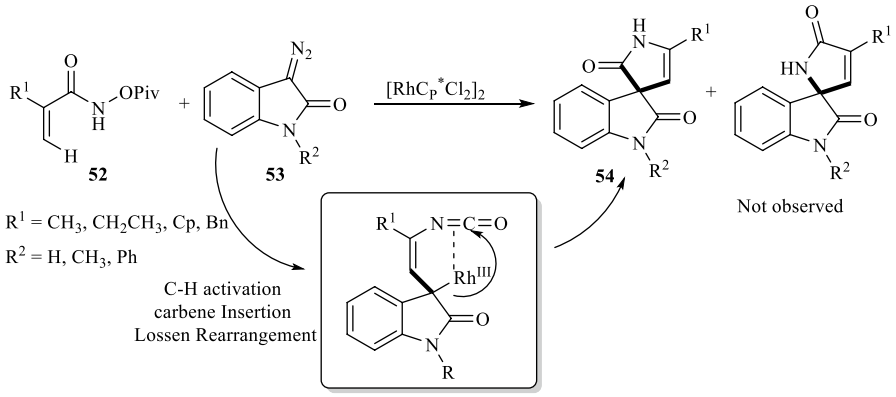



**Scheme 19** Synthesis of spiro[indoline-3,2′-pyrrolizines] **50** and **51**




**Scheme 20** Proposed mechanism of [3 + 2] cycloaddition reaction for the formation of spiro[indoline-3,2′-pyrrolizines] **50** and **51**

to give spirooxindole pyrrolone products **54** with excellent regioselectivities (Scheme 21). The potential application of this protocol in the next step of diversification for drug finding was illustrated in the directed presentation of spirooxindole pyrrolone skeleton into medicinal molecules pentoxifylline, endofolliculina, and pregnenolone [31].



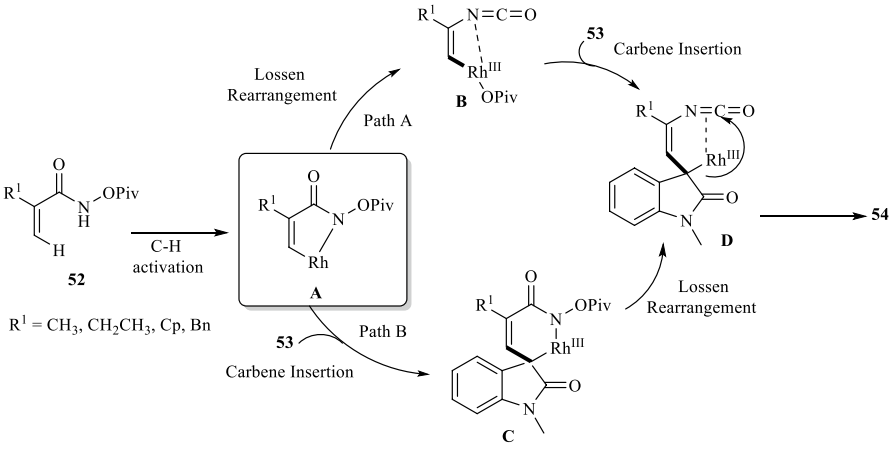

**Scheme 21** C($sp^2$)–H activation/annulation to synthesis spirooxindole pyrrolone scaffold **54**

The reaction proceeds via a tentative mechanism involving cleavage of the C–H bond with Rh(III), followed by carbene migratory insertion with the diazo substrate to obtain a novel alkyl rhodium intermediate **C**. In the following, a formal Lossen rearrangement offers isocyanate **D**, which, via further nucleophilic addition at the isocyanate, intramolecularly generates the final compound **54** (Scheme 22).

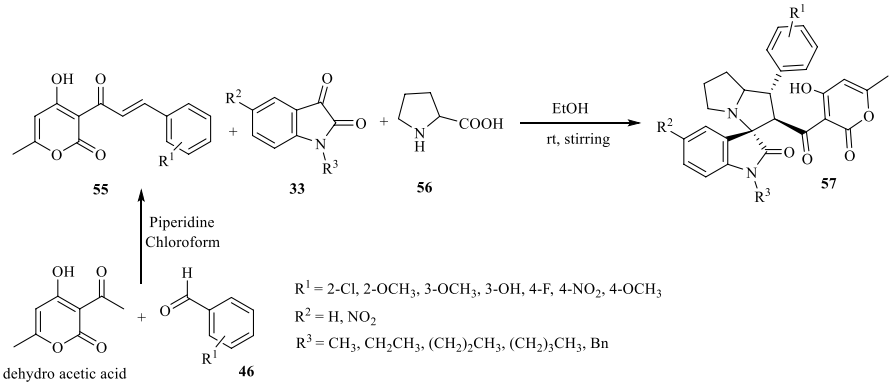
Tripathi et al. have described the synthesis of a new class of five-membered heterocyclic scaffolds named hexahydrospiro[indoline-3,3′-pyrrolizine]-2-one **57** in good-to-excellent efficiencies through [3 + 2] cycloaddition reaction in the regioselective procedure. The synthesized products were obtained via MCR of substituted 3-cinnamoyl-4-hydroxy-6-methyl-2*H*-pyran-2-one **55**, isatin **33**, *L*-proline **56** at ambient temperature conditions (Scheme 22). The final products are key cores of numerous natural compounds and may become potential biological drug scaffolds in the near future. The chalcone analogues **55** used in this reaction were produced via aldol condensation of substituted benzaldehyde **46** and dehydro acetic acid in dry chloroform using a catalytic amount of piperidine (Scheme 23) [32].

Shao and colleagues introduced various catalytic asymmetric synthetic protocols for the formation of tricyclic and tetracyclic 3,3′-pyrrolidonyl spirooxindoles. This method proceeds through a one-pot asymmetric propargylation catalyzed by a chiral Brønsted base for the formation of oxindole 1,6-enynes **A** from the common and available precursors, 3-allyl oxindole **58** and *C*-alkynyl *N*-Boc-acetal **59**, and a subsequent interchangeable site-selective and excellent diastereoselective electrophilic iodocyclization of 1,6-enynes via alkenyl-activation and alkenyl/alkynyl dual activation to form tricyclic 3,3′-pyrrolidonyl spirooxindoles **60** and tetracyclic 3,3′-pyrrolidonyl spirooxindoles **61** (Scheme 24) [33].

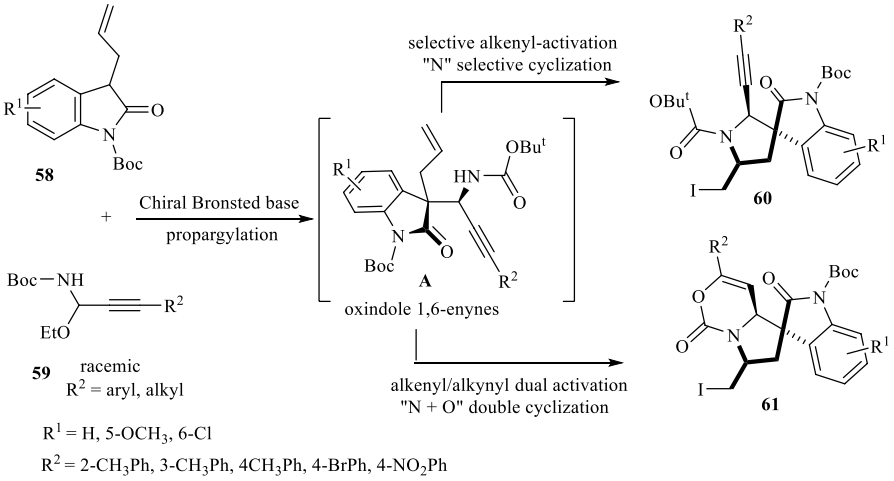
Although halogen-atom-promoted electrophilic cyclization (electrophilic halocyclization) of alkenes or alkynes has been widely discussed, electrophilic halocyclization of unconjugated enynes has been less studied due to the difference




**Scheme 22** Rational mechanism for the synthesis of spirooxindole pyrrolone **54**



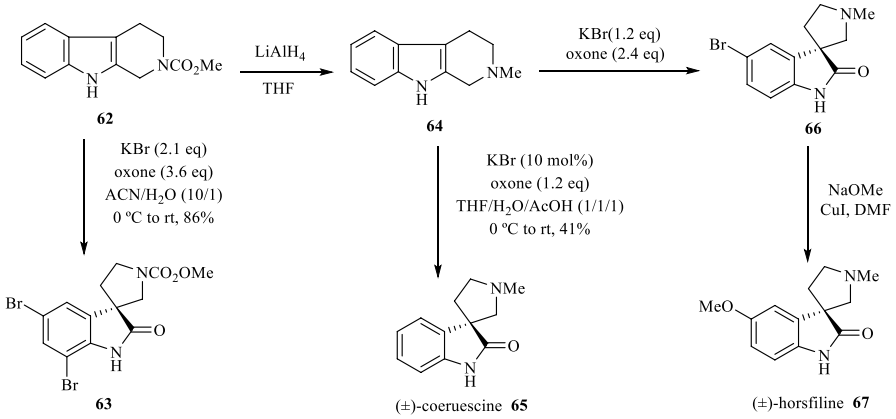

**Scheme 23** Formation of new hexahydrospiro[indoline-3,3′-pyrrolizine]-2-one **57**




**Scheme 24** Asymmetric synthesis of tri- and tetracyclic spirooxindoles

in the reactivity of alkenes relative to alkynes [34]. The heterocyclic products obtained from this type of reaction are very important due to having easily modifiable halogen handles [35].

The oxidation process of indoles is a basic organic conversion for the formation of a diversity of synthetically and medicinally valuable nitrogen-containing compounds. The electron-rich property of indoles leads to easy oxidation using many oxidation reagents. Since catalysis methods in the presence of secure oxidants ($H_2O_2$, oxone, $O_2$) is highly favorable, Tong and coworkers have introduced three unique, efficient halide catalyzed oxidation processes of tetrahydro-$\beta$-carbolines (THCs) indoles **62** applying oxone as the terminal oxidant, which leads to the formation of oxindoles **63**, **65** and **67** (Scheme 25) [36].




**Scheme 25** Oxidative rearrangement of tetrahydro-*β*-carbolines **62** for the formation of spirooxindole natural compounds

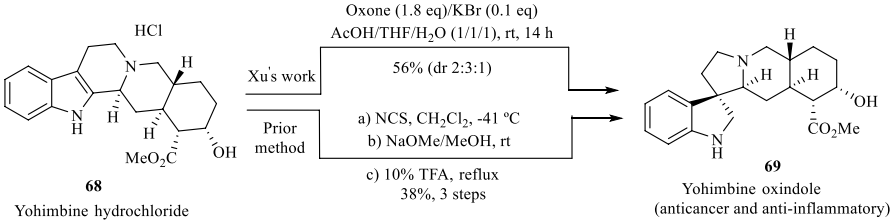
Compared to previous procedures, this method was relatively more useful due to the in situ formed halenium ion ($X^+$) catalyst, which has suitable reactivity towards the C2–C3 double bond of indoles, therefore largely preventing other competitive oxidations/rearrangements. Furthermore, there is no requirement for protection of indole nitrogen, while most past protocols needed to protect the indole nitrogen with electron-withdrawing groups (e.g., *N*-Ts, *N*-Boc, N-Ac, etc.) to improve the chemo-selectivity and regio-selectivity of the final compounds [36].

To indicate the synthetic value of this procedure, Tong and colleagues carried out the total synthesis of two well-known spirooxindoles as target natural compounds named (±)-coerulescine **65** and (±)-horsfiline **67** from THC **62** (Scheme 25). Reduction of THC **62** using $LiAlH_4$ and oxidative rearrangement of the obtained THC **64** in the presence of oxone-KBr in acidic medium (THF/AcOH/$H_2O$ = 1:1:1) produced (±)-coerulescine **65** with 39% yield in two steps. Whereas the oxidative rearrangement of THC **64** proceeds with stoichiometric KBr and 2.4 equivalent of oxone, consecutive one-pot oxidative rearrangement and bromination synthesizes C5-bromo spirooxindole **66** in 41% yield, which could be applied for CuI-catalyzed Ullmann ether synthesis to furnish (±)-horsfiline **67** in 60% yield [36].

Finally, they used this procedure for the biomimetic oxidative rearrangement of a natural alkaloid named Yohimbine hydrochloride **68**, and synthesized the related Yohimbine oxindole **69** (Scheme 26) with 56% efficiency [36], which seemed better than the previous three-step procedure [37] with only 38% overall efficiency.

### 2.2.2 Six-Membered Ring

Choudhury and coworkers have described a medium-dependent and metal-free three-component condensation of isatin **33**, 4-hydroxycoumarin **70** and aminopyrazole **71** in MW-assisted conditions for the formation of two diverse kinds of fused spirooxindoles **72** and **73**. Isatin **33**, 4-hydroxycoumarins **70** and aminopyrazole **71** reacted together under MW-assisted conditions in acetonitrile solvent and produced



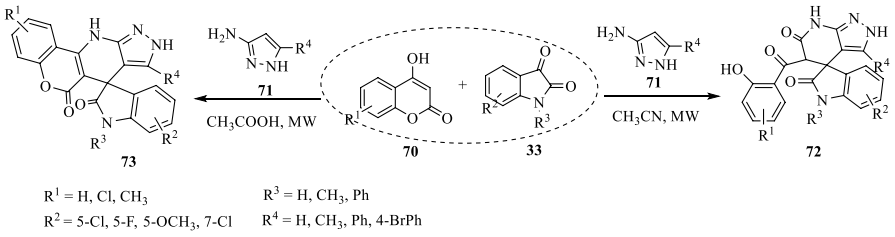

**Scheme 26** Biomimetic oxidative rearrangement to produce Yohimbine oxindole **69**

spirooxindoles fused with pyrazolo-tetrahydropyridinones **72** via opening the ring of the hydroxycoumarin core. Additionally, when acidic conditions are used as the reaction medium, related fused spirooxindoles containing a tetracyclic coumarin-dihydropyridine-pyrazole scaffold **73** were obtained. This medium-dependent three-component condensation led to the production of a class of pharmaceutically important spiroxindoles under metal-free conditions (Scheme 27) [38].

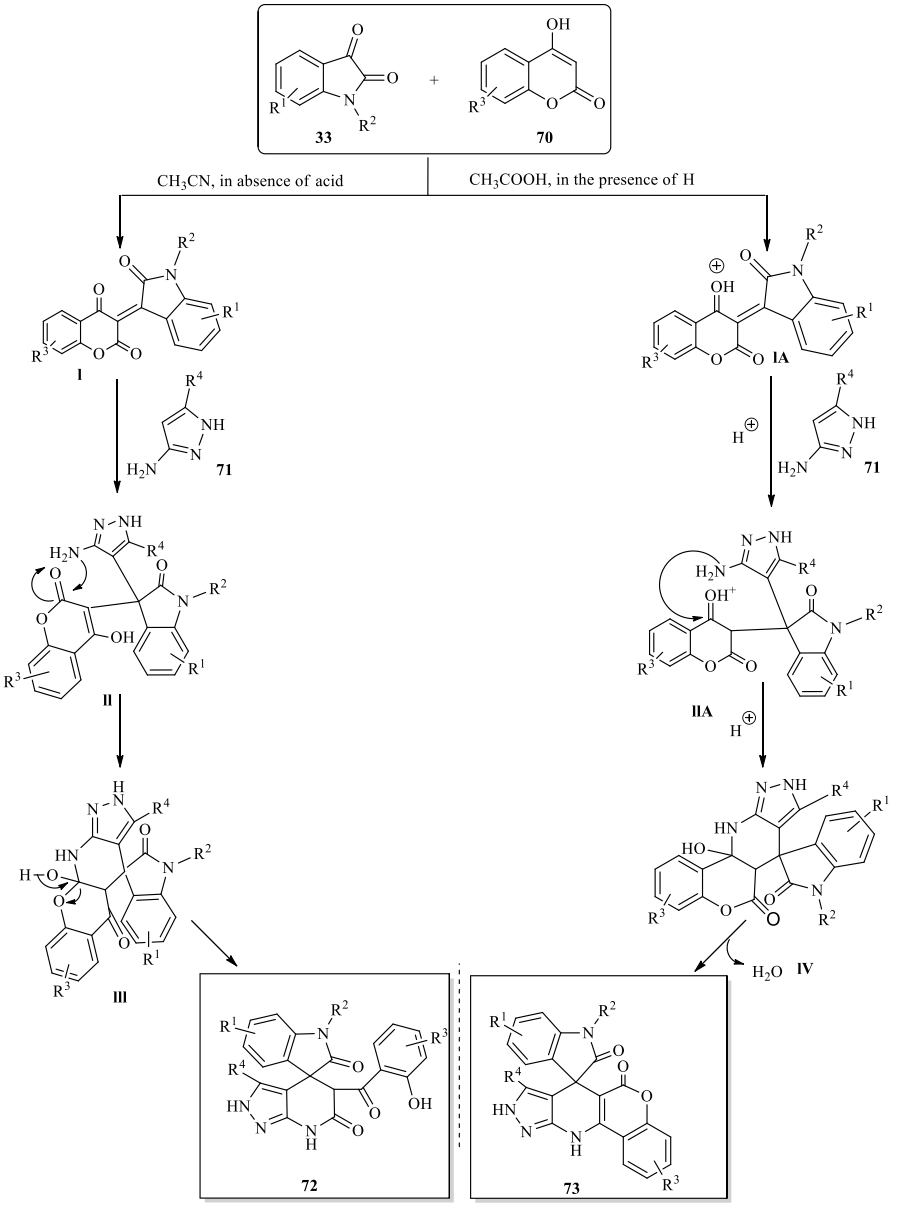
The proposed reaction mechanism for the synthesis of **72** or **73** is illustrated in Scheme 28. It is expected that 4-hydroxycoumarin **70** first becomes involved with isatin **33** to form intermediate **I** and then amino pyrazole **71** undergoes 1,4-addition to obtain tri-substituted methane **II**. In non-acidic conditions, **II** remains at the step of enol formation, so the masked carbonyl's reactivity is less than that of the ester part. Therefore, intramolecular cyclization happens in the ester group of the coumarin species and produces intermediate **III**, and eventually stable compound **72** synthesizes via ring-opening of the coumarin. Besides, by using acid, tri-substituted methane intermediate **II** remains as protonated form **IIA**, containing the active protonated carbonyl group (ketone) **IV**, so ring closure happens intramolecularly by involving the ketone group of the coumarin instead of the ester group, and product **73** is formed.

In order to expand the substrate scope, they have prepared new spirooxindole fused with coumarin-dihydropyridine-isooxazole tetracycle **75** by applying 3-amino-5-methylisoxazole **74** instead of aminopyrazoles (Scheme 29) [38].

Wu et al. [39] have developed an easy, efficient and environmentally benign method to produce the structurally diverse spirooxindole scaffolds named spiro[indole-[4*H*]pyrazolo[3,4-*b*]quinoline] **79** and spiro[indoline pyrazolo[3,4-*b*]



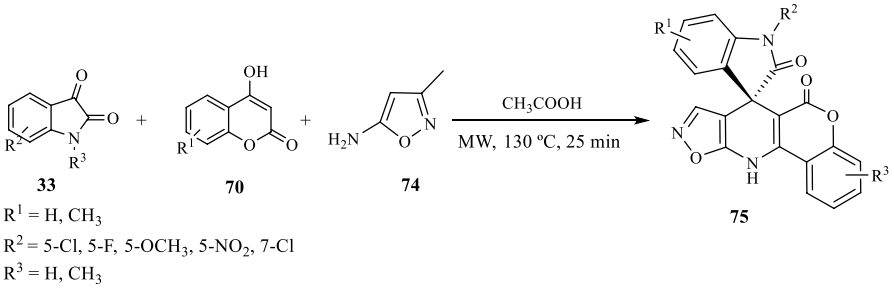

**Scheme 27** Synthesis of fused spirooxindoles **72** and **73** via the reaction of 4-hydroxy coumarin and amino pyrazole



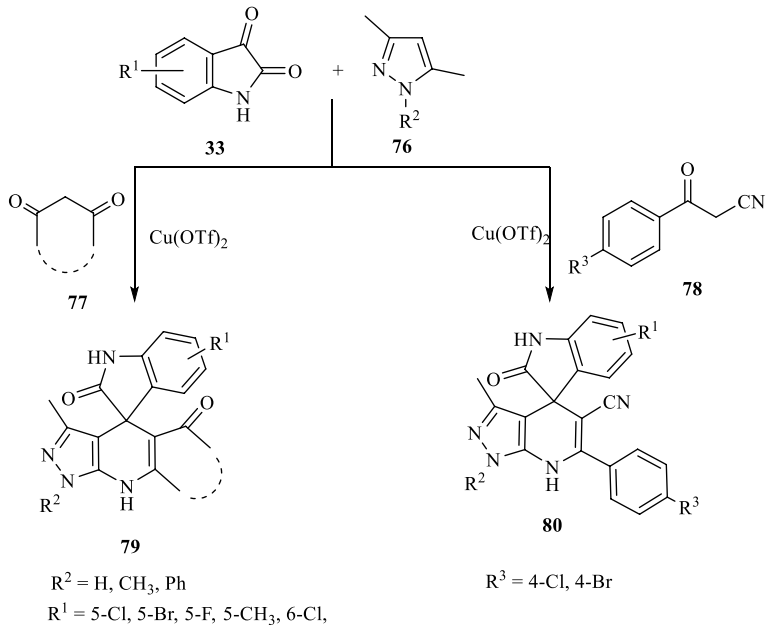

**Scheme 28** A rational mechanism for the formation of products **72** and **73**

pyridine]carbonitrile **80** through a three-component condensation of isatin **33**, 5-aminopyrazole **76**, and 1,3-dicarbonyl compounds **77** (or b-oxo-benzenepropanenitrile **78**) catalyzed by copper triflate [$Cu(OTf)_2$] in ethanol (Scheme 30).

A rational mechanism for this three-component condensation is demonstrated in Scheme 31. It is expected that, in the first step, the 1,3-diketone **77** involves with



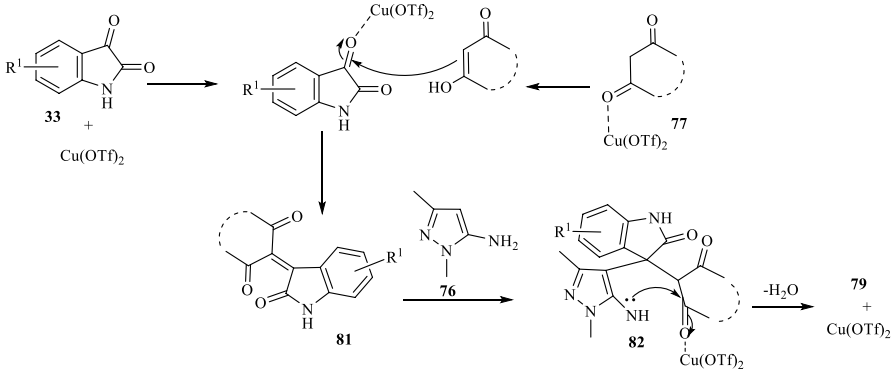

**Scheme 29** Formation of spirooxindole scaffolds containing coumarin-dihydropyridine-isoxazole tetracycles **75**




**Scheme 30** Synthesis of spiro[indole-[4*H*]pyrazolo[3,4-*b*]quinoline] **79** and spiro[indoline pyrazolo[3,4-*b*]pyridine]carbonitrile **80**

isatin **33** to form the condensation adduct **81**, which, under a Michael-type addition of 5-aminopyrazole **76** continues by the cyclocondensation of the intermediate **82** to obtain the related compounds **79**. But when *b*-oxo-benzenepropanenitrile **78** was used instead of 1,3-diketone, product **80** was produced by a similar mechanism [39].

Khojasteh-Khosro and Shahbazi-Alavi [40] developed an efficient and rapid procedure for the formation of new spirooxindoles named 10-methyl-8*H*-spiro[benzo[5,6]chromeno[2,3-*c*]pyrazole-11,3′-indol]-2′(1′*H*)-one **87** and 8-methyl-10-phenyl-10,11-dihydrospiro[pyrazolo[3,4-*b*]benzo[*h*]quinolin-7,3′-indol]-2′(1′*H*)-one **88** through a four-component reaction of phenylhydrazine

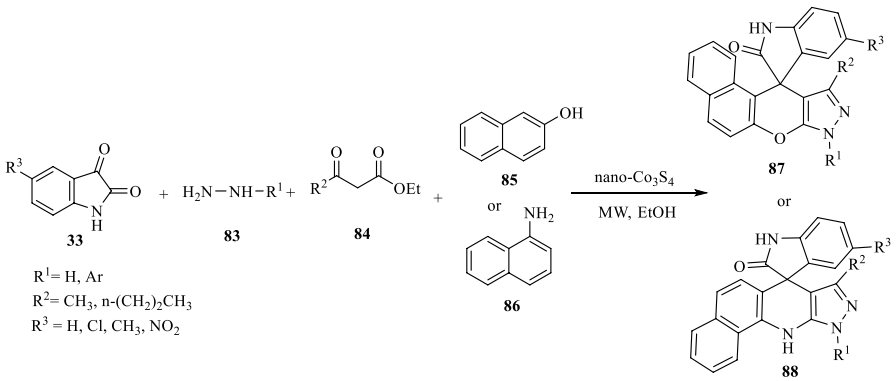


**Scheme 31** Rational mechanism for the $Cu(OTf)_2$-catalyzed synthesis of spirooxindoles **79**

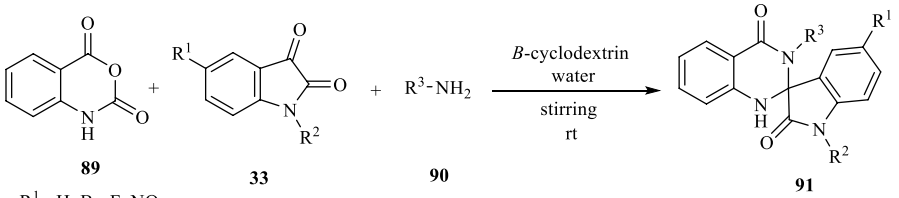
or hydrazine hydrate **83**, isatins **33**, ketoesters **84**, and 2-naphthol **85** or naphthylamine **86** in presence of nano-$Co_3S_4$ in MW-assisted reaction conditions (Scheme 32) [40].

Tripathi has introduced an efficient multicomponent synthetic method for the formation of new spiroindole quinazolines named spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-dione **91** from isatoic anhydride **89**, isatin **33**, and primary amine **90**, which is catalyzed by *β*-cyclodextrin in an aqueous medium (Scheme 33). Due to the use of environmentally friendly catalysts and green solvents, the method presented in this work is a green method to produce valuable spiroheterocycles [41].

Cyclodextrins are glyco macromolecules containing cyclic glucose oligomers with cylindrical shapes in such a way that the primary hydroxyl groups are located at the more restricted rim of the cylinder. Cyclodextrins are used as water-soluble catalysts for reactions in supramolecular catalysis including the reversible generation of host–guest complexes by non-covalent bonding as observed in enzymes. Cyclodextrins activate raw material by molecular distinction and catalyze reactions in a selective way.



**Scheme 32** Synthesis of new spirooxindoles **87** and **88** under microwave (MW) irradiation




$R^1$= H, Br, F, $NO_2$

$R^2$= H, $CH_2CH_3$, $(CH_2)_2CH_3$, Bn

$R^3$ = H, Ph, 3-ClPh, 4-ClPh, 4-$NO_2$Ph, 4-ClPh, 4-BrPh, 4-OHPh, 4-$OCH_3$Ph

**Scheme 33** Synthesis of various spiroindole quinazolines derivatives via an environmentally benign procedure

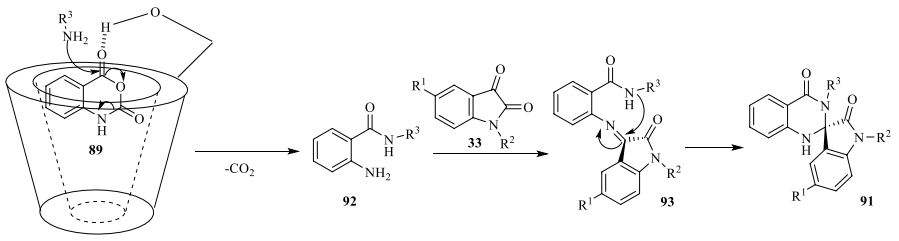
Tripathi tried to justify the possible mechanism of the reaction based on observations. The mechanistic protocol (Scheme 34) illustrated the role of cyclodextrin in activating the carbonyl carbon in isatoic anhydride **89** resulting in anhydride ring-opening and generation of intermediate **92**. Intermediate **92** then reacts with the ketonic functional group of isatin **33** to produce intermediate **93** and the final product **91** [41].

## 2.3 Fused with Oxygen-Heterocycle Containing Spiro-cyclic Compounds

### 2.3.1 Four-Membered Ring

In recent years, the existence of four-membered rings in compounds containing a spirocenter has gathered much consideration. For example, oxetanes have attracted wonderful interest from synthetic and medicinal researchers. Oxetanes not only exist in natural compounds and bioactive molecules but are also used as effective precursors in the synthesis of novel heterocyclic products due to the ring strain that leads to ring-opening or ring expansion processes [42, 43].

Marini and colleagues described an unprecedented Michael/intramolecular etherification cascade reaction of 3-hydroxyoxindoles **94** with phenyl vinyl selenone **95** for the formation of novel spirooxindole 2,2-disubstituted oxetanes **96** in water and in the presence of a base at ambient temperature without the addition of

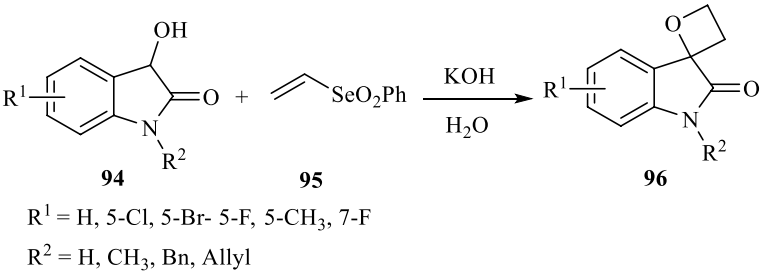



**Scheme 34** Plausible mechanistic pathway for synthesis of spiroindole quinazolines **91** using cyclodextrin as glyco macromolecules

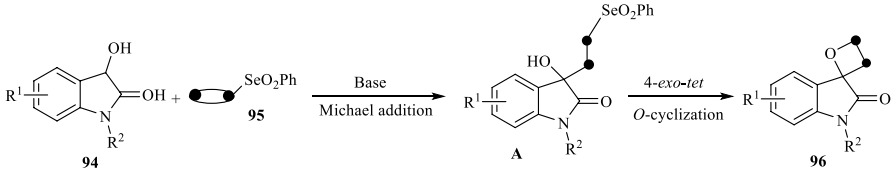
surfactants (Scheme 35). The spirooxindole oxetanes could be produced based on the bis-nucleophilic character of 3-hydroxyoxindoles and proceeded via the domino Michael addition-cyclization subsequence illustrated in Scheme 36. Methods for the synthesis of oxetanes, especially 2,2-disubstituted oxetanes, are still in demand, and the discovery of novel methods for enhancing structural diversity is highly favorable [44].

### 2.3.2 Five-Membered Ring

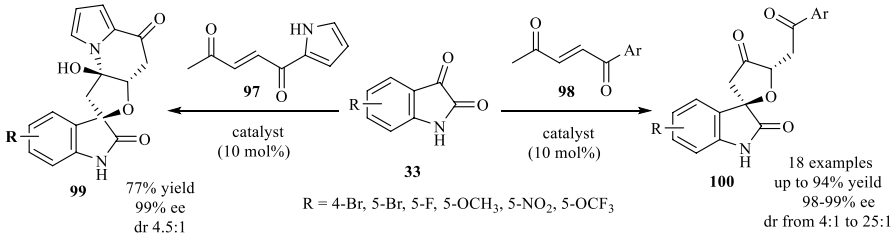
Kanger and coworkers have revealed an enantio- and regioselective organocatalytic cascade reaction for the formation of tetrahydrofuranyl spirooxindoles **99** and **100** starting from isatin **33** and enolizable unsaturated 1,4-diketones **97** and **98** as multifunctional synthons catalyzed by cinchonine-based thiourea (Scheme 37). In this method, excellent amounts of diastereoselectivity and enantioselectivity (ee up to 99%) were acquired [45].



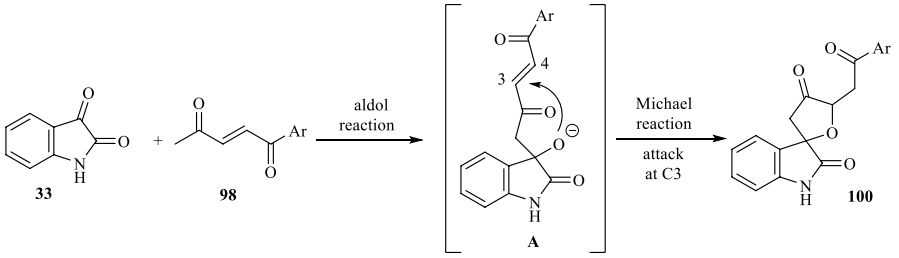

**Scheme 35** Synthesis of novel spirooxindole 2,2-disubstituted oxetanes **96**



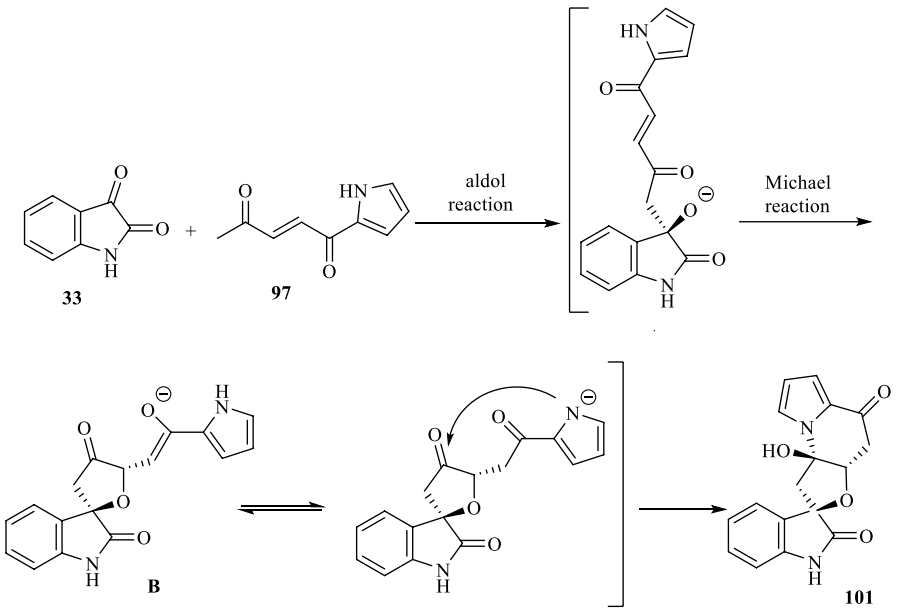

**Scheme 36** Synthetic routes to spirooxindole oxetanes **96**




**Scheme 37** Synthetic routes for the formation of tetrahydrofuranyl spirooxindoles **99** and **100**



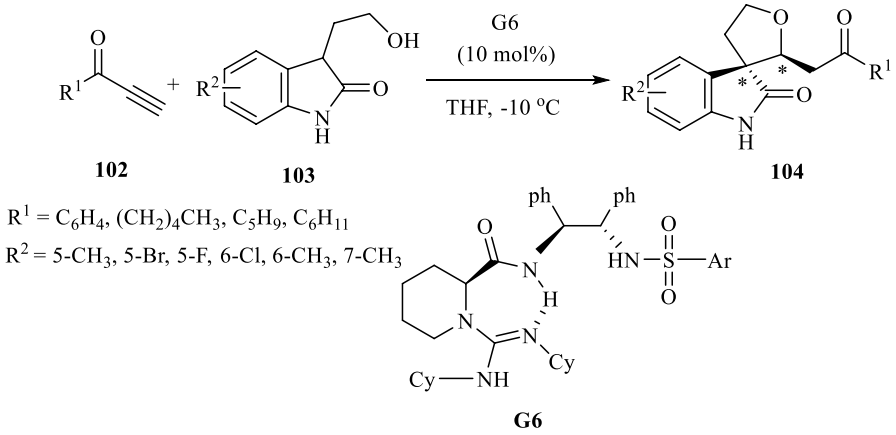

**Scheme 38** Schematic design for the synthesis of tetrahydrofuranyl spirooxindoles **100**



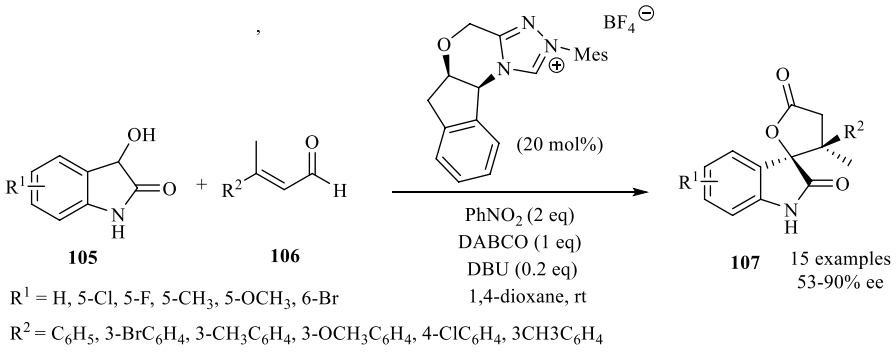

**Scheme 39** Synthesis of the pentacycle spirooxindole **101** through a triple cascade reaction

The proposed mechanism involves the aldol reaction between enol nucleophile generated by the reaction of isatin **33** and multifunctional enolizable unsaturated 1,4-diketones **98** subsequent by the intramolecular Michael reaction at C3 of intermediate **A** result in straight cyclization and the synthesis of spiro products **100** containing with quaternary and tertiary stereogenic centers (Scheme 38).

Kanger and coworkers also afforded a triple cascade reaction for the formation of pentacyclic spirooxindole compound **101** containing two quaternary and tertiary stereocenters in excellent enantioselectivities. This triple cascade reaction involves the aldol reaction, oxa-Michael reaction giving enolate **B**, which is in equilibrium with the deprotonated pyrrole, which, in the final nucleophilic attack of pyrrole to the carbonyl functional group of the tetrahydrofuranyl, leads to product **101** (Scheme 39) [45].




**Scheme 40** An asymmetric cascade double Michael addition for the formation of spirooxindoles containing dihydrofuran **104**

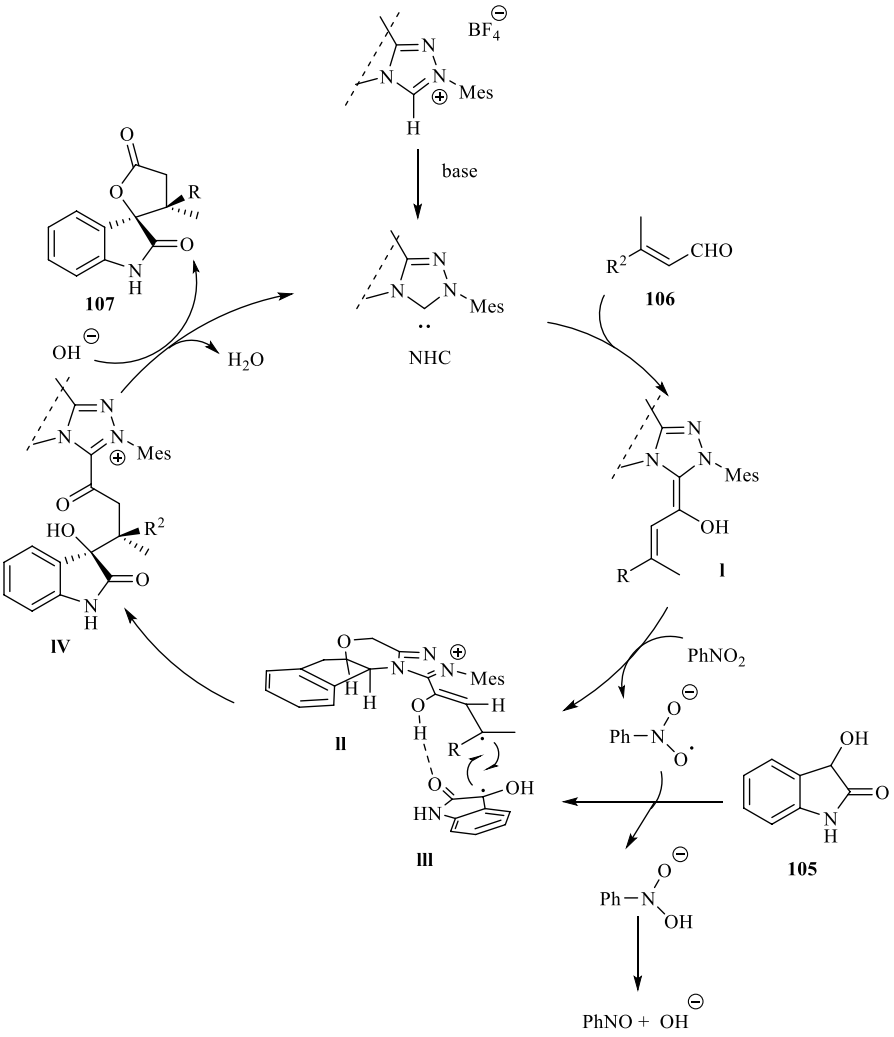



**Scheme 41** *N*-heterocyclic carbene (NHC)-catalyzed oxidative [3 + 2] annulation reaction for the synthesis of spirocyclic oxindole-*γ*-lactones **107**

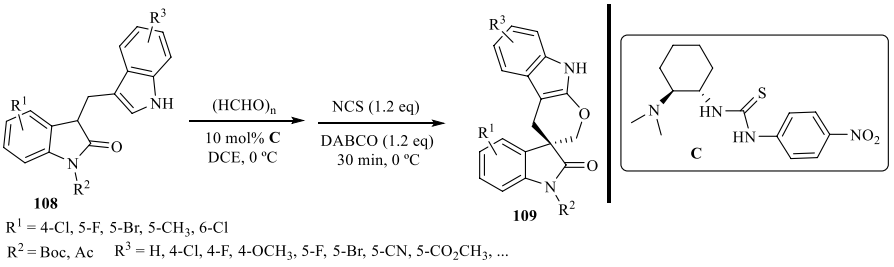
Liu's group described an asymmetric cascade double Michael addition between terminal alkynones **102** and 3-alkyl substituted oxindoles embellishing a OH end group **103** to produce 2′-substituted 3,3′-spirooxindoles comprising dihydrofuran **104** in the presence of a chiral guanidine organocatalyst with high diastereo- and enantioselectivities, which may be converted to potential medicinal targets (Scheme 40). This protocol provides an asymmetric synthetic method for the formation of (−)-salacin for the first time [46].

Ye and colleagues reported the reaction of dioxindoles **105** and *β*,*β*-disubstituted enals **106** based on oxidative [3 + 2] annulation catalyzed by *N*-heterocyclic carbene (NHC) for the synthesis of spirocyclic oxindole-*γ*-lactones **107** containing two adjacent quaternary stereocenters in good efficiencies with high diastereo- and acceptable enantioselectivities (Scheme 41) [47].

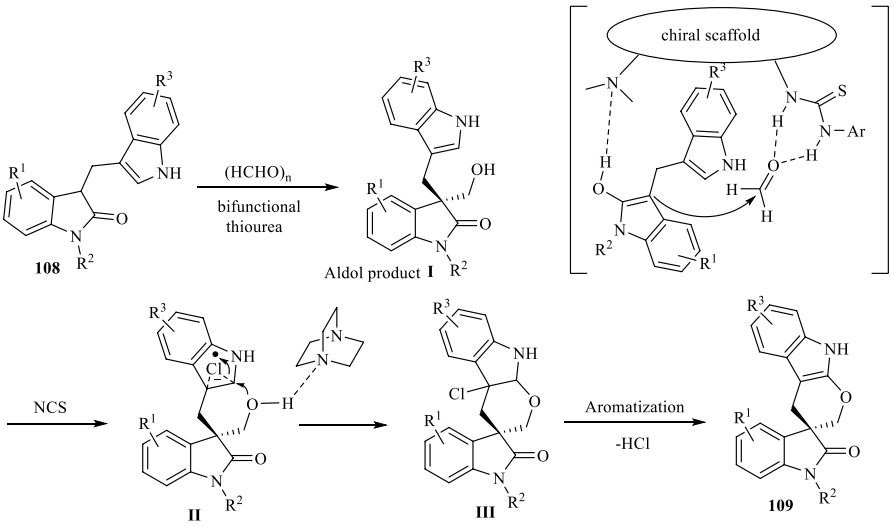
The proposed catalytic cycle is illustrated in Scheme 42. Initially, NHC reacts with aldehyde **106** to generate homoenol **I**, followed by single electron transfer by nitrobenzene leading to oxidation to obtain homoenol radical **II**. On the other, the enol radical **III** is produced from dioxindole **105**. In the following, via cross-coupling, two radicals afford intermediate **IV**, and, under basic conditions, lactonization occurs to synthesis compound **107** and recycle the NHC catalyst [47].




**Scheme 42** Plausible catalytic cycle for the synthesis of spirocyclic oxindole-γ-lactones **107**




**Scheme 43** Catalytic one-pot sequential aldol/chloroetherification/aromatization procedure for the formation of pentacyclic spirooxindoles




**Scheme 44** Rational mechanism for the formation of tetrahydropyrano[2,3-*b*]indole **109**

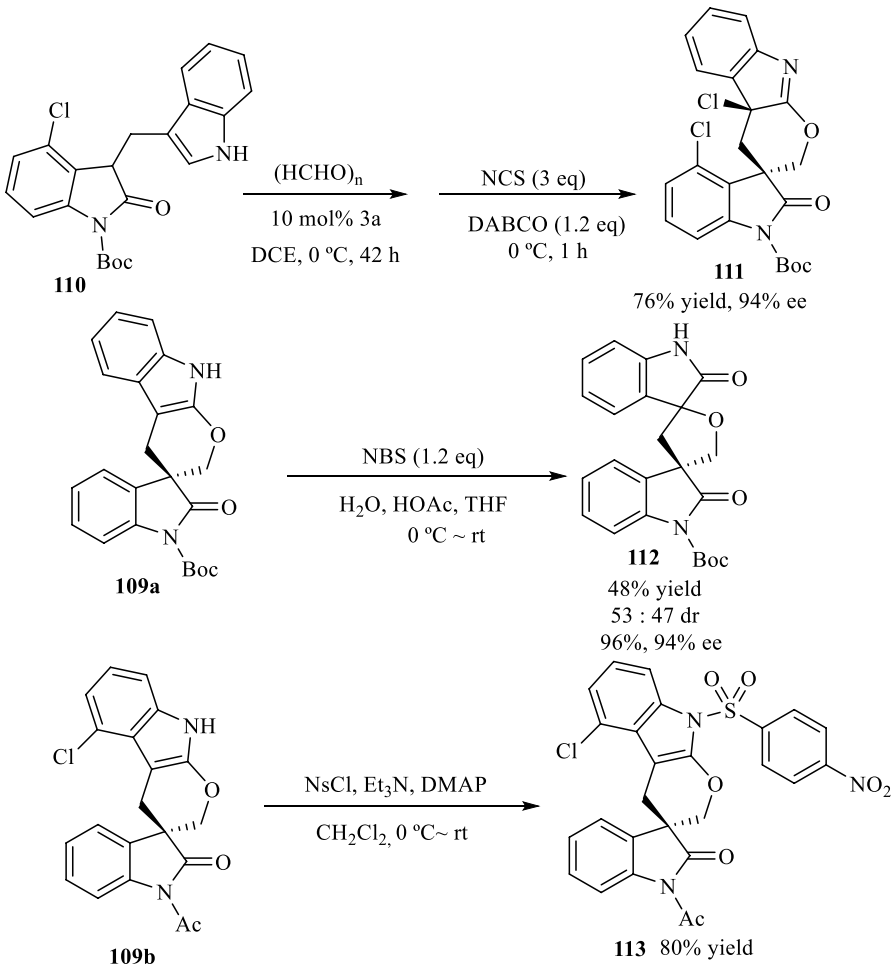
### 2.3.3 Six-Membered Ring

Jiang et al. [48] introduced a general method for the production of a wide range of enantioenriched chiral pentacyclic spirooxindoles comprising a tetrahydropyrano[2,3-*b*]indole skeleton **109** via a catalytic one-pot sequential aldol/chloroetherification/aromatization from 3-(3-indolomethyl) oxindole **108**, paraformaldehyde, and NCS (Scheme 43). In addition, the pentacyclic spirooxindoles could be converted to other compounds with structural diversity such bispirooxindole and spirocyclic oxindoles.

Based on previous studies, Jiang et al. [48] proposed a rational reaction mechanism (Scheme 44). Formaldehyde was generated gently in monomeric form from its polymeric form. Afterwards, the chiral bifunctional thiourea catalyst **C** has the ability to convert the intermolecular reaction of 3-(3-indolomethyl) oxindole **108**

and formaldehyde into an intramolecular-type reaction because of the simultaneous motivation and activation of 3-substituted oxindoles as nucleophile and formaldehyde as electrophile for high enantioselectivity. In the following, nucleophilic attack of the aldol compound **I** to NCS produced a chloronium ion **II**; then 1,4-diazabicyclo[2.2.2]octane (DABCO) can act as a possible Lewis base, stimulating ring-closure to produce a pyran core in **III**. In the final stage, aromatization with the release of HCl occurs, yielding a tetrahydropyrano[2,3-*b*]indole structure **109** [48].

In order to further expand the capabilities of this method, Jiang et al. [48] carried out different conversions of the products obtained in the previous step to increase molecular diversity of spirocyclic oxindoles (Scheme 45). After the aldol procedure in a one-pot process, substrate **110** could be readily involved with three equivalents of NCS and converted to dearomatizated product **111** in 76% efficiency and



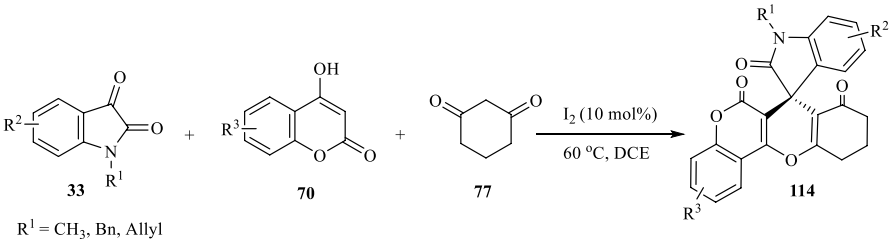

**Scheme 45** Direct conversion of products **109** to various spirocyclic oxindoles

94% ee. Furthermore, high diastereoselectivity was acquired due to the steric strain of the chlorine atom exist in the precursors. In particular, compound **109a** could undergo oxidative rearrangement in the presence of NBS-HOAc-$H_2O$-THF, providing the structure bispirooxindole **112** in a moderate yield, high enantioselectivity, and 1:1 dr. In addition, compound **109b** reacts with bulky *p*-nitrobenzene sulfonyl chloride using trimethylamine and 4-(dimethylamino)pyridine (DMAP), producing compound **113**. The only chiral quaternary carbon of the pentacyclic spirooxindoles **109** was generated in the first aldol reaction and was not transformed in the next step [48].

Zhang et al. described a three-component condensation promoted by iodine for the production of heterocyclic compounds named spiro[chromeno[4,3-*b*]chromene-7,3′-indoline]trione **114** via the green reaction system using molecular iodine as a suitable catalyst instead of Lewis acids. Several substituted isatins **33** used in this reaction strategy that react with 4-hydroxyl coumarins **70** and various cyclic 1,3-dicarbonyls **77** and offers good functional group diversity and yield (Scheme 46).

Two mechanism pathways for this reaction seem rational (Scheme 47), with the difference between them being the time of bond generation. In path a, *N*-methylisatin **33** reacts with 1,3-cyclohexanedione **77** to produce oxoindolylidene **I** followed by the reaction with 4-hydroxy-2*H*-chromen-2-one **70** to obtain intermediate **II**. In the following, intramolecular acetal generation **III** and removal of water leads to the synthesis of the final product **114**. In path b, initially, *N*-methylisatin **33** involves with 4-hydroxy-2*H*-chromen-2-one **70**, followed by the reaction with 1,3-cyclohexanedione **77** to produce compound **114** with the same path as path a. At all steps of the mechanism, it is suggested that iodine, as a suitable catalyst instead of Lewis acids, activates carbonyl groups [3].

Mirza and colleagues have described an effective and appropriate procedure for the electrocatalytic formation of nano-sized spirooxindole containing 4*H*-pyran scaffolds **116** via a one-pot, three-component and sustainable condensation of cyclic-1,3-diketones **77** [such as pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, cyclohexane-1,3-dione, 1*H*-indene-1,3(2*H*)-dione, cyclopentane-1,3-dione], malononitrile or ethyl cyanoacetate **115**, and isatins **33** in an undivided electrochemical cell in the presence of potassium bromide as the supporting electrolyte in ethanol solvent (Scheme 48).

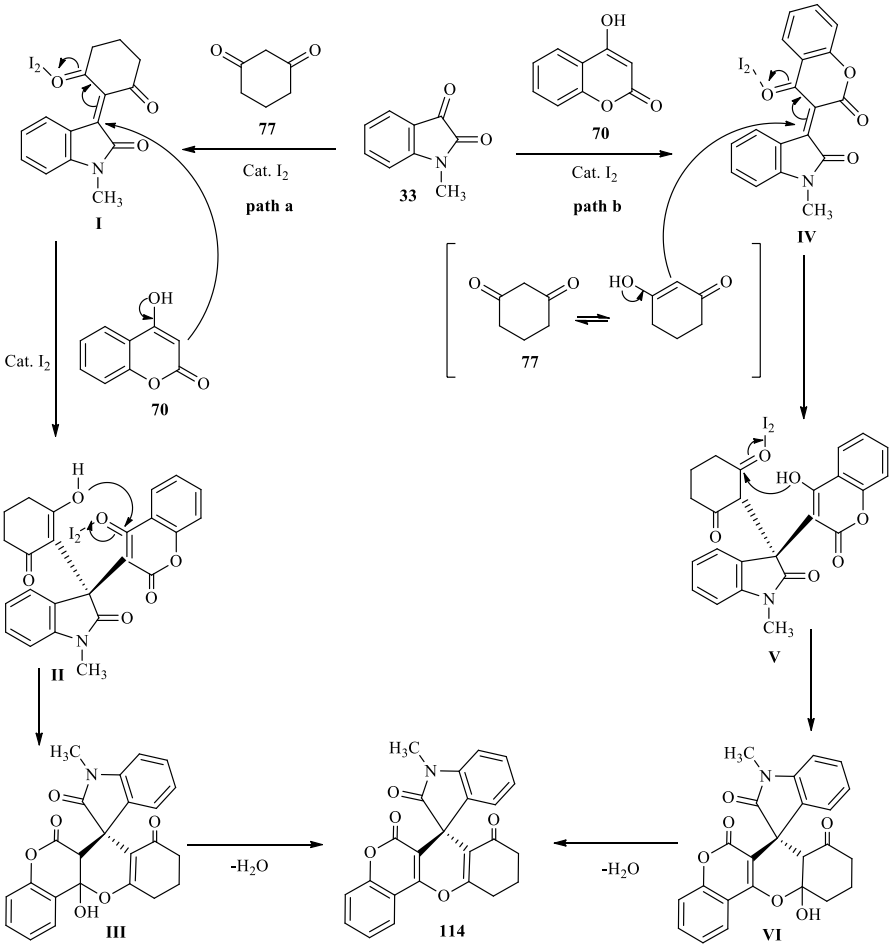



$R^1$ = $CH_3$, Bn, Allyl

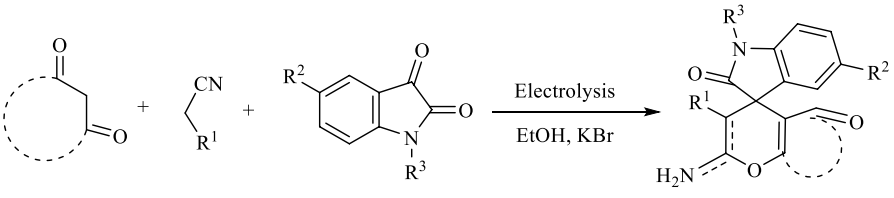
$R^2$ = H, 5-F, 5-Cl, 5-Br, 5-I, 5-$NO_2$, 5-$CH_3$, 5-$OCH_3$, 5-$NO_2$, 6-Cl, 7-Cl

$R^3$ = H, 6-Cl, 7-$OCH_3$

**Scheme 46** Synthesis of spiro[chromeno[4,3-*b*]chromene-7,3′-indoline]trione **114**




**Scheme 47** Plausible mechanistic pathways for the condensation of cyclohexane-1,3-dione with various isatins and 4-hydroxyl coumarins




77 115 33 116

$R^1$ = CN, $CO_2CH_2CH_3$

$R^2$ = H, Cl, Br, $CH_3$

$R^3$ = H, $CH_3$

**Scheme 48** Formation of nano-sized spirooxindole containing 4*H*-pyran derivatives **116** through a green electrosynthesis method

In Mirza's work, electrosynthesis was used as a dependable, cost-effective and highly efficient (76–92%) method for the synthesis of the expected products. The obtained spirooxindole containing 4*H*-pyran and chromene nanoparticles could introduce a valuable way to produce drugs in nano size that are very attractive in the fields of pharmacy and medicine [49].

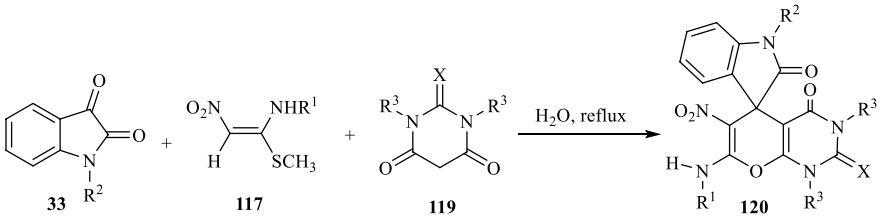
Bayat and coworkers have developed a sustainable, easy, catalyst-free, and one-pot multi-component condensation of *N*-alkyl-1-(methylthio)-2-nitroethenamine **117** (gain from the reaction between different amines **90** and nitroketene dithioacetal **118**) with isatin **33** and barbituric acids **119** for the formation of novel library of spiro[indolinepyranopyrimidine] products **120** (Scheme 49). This procedure proceeds through Knoevenagel condensation, Michael addition, and *O*-cyclization arrangement in water media and reflux conditions without using any catalyst [50].

A proposed mechanistic route for the synthesis of **120** is illustrated in Scheme 49. In the first step, isatin **33** interacts with barbituric acid **119** derivatives via Knoevenagel condensation to produce **121**, which, under Michael addition with *N*-alkyl-1-(methylthio)-2-nitroethenamine **117** (formed from the addition of different amines **90** to nitroketene dithioacetal **118**) yields **122**. Subsequently, intermediate **122** undergoes imine-enamine tautomerization to produce **123** followed by *O*-cyclization to synthesize **120** through the removal of methanethiol (Scheme 50) [50].

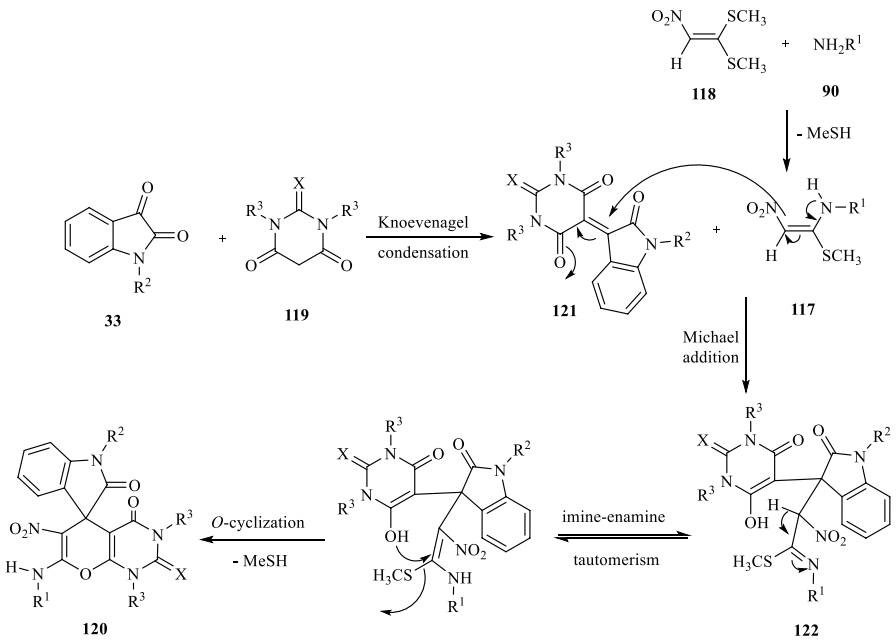
## 2.4 Fusion with More Than One Heteroatom Containing Spiro-Cyclic Compounds

### 2.4.1 Five-Membered Ring

Due to the broad application of organofluorines containing a group of fluorinated substances in pharmaceuticals, agrochemicals, and polymers, Budovská et al. [52] have developed and produced a class of novel biologically active trifluoromethyl including indole scaffolds such as (4-trifluoromethylphenylamino) or 3,5-bis(trifluoromethyl)phenylamino strictures through a spirocyclization procedure. This method simply employs thioureas as precursors, bromine as cyclization




**Scheme 49** Synthesis of novel spiro[indolinepyranopyrimidine]derivatives **120** based on *N*,*S*-ketene acetals



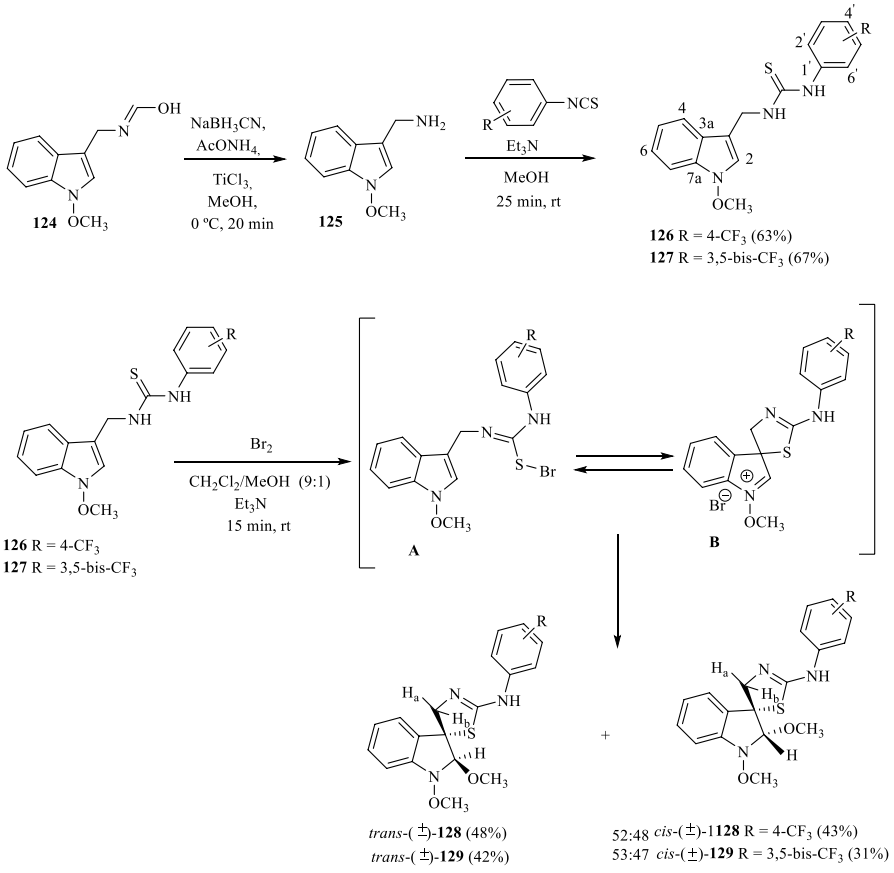

**Scheme 50** Synthetic mechanism for the formation of spiro[indolinepyranopyrimidine] derivatives **120** based on *N*,*S*-ketene acetals

agent, and methanol, 4-(trifluoromethyl)aniline, or 3,5-bis(trifluoromethyl)aniline as nucleophiles.

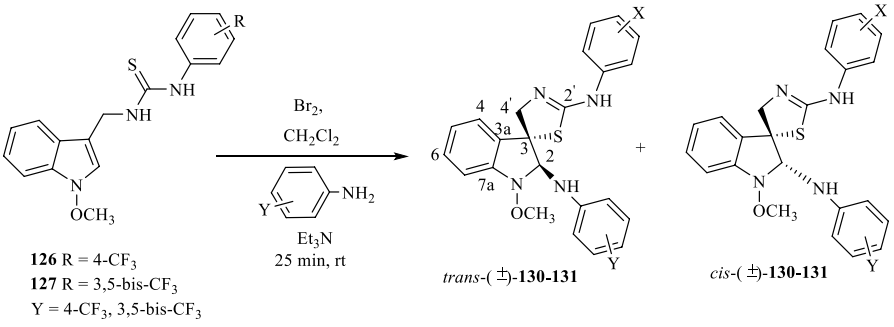
Initially, the thioureas **126** and **127** prepared via the reduction of 1-methoxyindole-3-carboxaldehyde oxime **124** with sodium cyanoborohydride catalyzed by titanium (III) chloride is converted to 1-methoxyindole-3-ylmethylamine **125** based on previously published methodology [51]. The unstable raw amine **125** was immediately engaged in reaction in the next step. The amine **125** reacts with commercially accessible 4-(trifluoromethyl)phenyl isothiocyanate or 3,5-bis(trifluoromethyl)phenyl isothiocyanate in methanol using triethylamine as a base catalyst, leading to the synthesis of *N*-(1-methoxyindol-3-yl)methyl-*N*′-(4-trifluoromethylphenyl) thiourea **126** and *N*-(1-methoxyindol-3-yl)methyl-*N*′-[3,5-bis(trifluoromethyl)phenyl]thiourea **127** (Scheme 51).

Subsequently, Budovská et al. [52] used this procedure to extend the diversity of products, considering the key bromospirocyclizations of thioureas **126** and **127** with methanol, which led to the synthesis of 2′-(4-trifluoromethylphenylamino) and 2′-[3,5-bis(trifluoromethyl)phenylamino] analogues of 1-methoxyspirobrassinol methyl ether **128** and **129** (Scheme 51) [52].

In order to achieve a higher antiproliferative effect, they surveyed the formation of 2,2′-diamino analogs of 1-methoxyspirobrassinol methyl ether containing (4-trifluoromethylphenylamino) or 3,5-bis(trifluoromethyl)phenylamino group **130** and **131**. Target compounds (±)cis and (±)trans **130** and **131** were produced




**Scheme 51** Synthesis of spirooxindoles **128** and **129** via cyclization reactions of thioureas **126** and **127**




**Scheme 52** Cyclization reactions of thioureas **126** and **127** to produce target compounds (±)cis and trans **130** and **131**

via bromospirocyclization procedure of thioureas **126** and **127** using 4-(trifluoromethyl)aniline or 3,5-bis(trifluoromethyl)aniline (Scheme 52) [52].

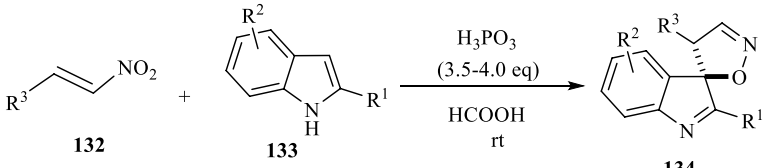
Aksenov et al. [53] have discovered an uncommon reactivity of nitrostyrenes **132** in phosphorous acid that allows these accessible precursors to react as 1,4-dipoles of CCNO-type in excellent diastereoselective [4 + 1] cycloaddition with indoles **133** to produce 4′*H*-spiro[indole-3,5′-isoxazoles] **134** with excellent levels of diastereoselectivity.

During this work, they encountered a class of $P_2O_5$ with low quality and involving considerable some red phosphorus. Polyphosphoric acid generated from this substance had a distinct pink color. Under this condition, the reaction of nitrostyrene **132** and 2-phenylindole **133** proceeded at room temperature and resulted in the production of significant amounts of unexpected spirocyclic compound **134** (Scheme 53). Indeed, they found that the reaction catalyzed by $H_3PO_3$ in formic acid produces **134** as the single product with quite high efficiency.

Based on analysis of experimental data acquired, Aksenov et al. [53] proposed a rational mechanism route (Scheme 54). Nitrostyrene **132** reacts with phosphorous acid to make intermediate **135**, which can undergo Michael addition of indole **133**. The electron-deficient substituents at C2 of indoles reduce nucleophilicity and lead to unsuccessful reactions of some substrates at this stage. In the following, deprotonation at C3 of the indole in **136** is followed by the intramolecular abstraction of a proton from the benzylic position by the phosphite ester of the aci-nitro center in **137**, leading to *N*-phosphoryloxyenamine oxide intermediate **138**. In a second step, deprotonation again led to hydroxylamine **139** as a tautomer product. Subsequently, acid-promoted 5-endo-trigcyclization of **139** happens to produce spiro-2,5-dihydroisoxazole compounds **140**, which, under reaction conditions may produce two tautomer products **134** or 4,5-dihydroisoxazole **141** [53, 54].

## 3 Conclusion

Spiroindole and spirooxindoles are important therapeutic agents with unique structurally skeletons, which have attracted tremendous interest from academic and industrial researchers because of their rigidity and particular 3D stereochemistry. In

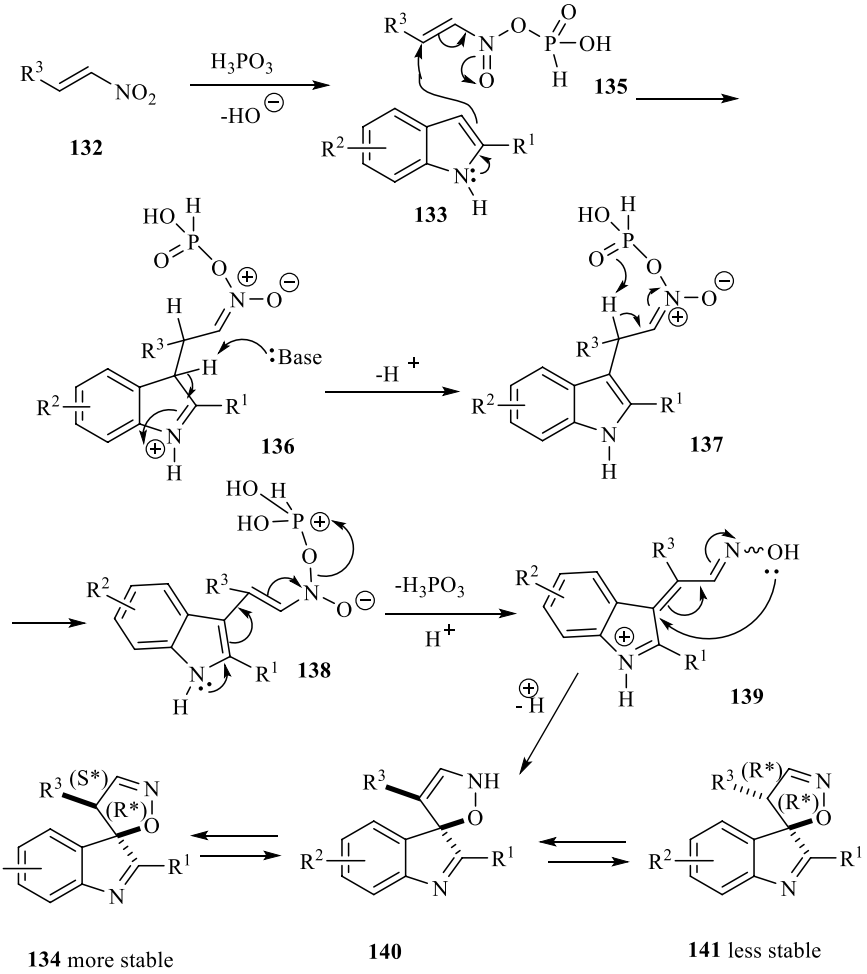



$R^1$ = $CH_3$, $C_6H_5$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$- 2-naphthyl, 2-thienyl

$R^2$ = H, 5-OCH3, 5-*i*$(CH_2)_2CH_3$

**$R^3$** = $C_6H_5$, 4-$FC_6H_4$, 4-$ClC_6H_4$, 4-$OCH_3C_6H_4$, n-$C_6H_{13}$, 2-furyl, *i*$(CH_2)_2CH_3$

**Scheme 53** Synthesis of 4′*H*-spiro[indole-3,5′-isoxazoles] **134** through a highly diastereoselective (4 + 1)-cycloaddition of indoles




**Scheme 54** Mechanistic rationale for transformation of indoles to 4′*H*-spiro[indole-3,5′-isoxazoles] **134** through [4 + 1] cycloaddition

the past 2 years, we witnessed significant progress in presenting synthetic procedures of these important classes of *N*-heterocycles utilizing diverse precursors, and this review has outlined recent advances in the synthesis of spiroindole and spirooxindole scaffolds, focusing on the past 2 years. This review will surely assist chemists in the discovery and introduction of new heterocyclic compounds. Consequently, the design and development of new synthetic methods for the synthesis of heterocyclic frameworks involving spirooxindole are expected to have considerable benefits, producing complex natural compounds and aiding the discovery of novel drug candidates in the future.

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**Declarations**

**Conflict of interest** There are no conflicts of interest to declare.

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