RSC Advances

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 32786

Recent synthetic strategies of spiro-azetidin-2-one, -pyrrolidine, -indol(one) and -pyran derivatives-a review

Mohammed B. Alshammari, [a] Ashraf A. Aly, *[b] Akil Ahmad,[a] Alan B. Brown [c] and Asmaa H. Mohamed[b]

Received 5th September 2023
Accepted 24th October 2023

DOI: 10.1039/d3ra06054c

rsc.li/rsc-advances

Spiro-heterocycles have received special attention in medicinal chemistry because of their promising biological activity. Over the years, many synthetic methodologies have been established for the construction of spirocyclic compounds. Spiro heterocycles such as spiro-azetidin-2-one, -pyrrolidine, -indol(one) and -pyran derivatives have been found to exhibit diversified biological and pharmacological activity in addition to their therapeutic properties. In view of these facts, we decided in this review to present representative synthetic approaches of the aforementioned spiro heterocycles, especially in the past 20 years.

1. Introduction

Spirocyclic compounds are characterized by having two rings sharing the same atom, the quaternary spiro carbon.[1–3] The inherent rigidity of spirocyclic compounds causes a decrease in the conformational entropy penalty when it comes to an interaction between a potential bioactive spiro compound and its putative molecular target.[1,4–7] Spiro compounds are considered spiro heterocyclic if the spiro atom or any atom in either ring are not carbon atoms. Spiro heteroatoms such as nitrogen, oxygen, or sulfur connecting the rings have been commonly observed. Moreover, there are also many classes where one or more heteroatoms appear in one or more of the rings that are joined at a carbon spiro atom. In this review, we focus on four classes of important spiro heterocycles identified as spiro-azetidin-2-one, -pyrrolidine, -indol(one) and -pyran derivatives.

1.1. Spiro-azetidine-2-one derivatives

Azetidine can be considered as a fairly typical cyclic amine. Strain in the four-membered ring is less than that in the three-membered aziridine system; as a result azetidines show few of the exceptional properties associated with aziridines. In spirocyclic β-lactams, the spiro carbon may be at positions C3 and/or C4 (Fig. 1).

The azetidin-2-one ring has given life-saving penicillin and cephalosporin antibiotics.[8] Further exploitation of the β-lactam ring has yielded biologically active new chemical entities exhibiting a variety of activities.[8] Over the years, β-lactams have also emerged as versatile building blocks (β-lactam synthon method) for the synthesis of amino acids, alkaloids and toxoids with potential biological properties. Interestingly, spiro[azetidine-2,3′-indole]-2′,4(1′*H*)-dione derivatives **Ia–e** (Fig. 2) showed antibacterial and antifungal activities.[9] The antibacterial activity of all the compounds against *Staphylococcus aureus* as Gram-positive, *Escherichia coli* and *Pseudomonas aeruginosa* as Gram-negative bacteria showed good potencies which are comparable to control drugs amoxicillin, gentamycin, and streptomycin. With bromo substituents at the 5′ and 7′ positions of indoline, **Ia–e** showed very good activity with MIC values of 6.25–12.5 μg mL^{-1}. Other derivatives have exhibited moderate activity against all three bacterial strains. Similar structure **II** (Fig. 2) have shown anthelmintic potency and were evaluated *versus* standard albendazole. Antibacterial activity was also tested for the synthesized compounds with standard ampicillin against the five different pathogens *Bacillus subtilis*, *Pseudomonas*, *aeruginosa*, *Escherichia coli*, *Proteus mirabilis* and *Staphylococcus aureus*.[10] Spiro-β-lactams **III** and dispiro-β-lactams **IV** (Fig. 2) have exhibited good to excellent antimalarial activities against chloroquine-resistant *Plasmodium falciparum*

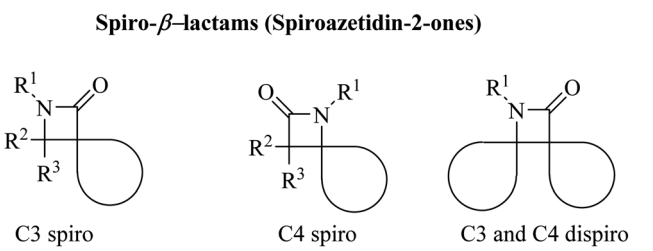


Fig. 1 Different structures of spiroazetidin-2-ones.

[a]*Chemistry Department, College of Sciences and Humanities, Prince Sattam Bin Abdulaziz University, Al-Kharij, Saudi Arabia. E-mail: m.alshammari@psau.edu.sa; aj.ahmad@psau.edu.sa*

[b]*Chemistry Department, Faculty of Science, Minia University, 61519, El-Minia, Egypt. E-mail: ashrafaly63@yahoo.com; ashraf.shehata@mu.edu.eg; asmaa.hamouda@mu.edu.eg*

[c]*Department of Chemistry and Chemical Engineering, Florida Institute of Technology, Melbourne, FL 32901, USA. E-mail: abrown@fit.edu*

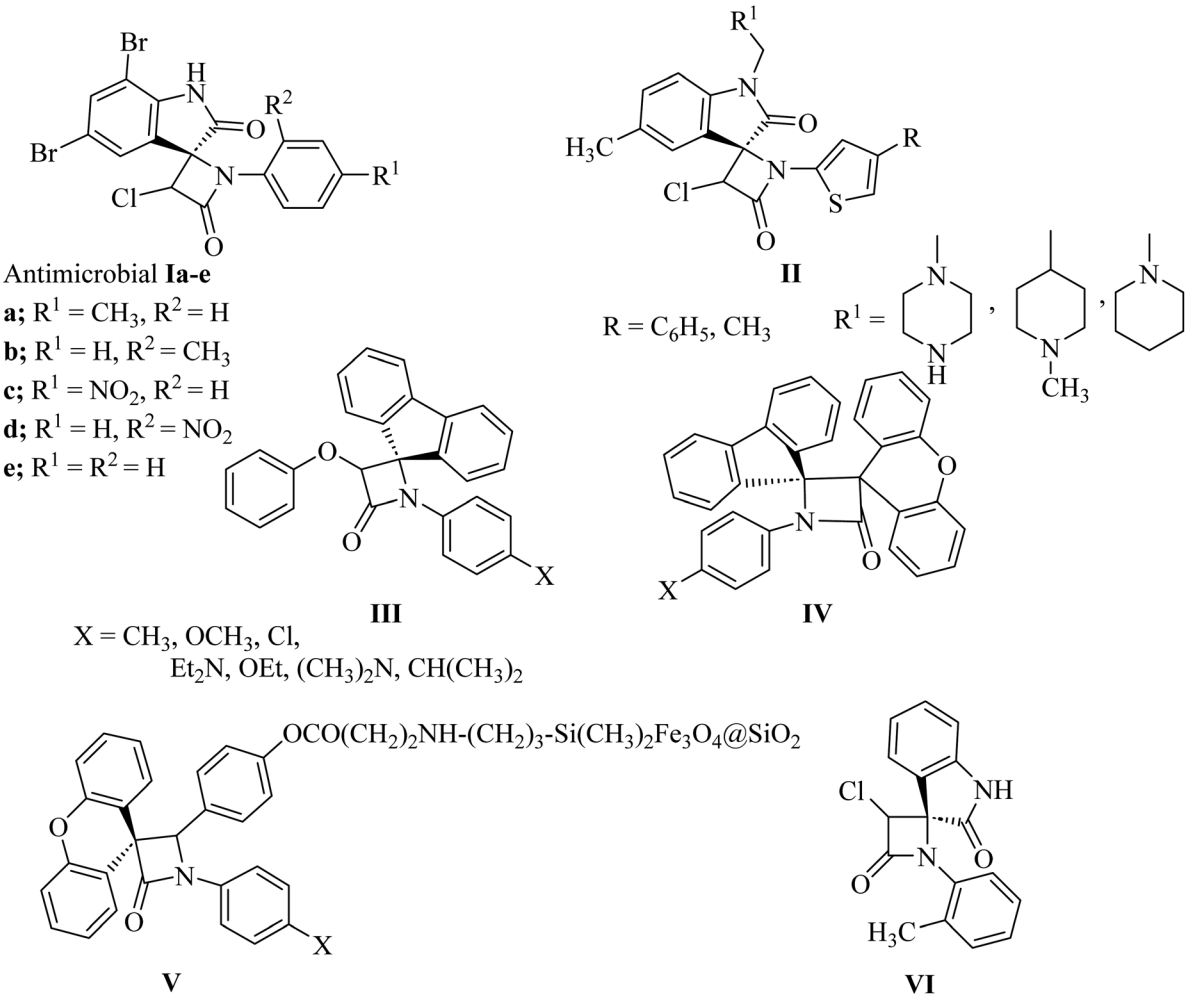


Fig. 2 Biologically active spiro azetidin-2-one derivatives I–VI.

K14 strain with IC_{50} varying from 5 to 32.2 mM.[11] The spirocyclic β-lactam **V** (Fig. 2), supported on superparamagnetic Fe_3O_4@-SiO_2 nano-particles, enhanced the antibacterial activity in comparison with the corresponding spirocyclic β-lactam, which was supposed to be due to the synergic effect of the Fe_3O_4@-SiO_2/β-lactam combination.[12,13] A number of spiro-azetidine-dione derivatives have been tested for anti-breast cancer activity, however, only 3-chloro-1-(*o*-tolyl)spiro[azetidine-2,3′-indoline]-2′,4-dione (**VI**) (Fig. 2) displayed a significant cytotoxicity (IC_{50} = 22.75–25.18 μM) for breast cancer cell lines, which was comparable to the standard control drug doxorubicin.[14]

Spiro-lactams include synthetic biologically active molecules such as antifungal spirooxindole β-lactam **VII**,[12] cholesterol absorption inhibitor (+)-SCH 54016 **VIII**,[15] antiplasmodial spiro penicillate **VIV**,[16–18] and NMDA receptor modulator NYX-2925 **X**[19] (Fig. 3).

1.2. Spiro-pyrrolidine derivatives

Pyrrolidine fragments are widespread in nature; in particular, they are structural units of numerous biologically active compounds[20,21] and natural alkaloid acting as an efficient glucosidase I inhibitors used in the therapy of type II diabetes. Such as azaspirene,[22] and casuarina[23] (Fig. 4). Some synthetic spiropyrrolidines were found to be promising antileukemic agents and anticonvulsants.[24–27] In addition, spiro pyrrolidine-2-ones such as Azaspirene (**XI**) are found in Nature.[28] The marine alkaloid amathaspiramide **XII** (Fig. 4), isolated from Zealand collection of the marine bryozoan *Amathia wilsoni*, shows potential antiviral, antimicrobial and cytotoxic activities.[29]

1.3. Spiro-indol(one) derivatives

In spiroindol(one)s, an indolone ring is substituted with another ring in a spiro arrangement. Spiro indol(one) derivatives occupy a unique place within organic chemical compounds due to their rigidity and 3D-geometrical structure.[30] These structural characteristics give rise to the versatile biological properties shown by analogs wherein C-2 or C-3 of the indolyl ring is spiro-cyclized with many heterocycles (**XIII–XVII**; Fig. 5).[31]

Spirotryprostatin A (**XVIII**) and spirotryprostatin B (**XVIV**) showed microtubule assembly inhibition, whereas pteropodine (**XX**) and isopteropodine (**XXI**) damped the operation of muscarinic serotonin receptors (Fig. 6).[32,33]

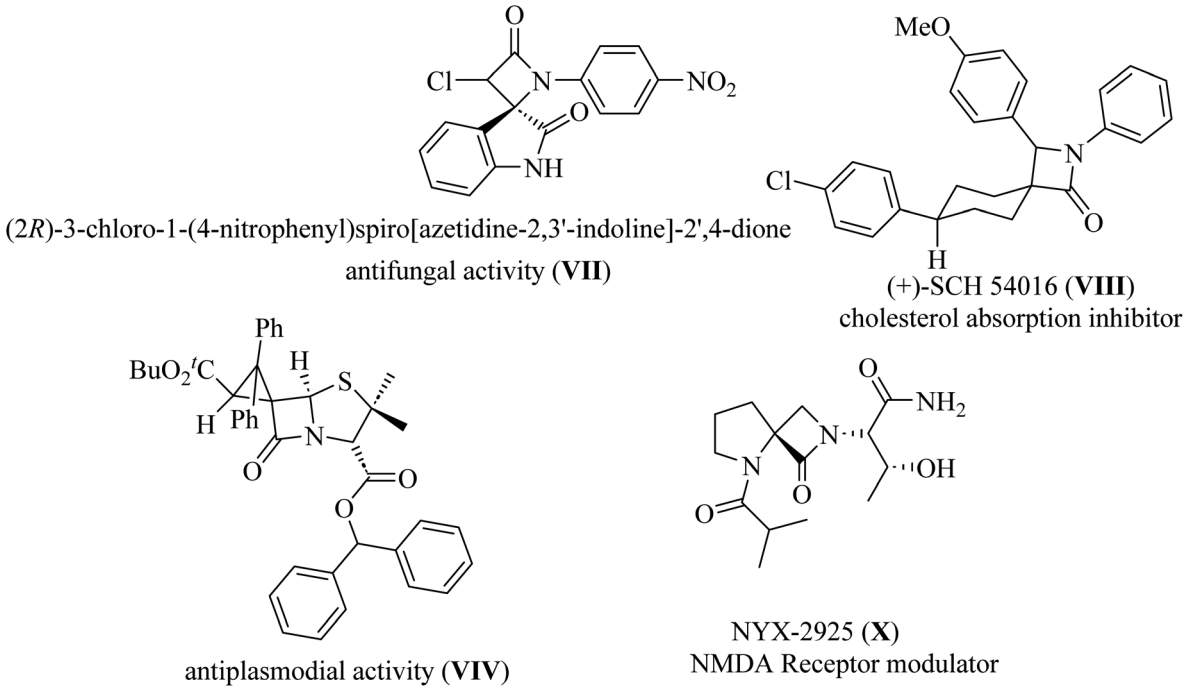


Fig. 3 Representative examples of biologically active spiro cyclic β-lactam VII–X.

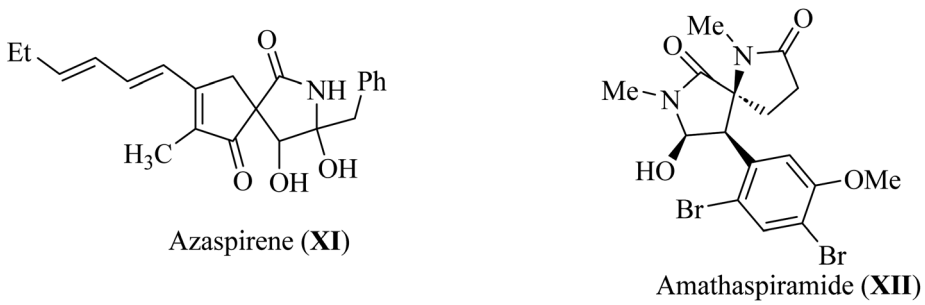


Fig. 4 Alkaloids naturally occurring pyrroldin-2-ones XI–XII.

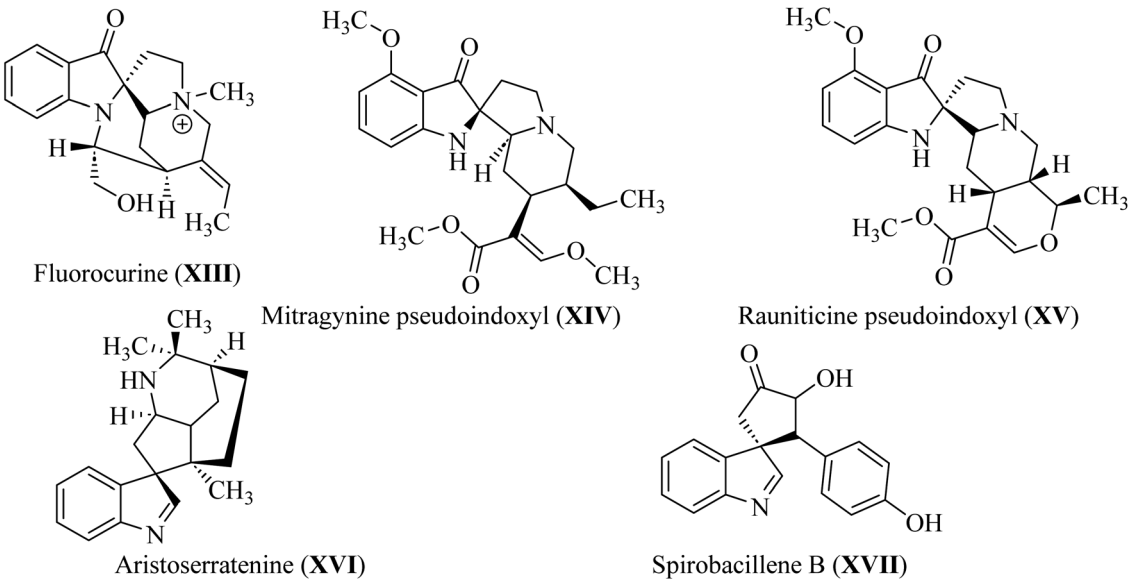


Fig. 5 Natural C-2 and C-3 spiroindol and spiroindol(one) containing compounds XIII–XVII.

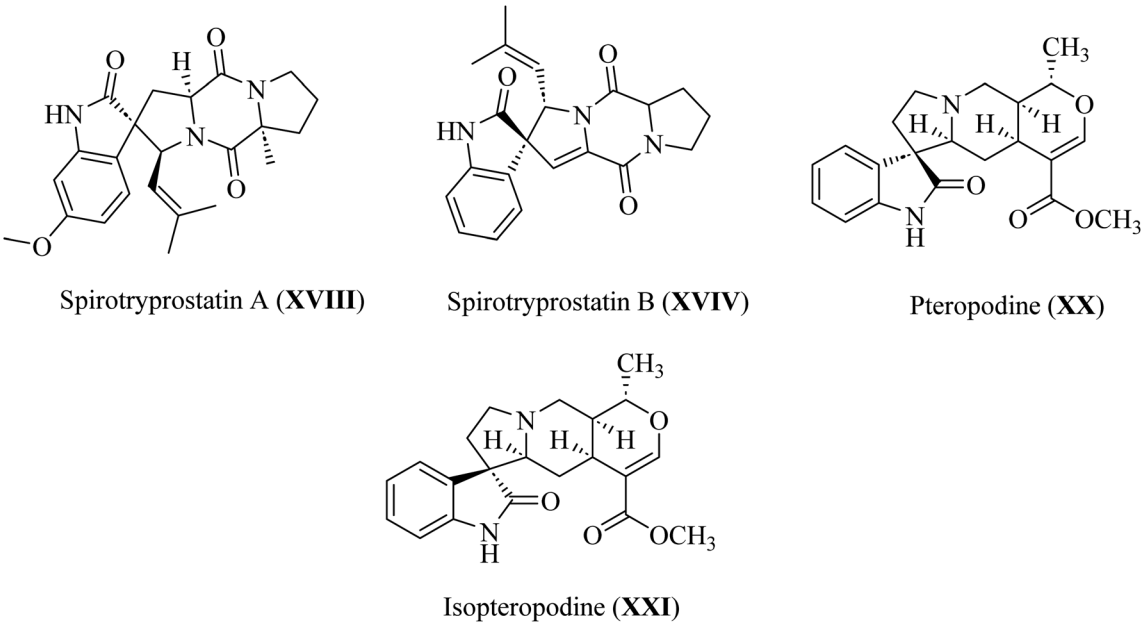


Fig. 6 Selected pharmaceutical structures containing spiro indol(one) scaffolds XVIII–XXI.

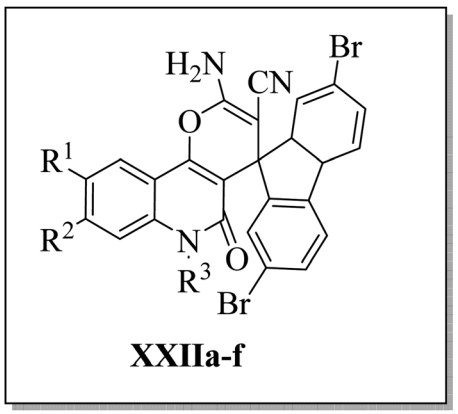
1.4. Spiro-pyran derivatives

Spiropyrans were discovered in the early twentieth century.[34] In the 1920s, Fisher and Hirshbergin observed their photochromic characteristics and reversible reaction.[34] Studies on photochromic compounds that have continued up to the present.[35,36]

Spiropyran and spirooxazine compounds can undergo reversible structural transformations under the influence of external stimuli; this induces a color change, as well as changes in their physical and chemical properties.[37,38] Spiropyrans and spirooxazines are the most investigated photochromic spiro compounds.[39,40] It is reported that spiropyrans and spirooxazines could also respond to other external stimuli such as thermal effects, pH, and stress.[41–43]

Aly *et al.*[44] designed and synthesized three series of 2′-aminospiro[pyrano[3,2-*c*]quinoline]-3′-carbonitrile derivatives **XXIIa–f** (Fig. 7), hypothesizing that small molecules with a spiro scaffold appended to a pyrano[3,2-*c*]quinoline analog could act as ATP-noncompetitive Src kinase inhibitors. **XXIIb**, **XXIIc**, and **XXIId** inhibited Src kinase activity with IC_{50}'s of 4.9, 5.9, and 0.9 μM, respectively. At the same time, they did not affect the MDM2/p53 interaction in HEK293 cells that have been reported to be affected by some spirocyclic compounds. Kinetic analysis for the inhibition of Srctide phosphorylation by **XXIId** revealed a mechanism of ATP-non-competitive inhibition. 1 μM of **XXIId** was enough to diminish Src, Fak, and paxillin phosphorylation in the MCF7 breast cancer cell line.[44]

This work is divided into four distinct classes of spiro heterocycles: spiro-azetidin-2-one, -pyrrolidine, -indol(one) or -pyran derivatives. We deal with building the aforementioned spiro heterocycles, according to the method's scope, selectivity, and reaction mechanism. Previously, a few reviews dealt with the syntheses of these types of spiro heterocycles;[45–47] however,



a: $R^1 = R^2 = R^3 = H$
b: $R^1 = Cl$, $R^2 = R^3 = H$
c: $R^1 = CH_3$, $R^2 = R^3 = H$
d: $R^1 = R^3 = H$, $R^2 = CH_3$
e: $R^1 = Br$, $R^2 = R^3 = H$
f: $R^1 = OCH_3$, $R^2 = R^3 = H$

Fig. 7 2′-Aminospiro[pyrano[3,2-*c*]quinoline]-3′-carbonitrile derivatives XXIIa–f as ATP-non-competitive Src inhibitors that suppress breast cancer cell migration and proliferation.

each review article dealt with only one of the four classes mentioned. We concentrate on the synthesis of these spiro compounds in the past 20 years, and discuss the biological activity of some of these classes.

2. Discussion

2.1. Synthesis of spiro-azetidin-2-one derivatives

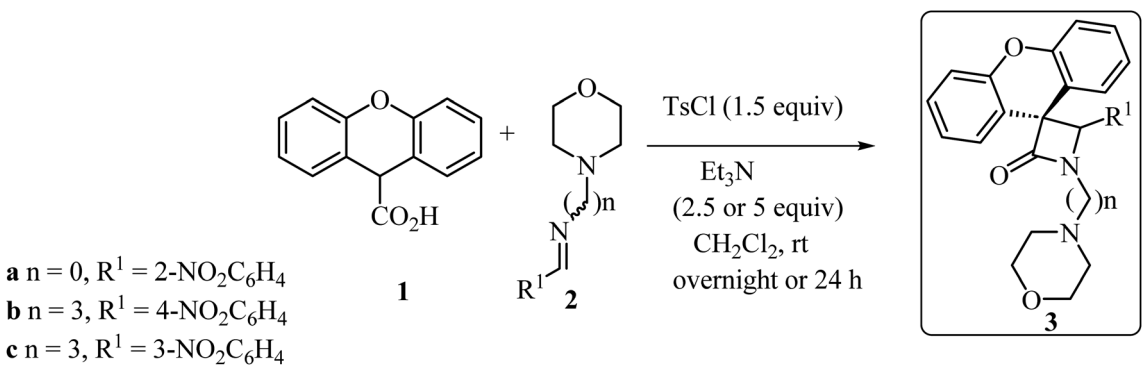
With the discovery and structural elucidation of the antibiotic penicillin, the Staudinger synthesis became of major importance in medicinal chemistry, as it allowed the synthesis of penicillin derivatives in the laboratory. Although several alternative methods have been developed, the Staudinger reaction remains the most common method for the synthesis of β-lactams, including spiro-β-lactams.[48] Heiran and co-workers synthesized C3 spiro-β-lactams **3** bearing a morpholine ring, in moderate to good yields (41–71%) (Scheme 1)[49] *via* cyclocondensation of xanthene-9-carboxylic acid (**1**) and aromatic imines in the presence of tosyl chloride (TsCl) and triethylamine (Et_3N) in dichloromethane (CH_2Cl_2).

In 2019, Novikov and co-workers[50] reported the domino synthesis of dispirocyclic *N*-vinyl β-lactams **7** from diazo-Meldrum's acid (**6**) and 2*H*-azirines **4** or 5-alkoxyisoxazoles **5** through $Rh_2(Piv)_4$-catalyzed 2-azabuta-1,3-diene formation, and subsequent Staudinger ketene-imine cycloaddition (Scheme 2).[50] The reaction was carried out in trifluorotoluene (TFT).

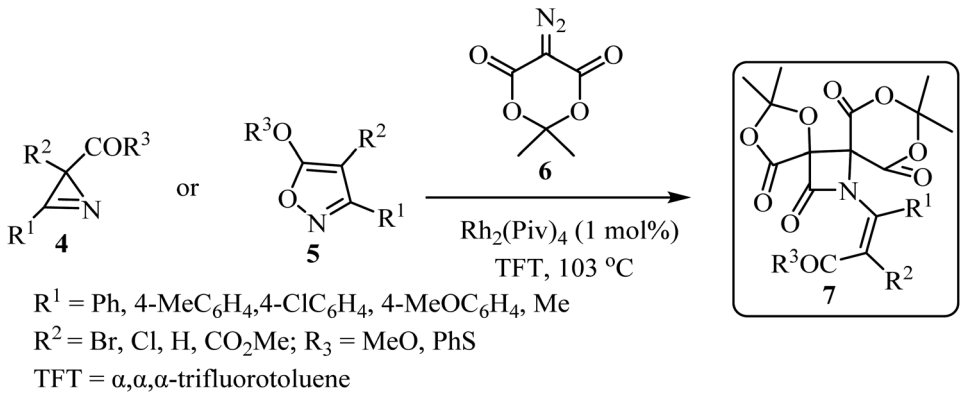
Concerning the reaction mechanism, the rhodium carbenoid **8** obtained from the Meldrum's acid derived diazo-compound **6**, adds to the azirines **4** or isoxazoles **5** forming adducts **9** or **12**, respectively (Scheme 3). Both pathways lead to the same 2-azabuta-1,3-diene **13** product. A parallel Meldrum's acid carbenoid Wolff rearrangement leads to the *in situ* generation of a ketene **11**, which undergoes a [2 + 2] Staudinger cycloaddition with **13** to give β-lactam **7**. By using different substituent groups on both azirine and isoxazole, nine different dispirocyclic *N*-vinyl β-lactams **7** were obtained in low to moderate yields (22–67%).[50]

A convenient procedure reported by Zhao, Deng and co-workers led to the synthesis of twenty-two enantio-enriched spirooxindole-β-lactams **17** bearing two vicinal stereogenic centers.[51] The molecules were obtained in high yields (up to 98%), with good to high diastereo-selectivity and excellent enantioselectivities (Scheme 4). The reaction happens through a homo benzotetramisole (HBTM)-catalyzed Mannich/lactamization cascade reaction of isatin-derived imines **14** with aryl acetic acids **15** (Scheme 4).[51]

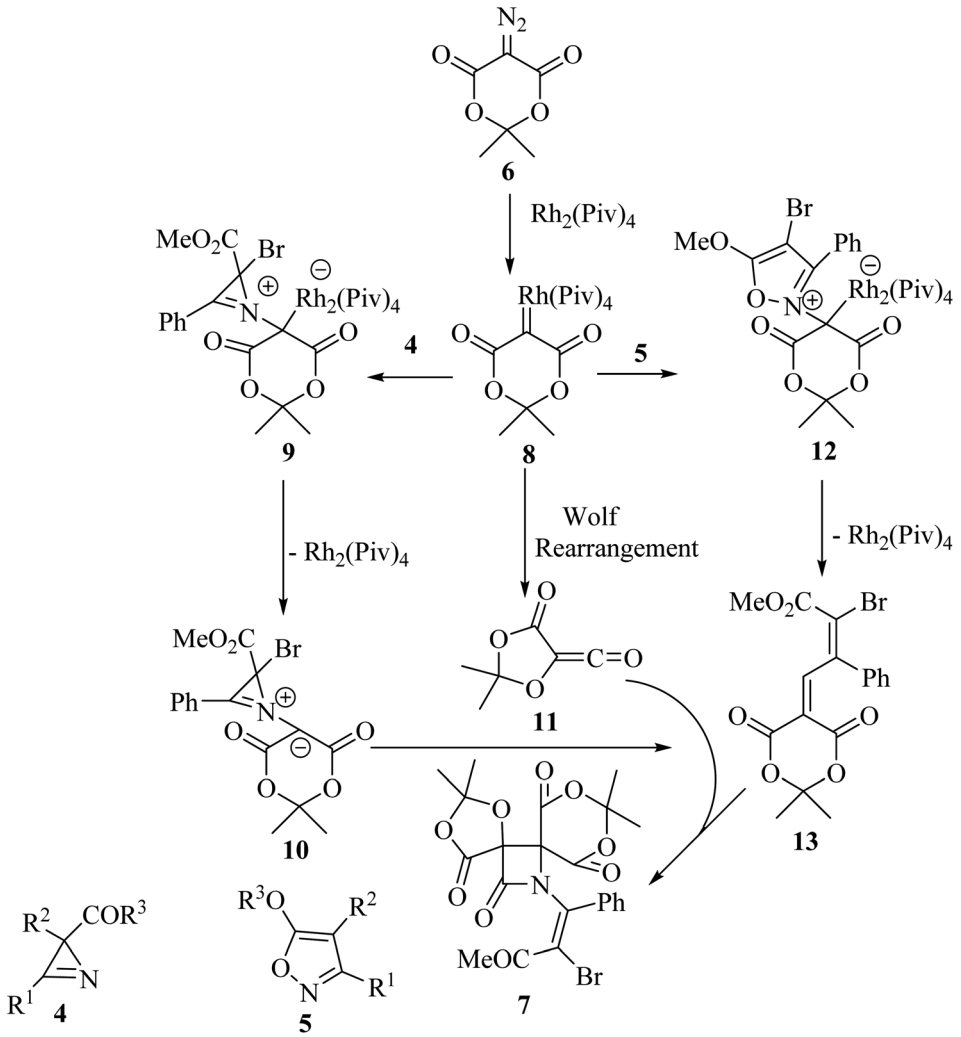
Concerning the proposed reaction mechanism,[51] the first step of the reaction involves a reaction between the aryl acetic acid **15** and pivaloyl chloride which generates a mixed anhydride **18**, responsible for the HBTM acylation which afforded intermediate **19** (Scheme 5). Deprotonation of intermediate **19** occurs on the C1-ammonium enolate to give intermediate **20**,



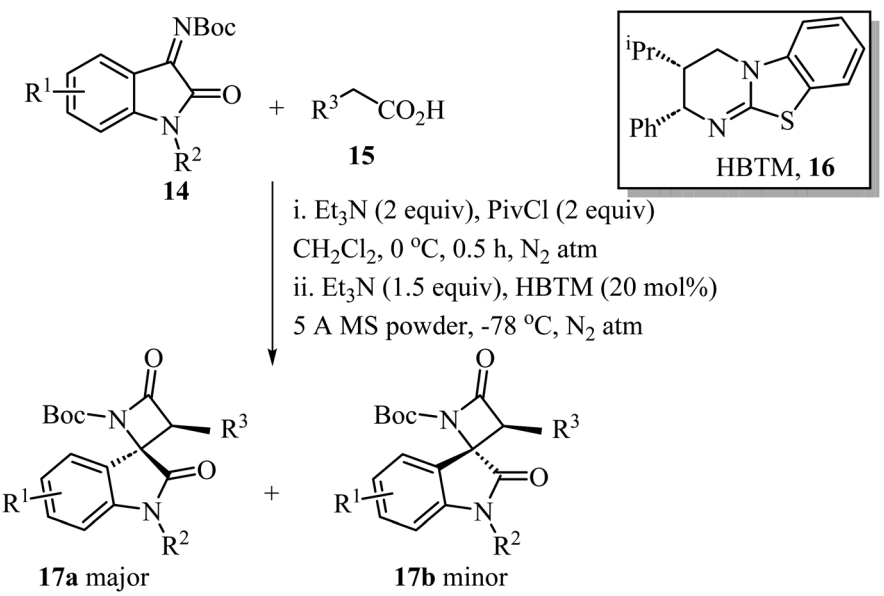
Scheme 1 Staudinger synthesis of spiro-β-lactams **3** containing the xanthene moiety.



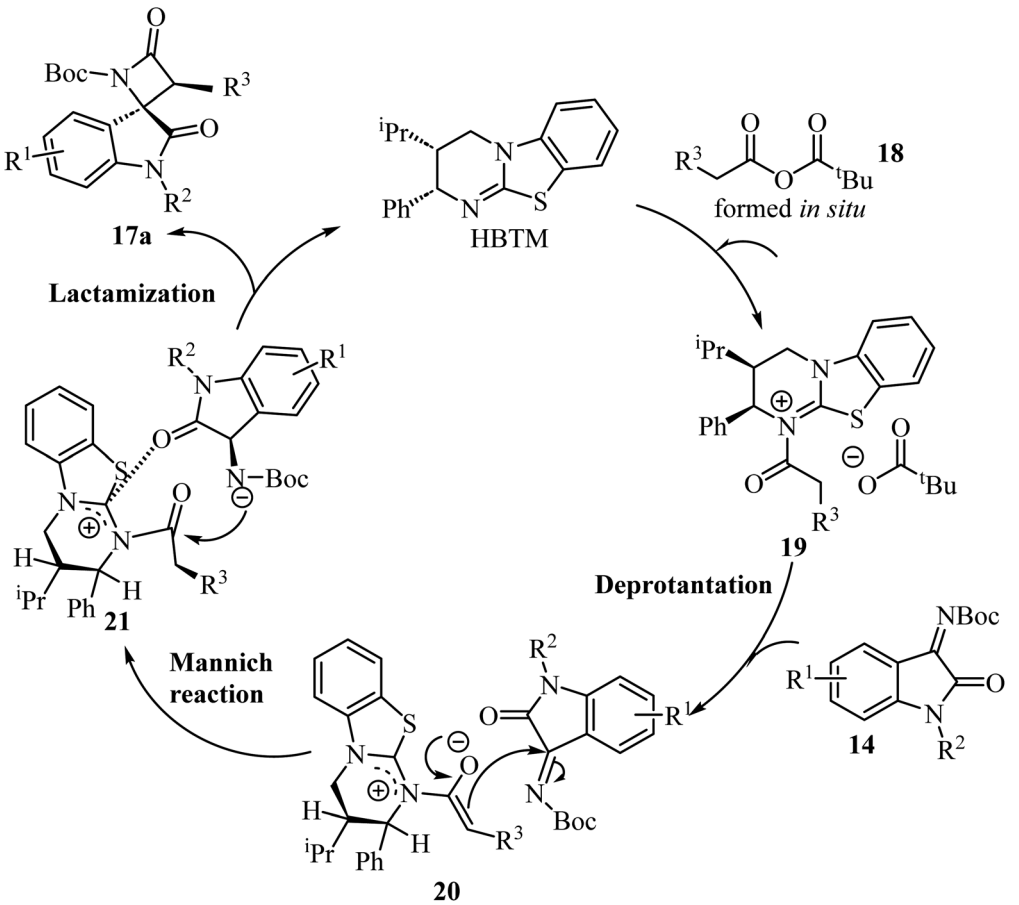
Scheme 2 Synthesis of dispirocyclic *N*-vinyl-β-lactam **7** from diazo Meldrum's acids (**6**) and 2*H*-azirines or 5-alkoxyisooxazoles **5**.



Scheme 3 Mechanism described the formation of compound 7.



Scheme 4 HBTM catalyzed Mannich/lactamization cascade reaction of isatin derived imine 14 with aryl acetic acids 15.

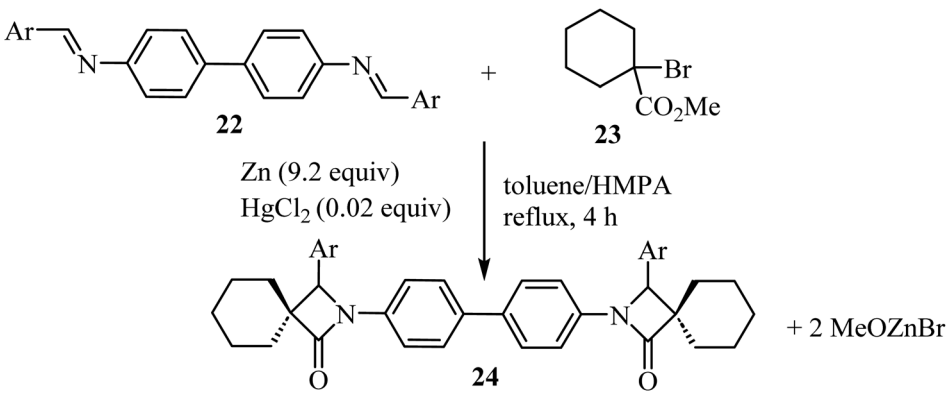


Scheme 5 A plausible mechanism for the formation of **17a**.

which subsequent *Si*-face-attack Mannich reaction afforded intermediate **21**. On the last step of the catalytic cycle, intermediate **21** underwent an intramolecular lactamization providing the desired *cis*-spiro-oxindole β-lactam product **17a** and regenerating the HBTM catalyst (Scheme 5).

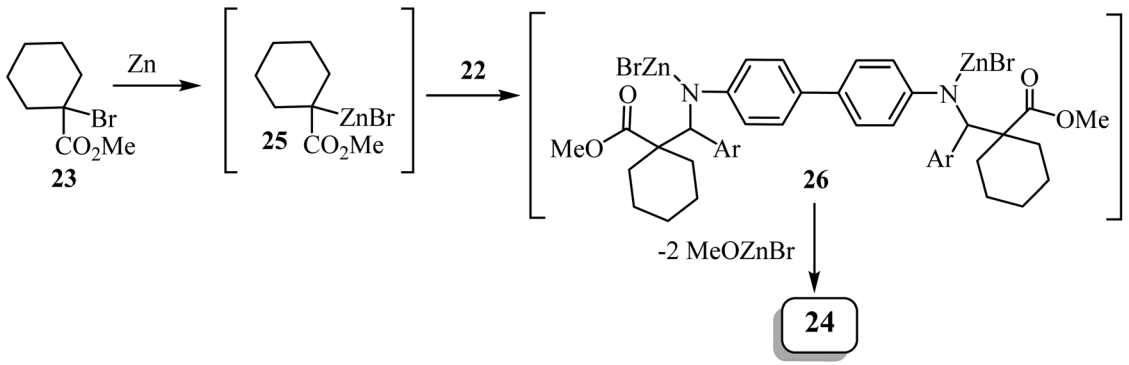
Kirillov *et al.* synthesized a library of eleven bis(spiro-β-lactams) **24**, using the Reformatsky reaction between methyl-1-bromo-cyclohexanecarboxylate (**23**) and *N*,*N*-bis-(arylmethylidene)benzidines **22** as the first step (Scheme 6).[52]

Zinc metal would presumably react with methyl 1-bromocyclohexanecarboxylate to form Reformatsky reagent **25**, which would react with the bis-imine to form the corresponding adduct **26** (Scheme 7). The adduct spontaneously cyclizes and forms the lactam ring, affording the bis-spiro-cyclohexane-β-lactam **24**[52]



Ar = Ph, 4-MeC_6H_4,4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4-$(OCH_2O)C_6H_3$, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-$(NMe_2)C_6H_4$, 3-BrC_6H_4, 4-FC_6H_4; HMPA = Hexamethylphosphoramide

Scheme 6 Zinc mediated reaction between *N*,*N*-bis(arylmethylidene)benzidines **22** and a α-bromoalkancarboxylate **23**.



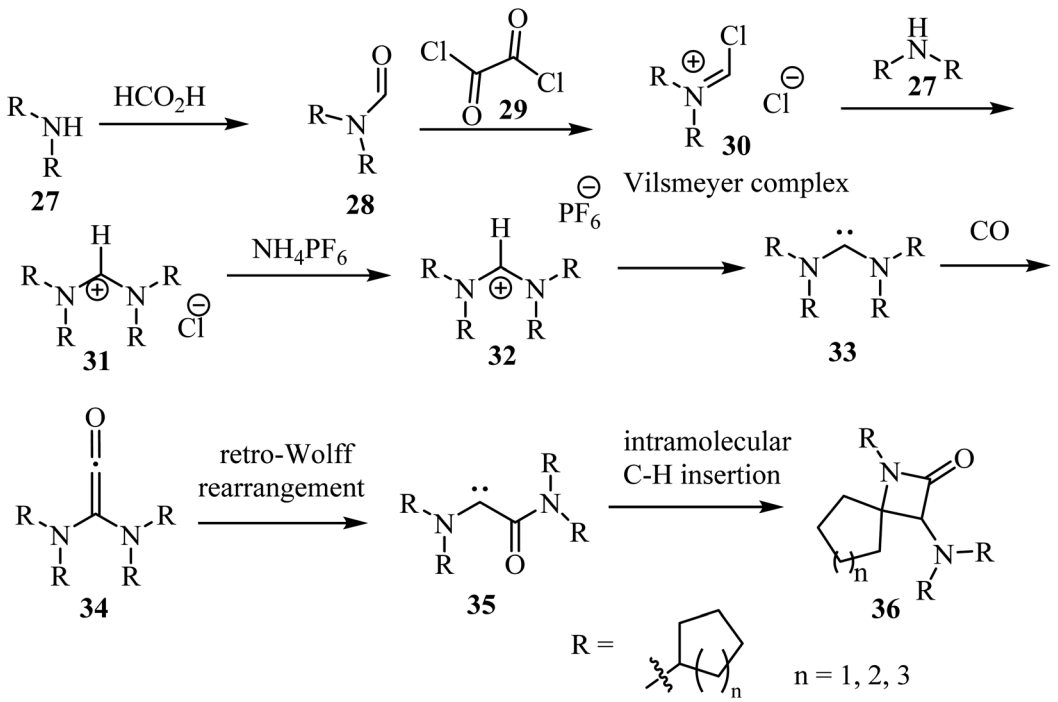
Scheme 7 Rationale for the formation of compound **24**.

with elimination of bromo-zinc methoxide. Bis(spiro-β-lactams) **24** were isolated in good yields (69–84%) (Scheme 7). The reaction was also expanded to synthesize nine spiro-cyclopentane-containing β-lactams by using methyl 1-bromocyclopentanecarboxylate as the starting carboxylate, in yields ranging from 54% to 84%.

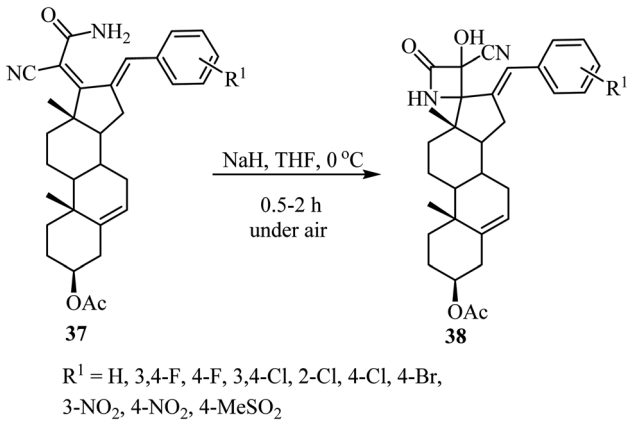
Siemeling *et al.*,[53] reported a metal-free synthesis of racemic spiro-β-lactam derivatives **36** by exploring the reactivity of acyclic diaminocarbenes **33**, containing cycloalkyl substituents and using carbon monoxide as building block (Scheme 8). Compounds **33** were synthesized from secondary amines (*cyclo*-$C_nH_{2n-1})_2NH$ ($n = 5$, 6, 7). The amines **27** were formylated with formic acid into compounds **28**, which reacted with oxalyl (**29**) to give the corresponding Vilsmeier complex **30**. The latter reacted with the secondary amines to afford formamidinium chlorides **31**.[53] Anion exchange was performed with ammonium hexafluorophosphate to afford the corresponding formamidinium hexafluorophosphates **32**, which were converted into carbenes **33** upon treatment with $NaN(SiMe_3)_2$. The synthesis of the spirocyclic β-lactams **36** proceeded *via* carbonylation of the acyclic diaminocarbenes **33** leading to diaminoketenes **34**, which underwent a retro-Wolff rearrangement to give (amido)(amino)carbenes **35** followed by an intramolecular C–H insertion to afford the final products **36** in yields ranging from 65% to 91% (Scheme 8).[53]

The synthesis of steroidal spiro-β-lactams **38**, bearing a cyanohydrin functional group, from steroidal dienamides **37** has been reported (Scheme 9).[54] The spirocyclic products were obtained in low to moderate yields (22–68%) under mild conditions and short reaction time in a one-pot procedure.[54]

The proposed mechanism involves an intramolecular lactamization of steroidal dienamides **37** *via* a selective 4-*endo N*-

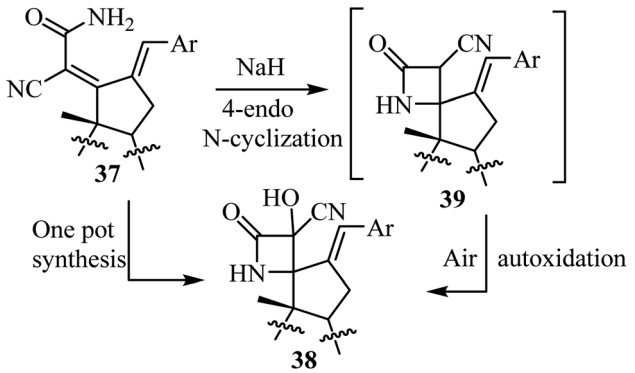


Scheme 8 Carbonylation of acyclic diaminocarbenes leading to spiro β-lactams **36** containing cycloalkyl substituents.



Scheme 9 Steroidal spiro β-lactams **38**; synthesis from dienamides **37** through a cascade 4-endo *N*-cyclization/aerobic oxidation sequence.

cyclization, followed by a base-mediated aerobic oxidation which introduces a hydroxyl group at the α-position of the 2-azetidinone ring, generating the final spirocyclic product **38** [54] (Scheme 10).



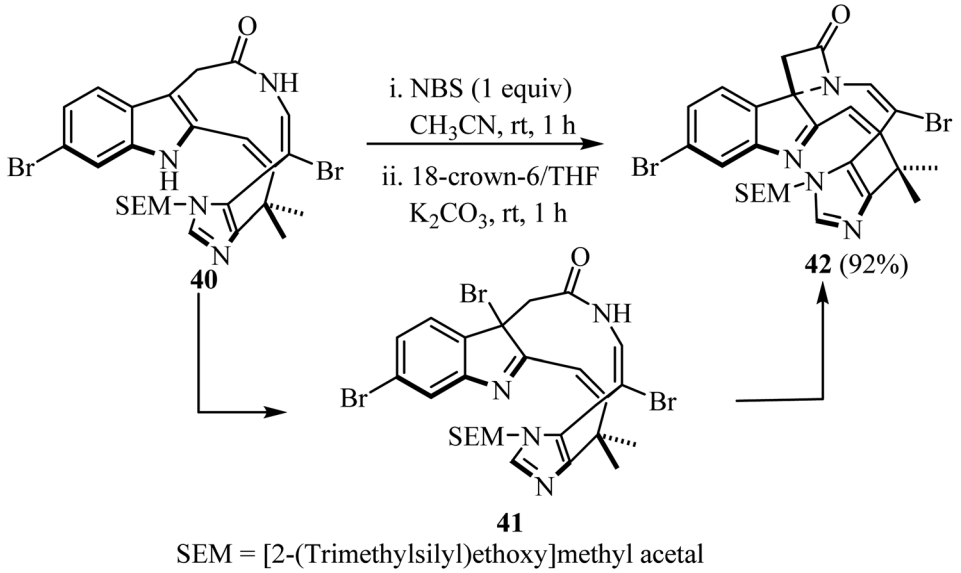
Scheme 10 Plausible mechanism for the formation of compound **38**.

Recently, Nishikawa *et al.*[55] disclosed the synthesis of a spiro-indolenine-β-lactam **42** analogue of alkaloid Chartelline C (Scheme 11). The two-step synthesis comprised the initial formation of a bromoindolenine intermediate **41** *via* a *N*-bromosuccinimide (NBS)-mediated chemoselective bromination of bromoenamide **40** at C3, followed by intramolecular lactamization in the presence of 18-crown-6 and K_2CO_3/CH_3CN. The target spirocyclic indolenine-β-lactam **42** was obtained in 92% yield.[55]

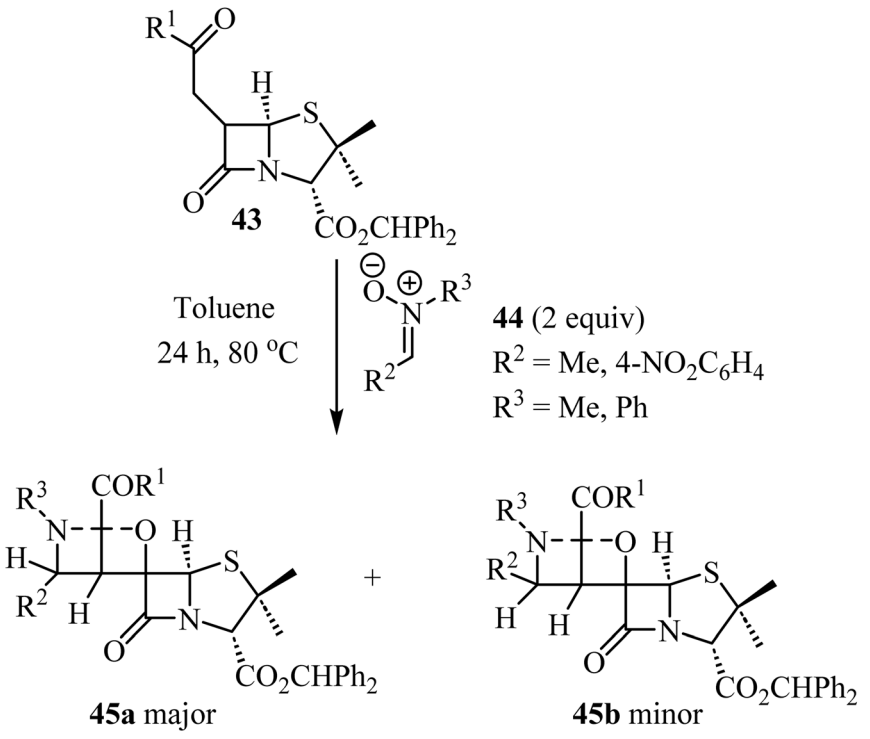
The use of *C*-aryl-*N*-substituted nitrones **44** as dipoles in 1,3-dipolar cycloadditions with 6-alkylidene-penicillanates **43** to synthesize spiro-β-lactams was explored by Pinho e Melo *et al.* (Scheme 12).[56] The generation of three consecutive stereogenic centers proved to be regio- and stereoselective and afforded chiral spiroisoxazolidine-penicillanates **45** in moderate to good overall yields, using mild conditions.[56] The major products **45a** were obtained through an *endo* 1,3-dipolar cycloaddition with addition of the nitrone to the α-side of the β-lactam and were obtained efficiently (26–80% yield); the stereoisomeric *exo*-cycloadducts **45b** were isolated as minor products (7–27% yield). Two cases were stereospecific, only affording the major product **45a.**

Recently Luo *et al.* reported a phosphine-mediated reductive cyclopropanation reaction of α-keto esters **46** with α-methylene-β-lactams **47** (Scheme 13).[57] That metal-free protocol provided the efficient *syn* synthesis of highly functionalized spirocyclopropyl β-lactams **48** through a mechanism involving the initial oxophilic addition of the phosphine to α-ketoester to generate Kukhtin-Ramirez intermediates (*e.g.* oxyphosphonium enolate **49b**), which can behave as a carbene surrogate. Subsequent Michael addition of these intermediates to the electron deficient β-lactam exocyclic double bond followed by a 3-*exo-tet* cyclization furnishes spirocyclic lactams as diastereoisomeric mixtures.[57]

The synthesis of a library of spiropyrrolo-quinoline β-lactams **54** was described, using four-component Ugi-adducts **53** as



Scheme 11 Chartelline-core spiroindolenine-β-lactam **42** synthesis *via* bromide mediated spirolactamization of a bromoenamide.

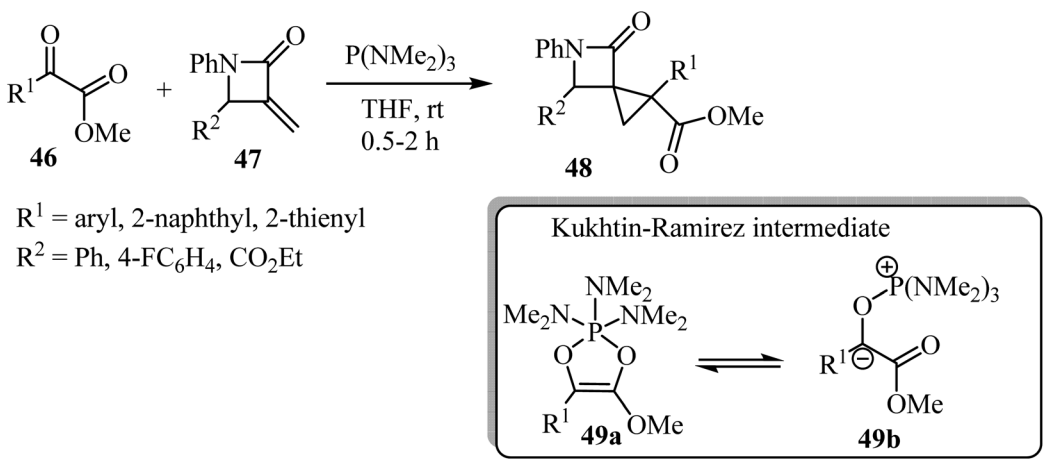


Scheme 12 1,3-Dipolar cycloaddition between 6-alkylidene penicillanates **43** and nitrones **44**.

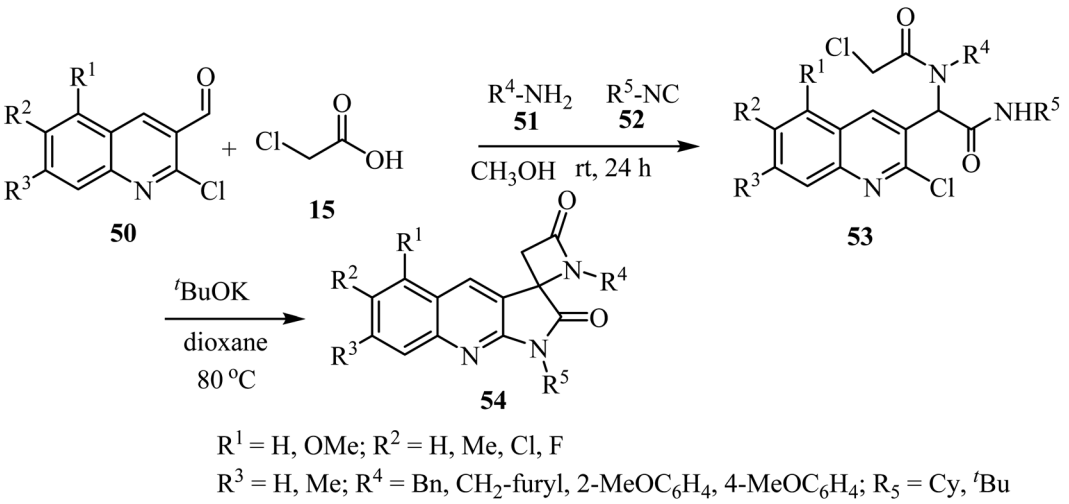
precursors (Scheme 14).[58] These spirocyclic-bis-β-lactams **54** were obtained as racemic mixtures in moderate to high yields (54–88%). The Ugi-adducts **53** were synthesized through a four-component reaction of 2-chloro-3-formylquinolines **50**, 2-chloroacetic acid (**15**), amines **51**, and isocyanides **52** (Scheme 14). The proposed spirocyclization mechanism depends on two sequential cyclizations of the Ugi-adduct, under basic conditions. The first cyclization involves the γ-lactam ring formation *via* intramolecular aromatic nucleophilic substitution, followed by formation of the β-lactam ring through a nucleophilic acyl substitution.[58]

2.2. Synthesis of spiro pyrrolidine derivatives

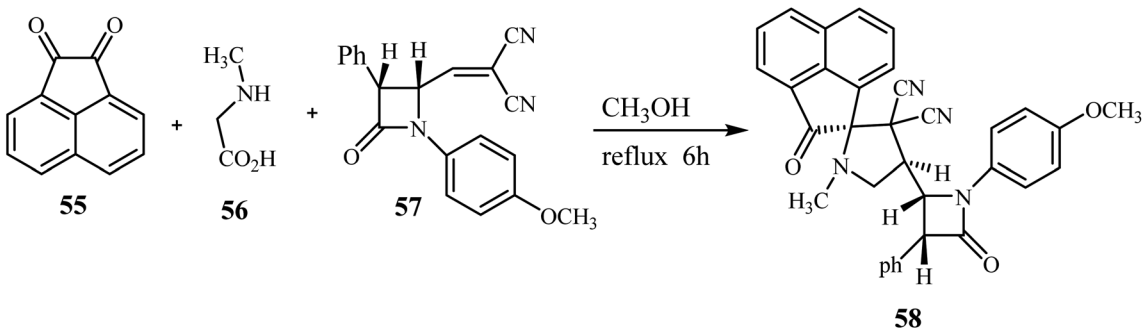
The azomethine ylide generated *in situ* by the condensation of acenaphthenequinone (**55**) with sarcosine (**56**) underwent smooth cycloaddition reaction with **57** regio- and stereoselectively in refluxing CH_3OH for 6 h affording exclusively the single diastereomer **58** in excellent yield (Scheme 15).[59]



Scheme 13 $P(NMe_2)_3$-mediated cyclopropanation of α-methylene-β-lactams **48**.



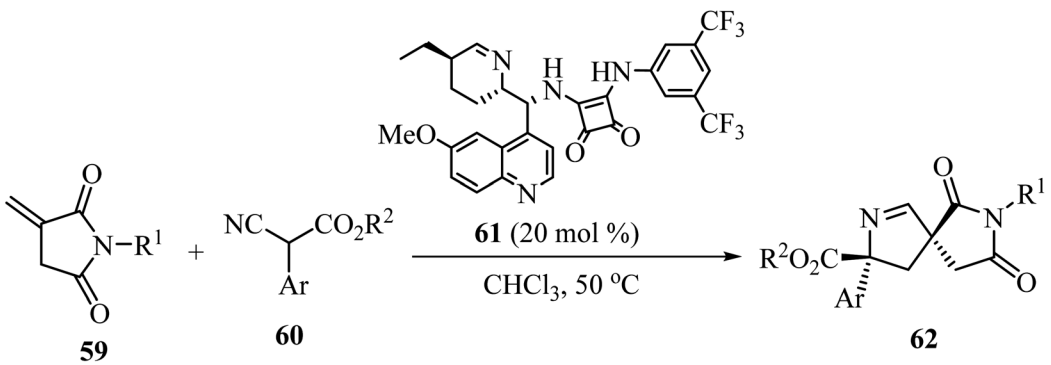
Scheme 14 Synthesis of spirocyclic-bis-β-lactams-lactams **54** from four-component Ugi-adducts precursors.



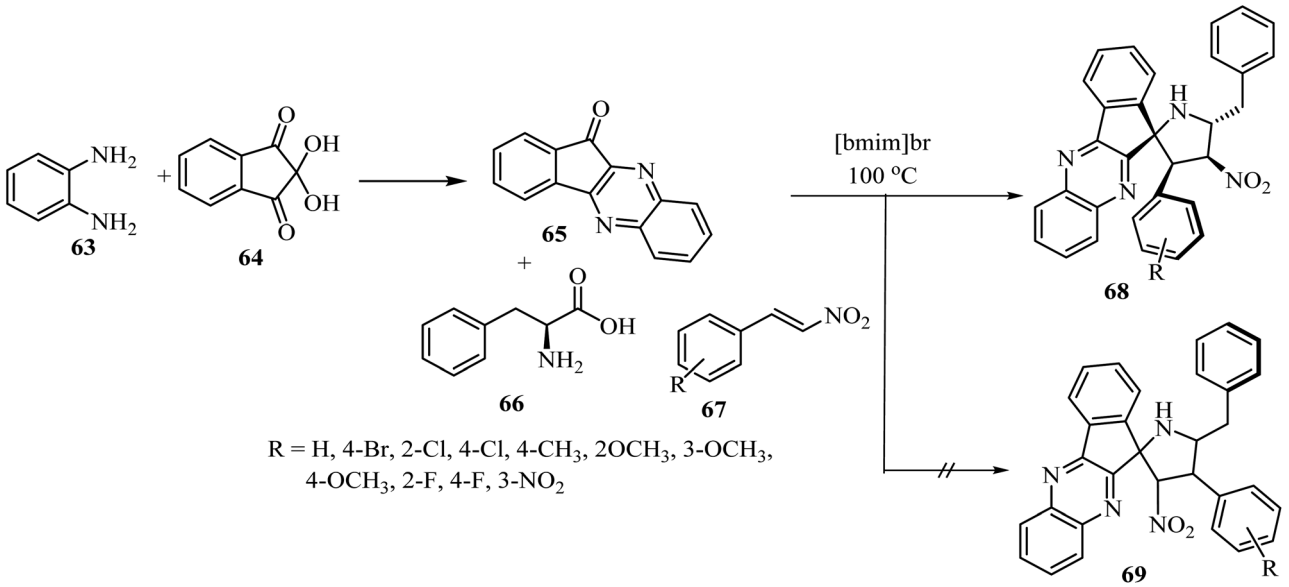
Scheme 15 Synthesis of β-lactam grafted spiro acenaphthenopyrrolidines **58**.

In 2019, Zhao and coworkers described the asymmetric synthesis of spiro pyrrolines **62** from isocyanoacetates **60** and nitaconimides **59** as Michael acceptors (Scheme 16).[60] The process was catalyzed by squaramide **61** derived from dihydroquinine and provided the corresponding spirocyclic compounds **62** with good diastereo- and enantio-selectivity.[60]

The spiro pyrrolidine tethered indenoquinoxaline heterocyclic hybrids **68** were synthesized by heating of β-nitrostyrene (**67**), *o*-phenylenediamine (**63**), ninhydrin (**64**), and L-phenylalanine (**66**) with stirring in [bmim]Br medium for 1 h at 100 °C (Scheme 17).[61] Interestingly, the reaction was completely regioselective: the expected regioisomer **69** was not formed



Scheme 16 Formal [3 + 2] cycloaddition reaction of *N*-itaconimides **59** and isocyanoacetates **60** catalyzed by a chiral squaramide.

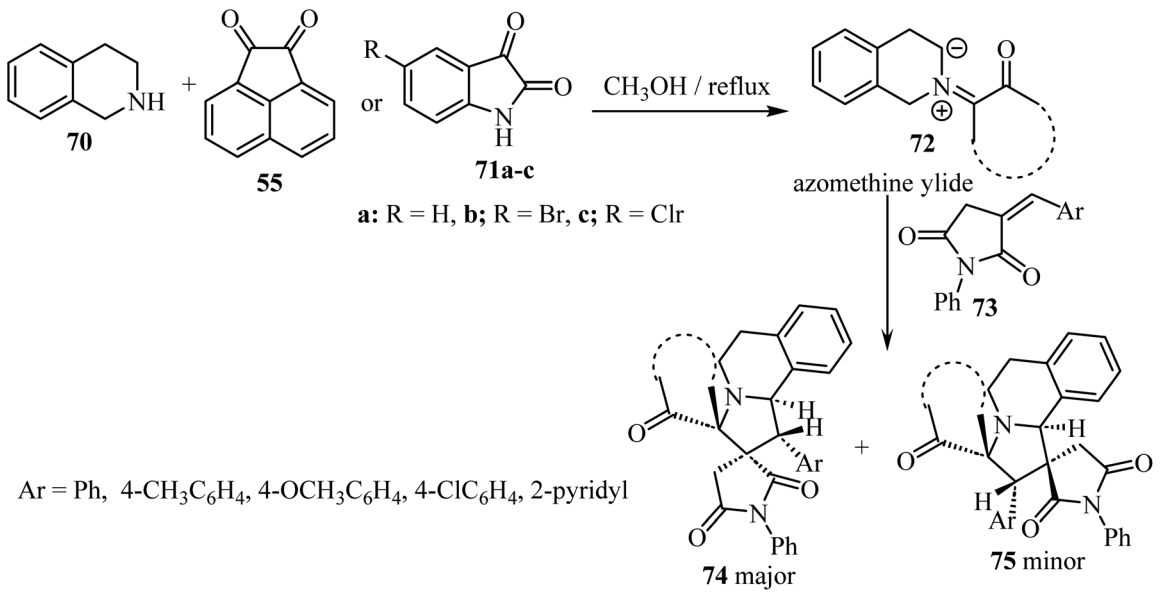


Scheme 17 Synthesis of spiro-pyrrolidine tethered indenoqunoloxaline **68**.

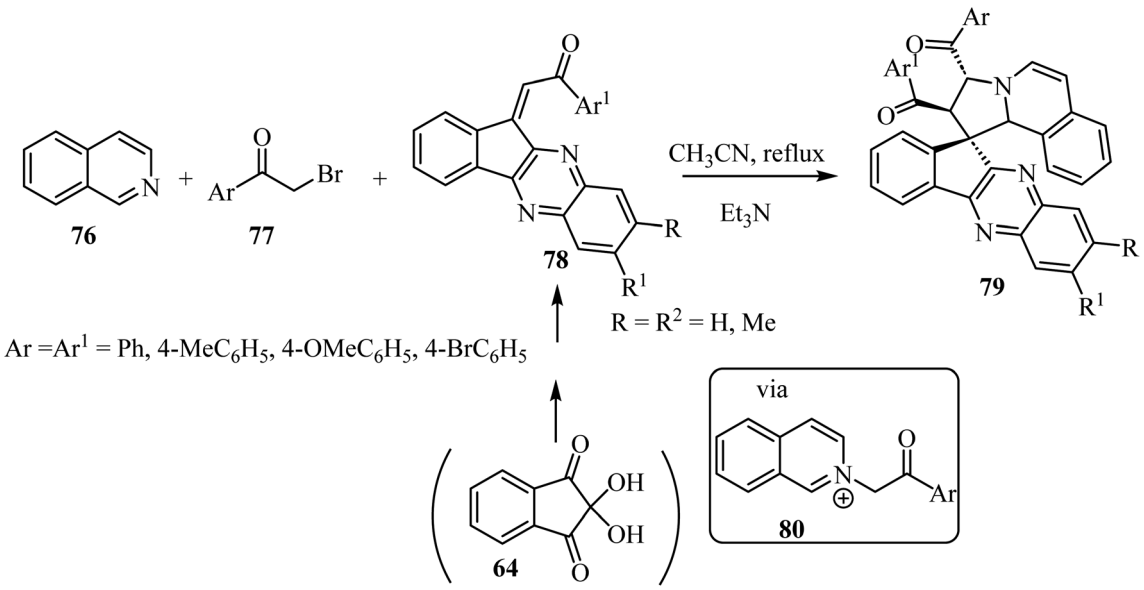
(Scheme 17).[61] *In vitro* activity of these spiroheterocyclic hybrids against *Mycobacterium tuberculosis* H37Rv, using MABA assay, revealed that the compound with nitro group on the phenyl ring is the most active candidate (1.56 μg mL^{-1}) of the series and has an activity similar to that of the standard drug Ethambutol.[61]

A diastereoselective approach[62] to dispiropyrrolo[2,1-*a*]isoquinoline fused pyrrolidine-2,5-diones bearing two adjacent spirocarbons comprised a three-component 1,3-dipolar cycloaddition between cyclic diketones (isatin derivatives **71** or acenaphthenequinone, **55**) with tetrahydroisoquinoline **70**, to give *N*-ylides **72**; these reacted with *α*-alkylidene succinimides **73** as dipolarophiles (Scheme 18). Among the various screened solvents (such as CH_3OH, EtOH, CH_3CN, and toluene), methanol (CH_3OH) was selected as the most effective solvent and an unprecedented regioselectivity was observed in this cycloaddition reaction resulting in two products **74**/**75**.[62]

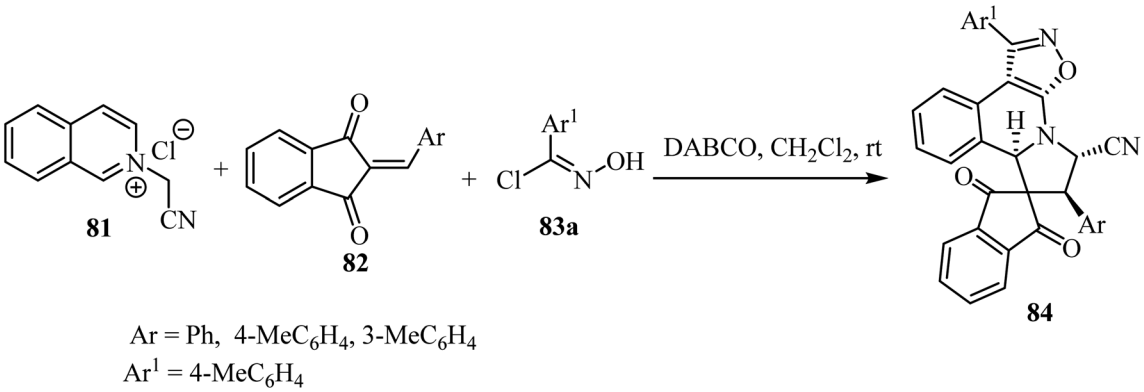
The construction of spiropyrrolo[2,1-*a*]isoquinolines containing the indenoquinoxaline frameworks **79** was achieved through the 1,3-dipolar cycloaddition reaction of isoquinolinium ylides, generated *in situ* by the reaction of isoquinoline (**76**) and phenacylbromides **77** in the presence of Et_3N, with 1-aryl-2-(11*H*-indeno[1,2-*b*]quinoxalin-11-ylidene) ethanoates **78** (Scheme 19).[63] The complex spiroheterocyclic products **79** contain four contiguous chiral centers.



Scheme 18 Synthesis of dispiropyrrolo[2,1-*a*]isoquinoline fused pyrrolidine-2,5-diones **74** and **75**.



Scheme 19 Spiropyrrolo[2,1-*a*]isoquinolines containing the indenoquinoxaline **79**.



Scheme 20 Synthesis of spiro[indene-2,8′-isoxazolo[5,4-*c*]pyrrolo[2,1-*a*]isoquinolines **84**.

Importantly, the cycloaddition reaction affords only one regioisomer with high diastereoselectivity.[64–66]

The one-pot cascade double [3 + 2] cycloaddition reaction of *N*-cyanomethyl isoquinolinium chloride **83** with 2-arylidene-1,3-indandiones **82** and (*E*)-*N*-hydroxybenzimidoyl chlorides **83**, was carried out to access spiro[indene-2,8′-isoxazolo[5,4-*c*]pyrrolo[2,1-*a*]isoquinolines **84** in good yields with high diastereoselectivity (Scheme 20).[67] The transformations were best performed in the presence of DABCO (1,4-diazabicyclo[2.2.2] octane) in CH_2Cl_2 as a solvent.[67]

2.3. Synthesis of spiroindol(one) derivatives

Spiroindol(ones), which contain a spirocycle fused at the C2 or C3 of the oxindole moiety, are a known subset of indoles and form the core building blocks of highly functionalized organic structures. The procedures to obtain various spiro indolines and spiro indoles reported in the literature[68] 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. 8.[68]

The electron-rich property of indoles leads to easy oxidation using many reagents. Since catalysis methods in the presence of secure oxidants (H_2O_2, Oxone, O_2) is highly favorable, Tong and co-workers[69] have introduced three unique, efficient halide catalyzed oxidation processes of tetrahydro-*β*-carbolines (THCs) indoles applying oxone as the terminal oxidant, which leads to the formation of oxindoles **86**, **88** and **90** (Scheme 21).[69]

Spirooxindolopyrrolidine hybrid heterocycles **92**, containing *β*-lactam subunits, were prepared as single diastereoisomers *via* 1,3-dipolar cycloaddition of Baylis–Hillman adducts **91** with azomethine ylides derived from isatins **71** and *α*-amino acid **66** under heating at 100 °C in [bmim]Br (Scheme 22).[70] The *in vitro* antimycobacterium tubercular activity of hybrids **92** was assessed against *Mycobacterium tuberculosis* H37Rv. Members of the series with no substitution or chloro-substitution on the oxindole ring showed the most potent activity with a MIC 0.78

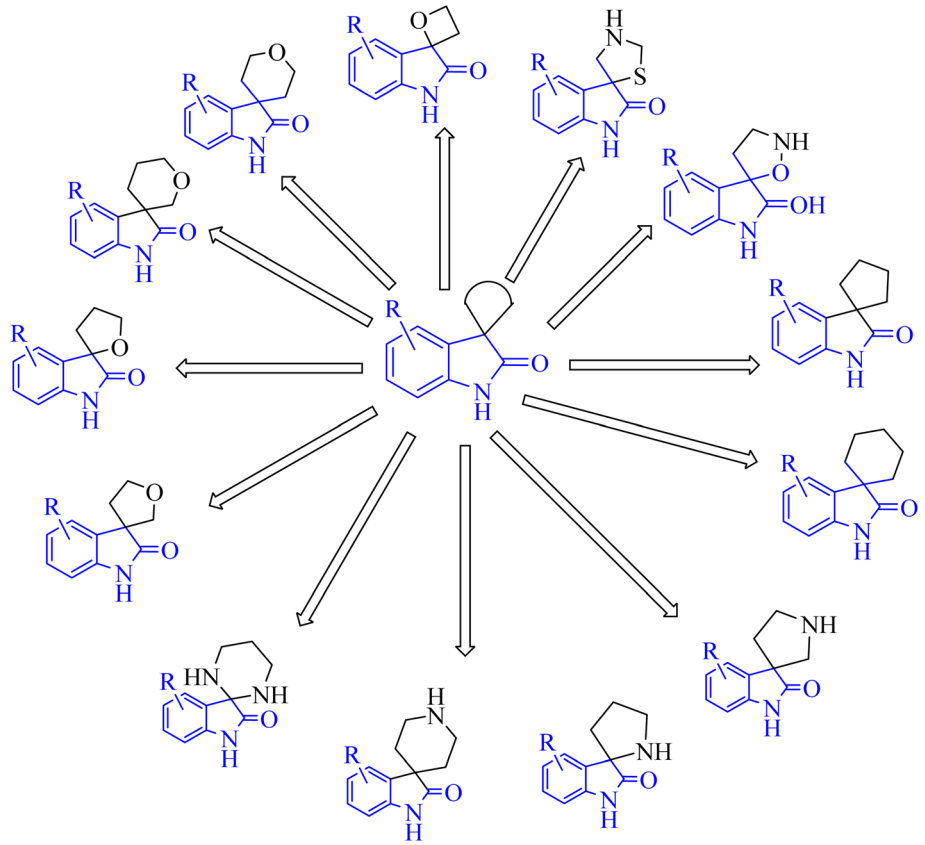
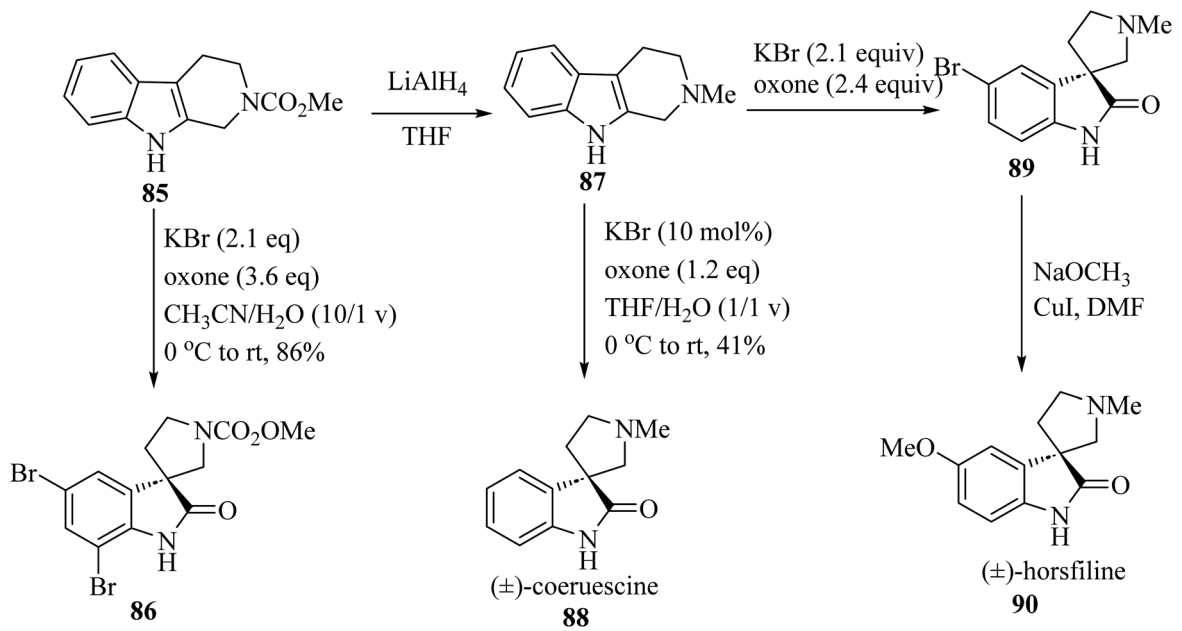


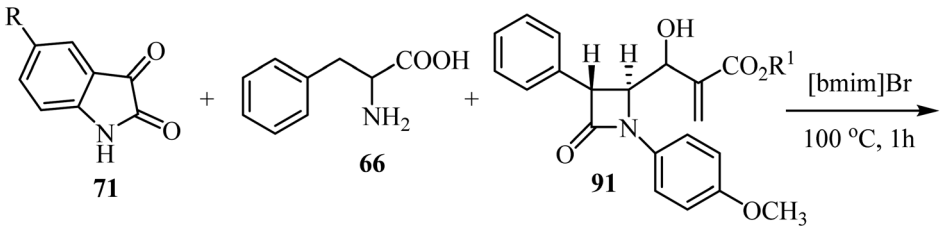
Fig. 8 Diagram showed different spiro indol(one) derivatives.

μg mL^{-1} and 1.56 μg mL^{-1}, respectively, which were two-fold and equal activity than the standard drug, Ethambutol (MIC = 1.56 μg mL^{-1}).[70]

Shao and colleagues introduced various catalytic asymmetric synthetic protocols for the formation of tricyclic and tetracyclic 3,3′-pyrrolidonyl spirooxindoles **96** and **97** (Scheme 23).[71] This

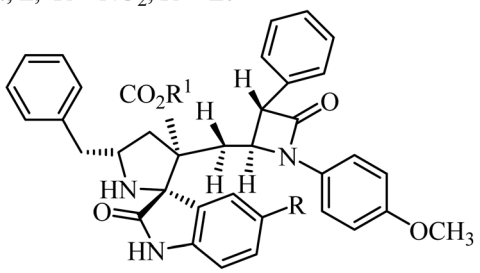


Scheme 21 Oxidative rearrangement of tetrahydro-β-carbolines for the formation of spirooxindole natural compounds **86**, **88** and **90**.



71 66 91

a, R = H, R^1= CH_3, **b**, R = Br, R^1= CH_3; **c**, R = Cl, R^1= CH_3, **d**, R = NO_2, R^1= CH_3
e, R = H, R^1= Et; **f**, R = Cl, R^1= Et; **g,** R = OCF_3, R^1= Et; **h**, R = NO_2, R^1= Et

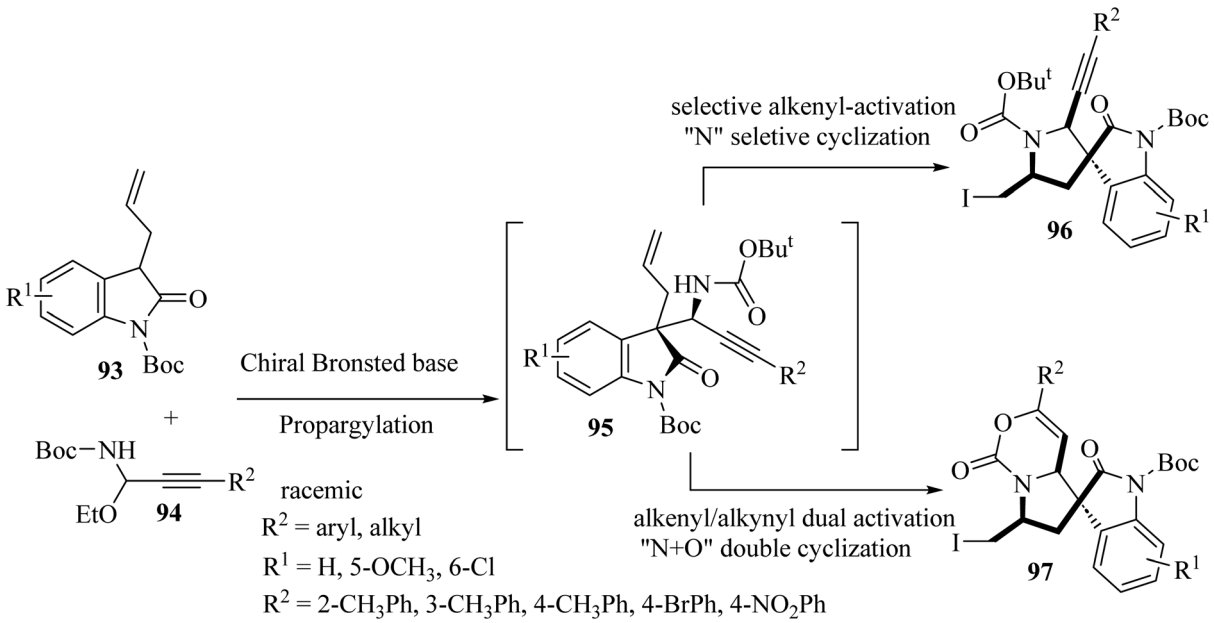


92

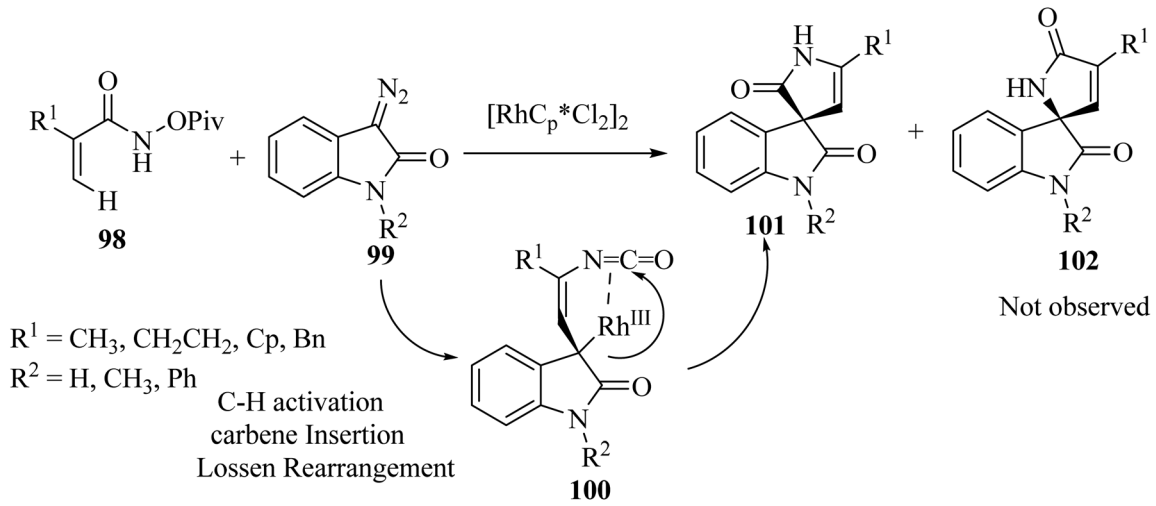
Scheme 22 Synthesis of spiro oxindolopyrrolidine **92**.

method proceeded through a one-pot asymmetric propargylation catalyzed by a chiral Brønsted base for the formation of oxindole 1,6-enynes **95** from the common and available precursors, 3-allyl oxindoles **93** and *C*-alkynyl *N*-boc acetal **94**, 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 **96** and tetracyclic 3,3′-pyrrolidonyl spirooxindoles **97** (Scheme 23).[71] The obtained tricyclic and tetracyclic spirooxindoles were preliminarily evaluated for *in vitro* anticancer activities. They displayed potential anticancer activities and some compounds exhibited the best inhibitory activity against HeLa and SGC7901 cell lines with IC_{50}'s of 13.2 and 17.6 μM, respectively.[71]

Rh(III)-catalyzed domino annulations of *N*-(pivaloyl-oxy) acrylamides **98** with diazooxindole **99** gave spiro-oxindole pyrrolone products **101** with excellent regioselectivities; the alternative regioisomer **102** was not observed (Scheme 24). The potential application of this protocol in the next step of diversification for drug finding was illustrated in the directed presentation of spiro-oxindole-pyrrolone skeleton into medicinal molecules pentoxifylline, endo folliculin, and pregnenolone.[72]



Scheme 23 Asymmetric synthesis of tri-and tetracyclic spiro oxindoles **96** and **97**.

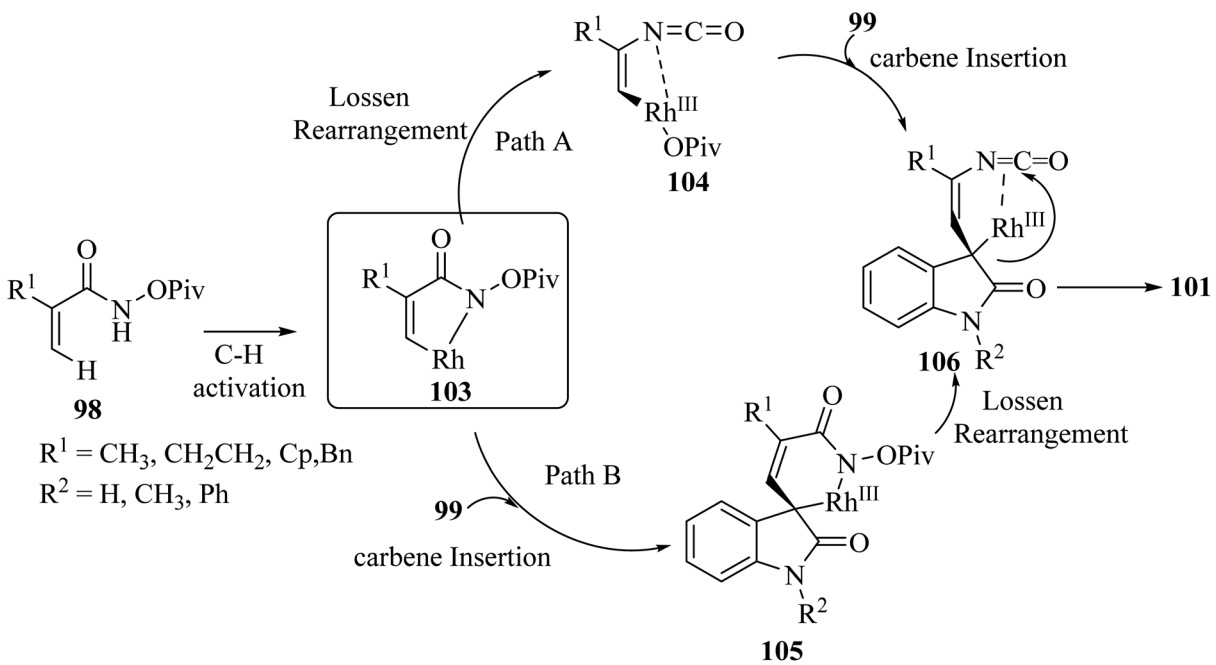


Scheme 24 C(sp^2)–H activation/annulation on to synthesis spiro oxindole pyrrolone scaffolds **101**.

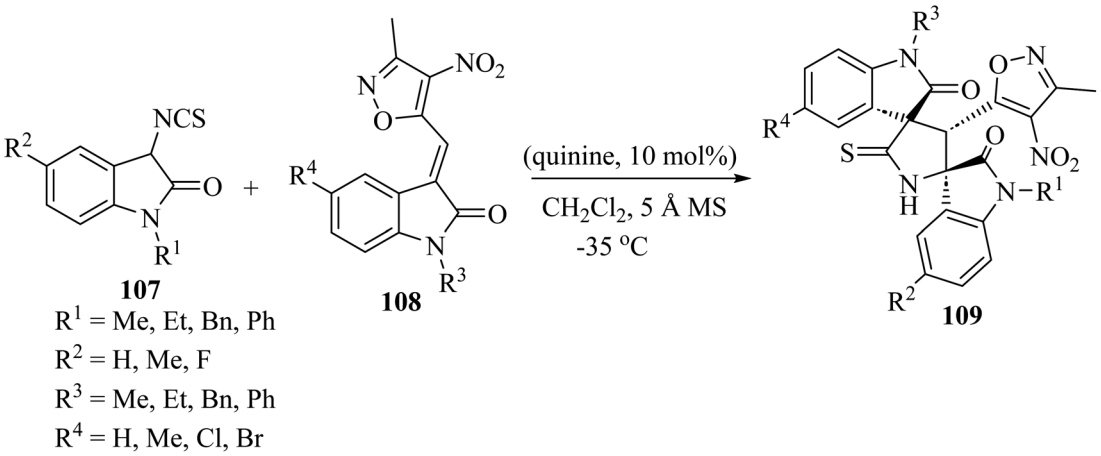
It was tentatively proposed that the reaction involves cleavage of the C–H bond with Rh(III), followed by carbene migratory insertion with the diazo-substrate to obtain an alkyl rhodium intermediate **105**. Then, a formal Lossen rearrangement offers isocyanate **106**, which, *via* further nucleophilic addition at the isocyanate, intramolecularly generates the final compound **101** (Scheme 25).[72]

Providing an electron-withdrawing moiety for alkylidenyloxindoles acting as dipolarophiles, the asymmetric Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles **107** and 3-methyl-4-nitro-5-isatylidenyl isoxazoles **108**, catalyzed by quinine, yielded enantiomerically enriched isoxazole-dispirobisoxindoles **109** (Scheme 26).[73] Although enantioselectivities were found to be dependent on the protecting group of the nitrogen atom of the isothiocyanato oxindole **107** and the isatylidenyl isoxazole **108**, and on the electronic character of the substitution of both aromatic rings, excellent diastereo-selectivity was achieved in almost all cases and high reactivity was observed, with reaction times of only 30 min.[73]

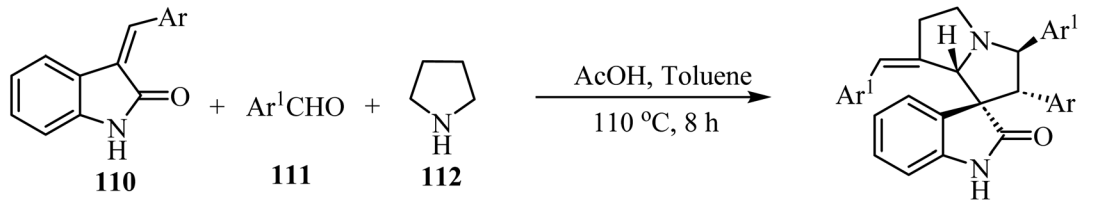
The synthesis of complex spiro heterocyclic compounds **113** has been pursued, by cycloaddition of *in situ* generated azomethine ylides with 3-alkylidene-2-oxindoles **110** as dipolarophiles. This acetic acid-promoted three component reaction **110**, aldehydes **111** and pyrrolidine (**112**) gives the resulting cycloadducts with good yields and diastereoselectivity (50–80%



Scheme 25 Rational mechanism for the synthesis of spiro oxindolpyrrolone **101**.



Scheme 26 Synthesis of isoxazole-dispiro-bis-oxindoles **109** from 3-isothiocyanato oxindoles **107** and isatylidenyl isoxazoles **108** by an organocatalytic process promoted by quinine.

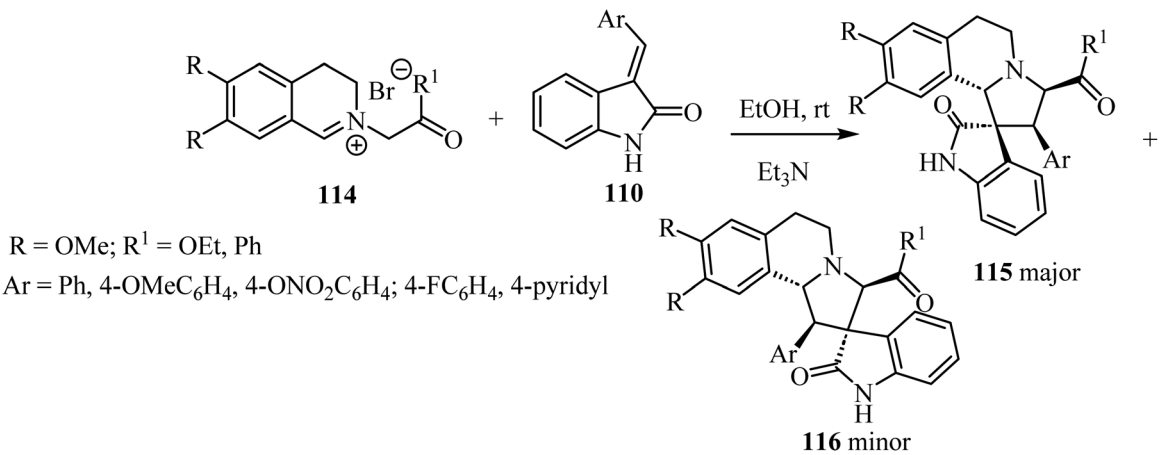


a; Ar = Ar^1 = 2-CH_3-C_6H_4, **b**; Ar = Ar^1 = 3-CH_3-C_6H_4, **c**; Ar = Ar^1 = 4-CH_3-C_6H_4, **d**; Ar = Ar^1 = 2-Cl-C_6H_4, **e**; Ar = Ar^1 = 3-Cl-C_6H_4, **f**; Ar = Ar^1 = 4-Cl-C_6H_4, **g**; Ar = Ar^1 = 4-Br-C_6H_4, **h**; Ar = 2-CH_3-C_6H_4, Ar^1 = 4Cl-C_6H_4, **i**; Ar = 4-Cl-C_6H_4, Ar^1 = Ph, **j**; Ar = 4-Cl-C_6H_5, Ar^1 = 4-Br-C_6H_4

Scheme 27 Synthesis of spiroindoles **113**.

yields, single diastereomer). The reaction mechanism involved β-C–H functionalization of pyrrolidine, generation of the azomethine ylide intermediate and subsequent 1,3-dipolar cycloaddition (Scheme 27).[74] The resulting spiro oxindole derivatives were investigated by evaluation against mouse colon cancer cells CT26 and human liver cancer cells HepG2 by MTT assay.[74]

1,3-Dipolar cycloaddition reaction of isoquinolinium salts **114** with 3-arylideneindoline-2-ones **110** (Scheme 28) in the



Scheme 28 1,3-Dipolar cycloaddition reaction of isoquinolinium salts **114** with 3-arylidene-indoline-2-ones **110**.

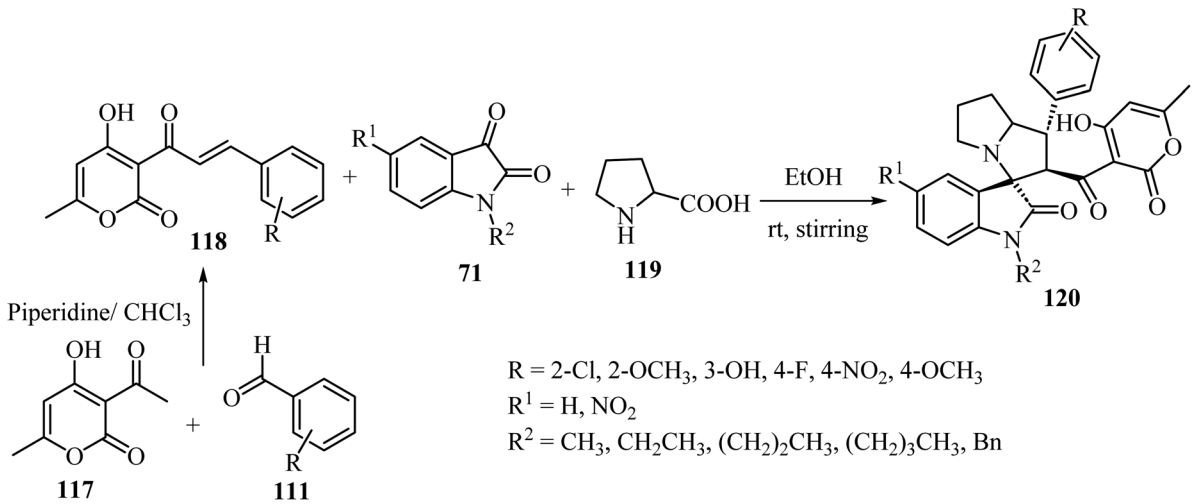
presence of trimethylamine (Et_3N) accomplished the regioselective formation of spiro pyrrolidine oxindoles **115**/**116** (Scheme 28). The main products **115** were formed in most cases as a white precipitate in the reaction mixture, and could be separated by simple filtration to give the single diastereoisomer **115** (in up to 75% yield). The minor isomer **116** could be isolated from the mother liquor using preparative HPLC.[75]

Tripathi *et al.*[76] have described the regioselective synthesis of hexahydrospiro[indoline-3,3′-pyrrolizine]-2-ones **120** in good-to-excellent efficiencies through [3 + 2] cycloaddition. The products were obtained *via* reaction of substituted 3-pyran-2-ones **118**, isatin derivatives **71**, and L-proline (**119**) at ambient temperature (Scheme 29). The chalcones **118** used in this reaction were produced *via* aldol condensation of substituted benzaldehydes **111** and 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**117**) in dry chloroform ($CHCl_3$) using a catalytic amount of piperidine (Scheme 29).[76]

Scheme 30 shows that the dispiro-2′,4′-(2-oxindolo)indolizidine **122** skeleton[77] was obtained at room temperature in EtOH or water (83–97% yield). Condensation between tetrahydroisoquinoline **70** and isatin derivatives **71** provided an azomethine ylide intermediate, whose subsequent cycloaddition with the appropriate dipolarophile gave the target molecules **122** as single diastereoisomers. Curiously, these reactions occurred in the absence of a basic agent. Inexpensive ZnO nanoparticles (NPs) were tested in order to determine their recyclability. Unfortunately, the efficiency of the nano-catalyst declined at every cycle, and after the third one the nanoparticles resulted as aggregates[77] (Scheme 30).

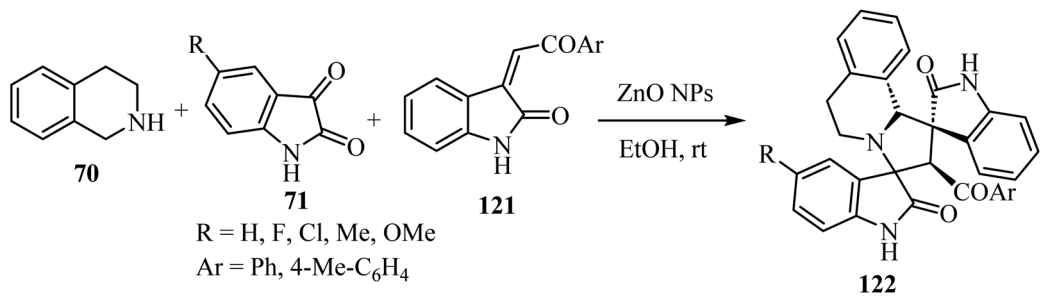
Synthesis of *N*-allyl-bis(methoxyphenylmethylidene) piperidone (**127**), starting with piperidin-4-one·HCl (**123**), is outlined in Scheme 31. The spirooxindole-pyrrolidine **128** was extracted in good yield (86%) *via* the cycloaddition of dipolarophile **127**[78] with the azomethine ylide generated *in situ* from isatin derivatives **71** and sarcosine (**56**) at reflux in CH_3OH for 1 h. The same reaction was performed in [bmim]Br at 100 °C (Scheme 31). TLC analysis of the reaction mixture revealed completion of the reaction in about 30 min with formation of the sole reaction product. The reaction mixture was then extracted with ethyl acetate and further purified by column chromatography. The reaction in [bmim]Br afforded a slightly better yield (90%) of **128** over the conventional heating employing CH_3OH (86%) (Scheme 31).[78]

Yan's group[79] have described a procedure for the formation of CF_3-containing spiro-oxindole-pyrrolidinepyrazolone compounds **131** *via* organo-catalytic [3 + 2] cycloaddition. This reaction involves the cycloaddition of α,β-unsaturated pyrazolones **129** with *N*-2,2,2-trifluoroethylisatin ketimines **130** in $CHCl_3$ at ambient temperature in the presence of a cinchonine-derived squaramide **65** catalyst to produce a pyrrolidine spiro-



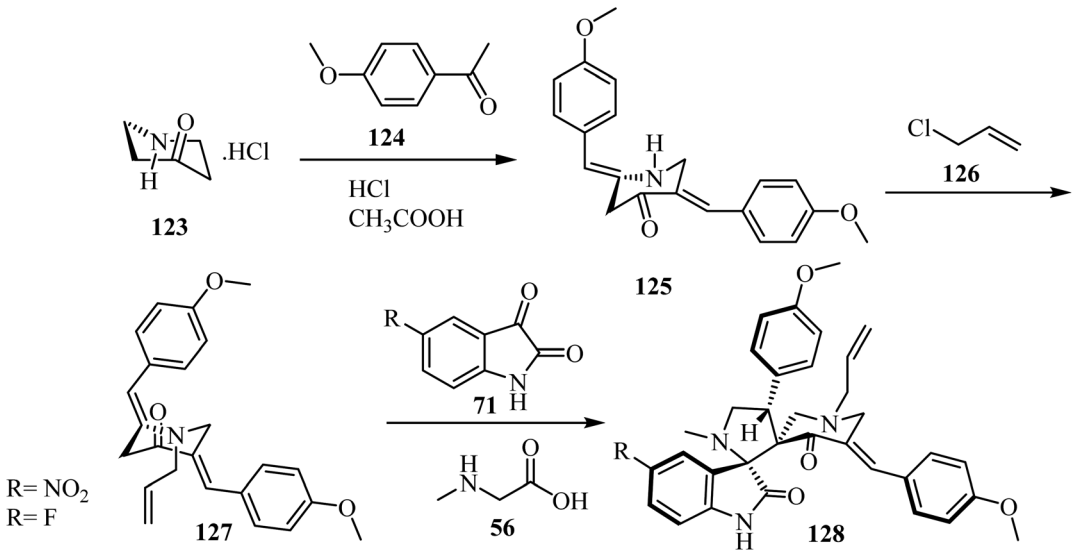
118 71 119 120 117 111

Scheme 29 Formation of hexahydrospiro[indoline-3,3′-pyrrolizine]-2-ones **120**.

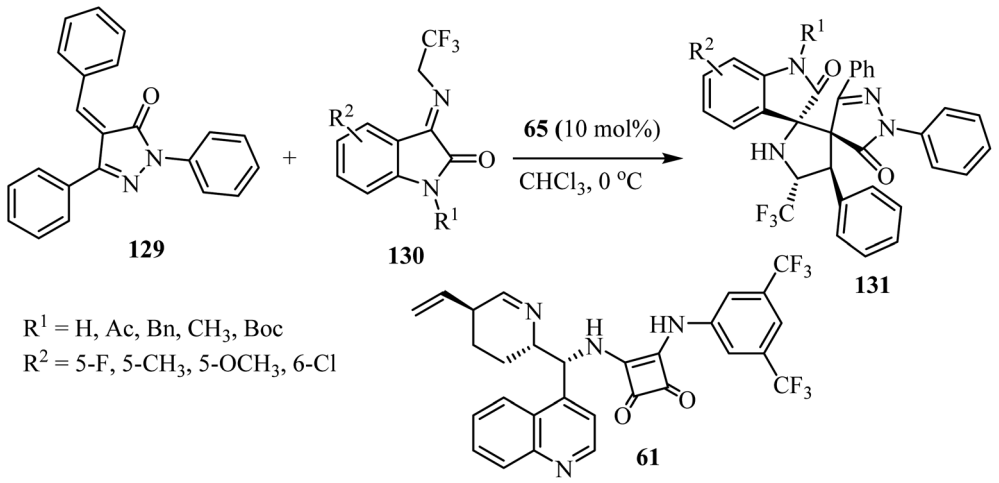


70 71 121 122

Scheme 30 Three component azomethine ylide cycloadditions catalyzed by unsupported partially aggregated ZnO nanoparticles (NPs).



Scheme 31 Synthesis of spirooxindole-pyrrolidine hybrids **128**.



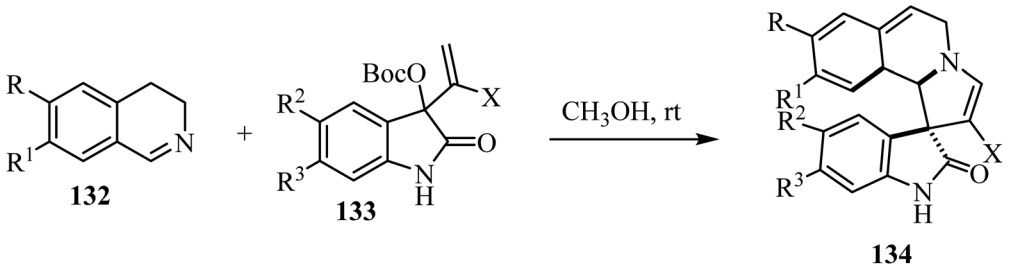
Scheme 32 Synthesis of spiro-indolones **131**.

fused with both oxindole and pyrazolone (**131**) with four adjacent stereocenters and two adjacent spiro-quaternary chiral centers, in high efficiencies and stereoselectivities (Scheme 32).[79]

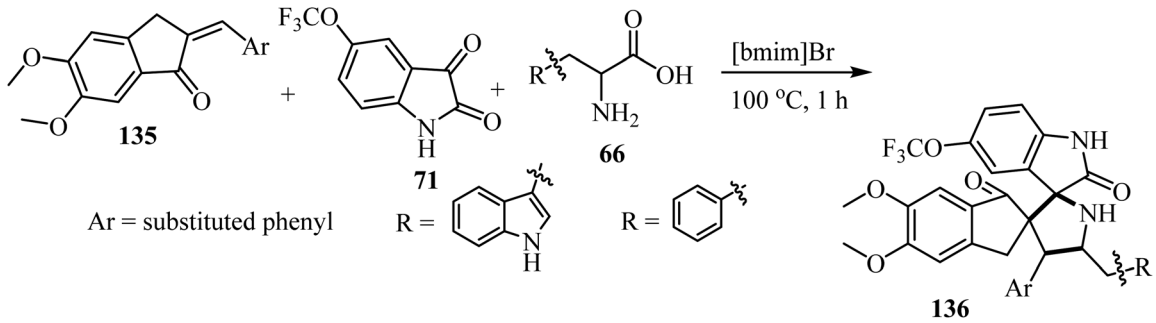
A mild catalyst-free [3 + 2] cyclization of dihydroisoquinolines **132** and the isatin-based Morita–Baylis–Hillman (MBH) carbonates **133** has been investigated (Scheme 33).[80] The combination of dihydroisoquinolines and the spirooxindole skeletons was achieved, leading to richly decorated spiro heterocycles **134** in moderate to good yields with good stereocontrol.[80]

The one-pot three-component cycloaddition reaction of 2-arylmethylidene-5,6-dimethoxyindenones **135** with azomethine ylides generated *in situ* from 5-(trifluoromethoxy)isatin (**71**) and tryptophan/phenylalanine **66** in [bmim]Br furnished the spiropyrrolidine heterocyclic hybrids **136** in moderate to good yields. Among the spiro pyrrolidine heterocyclic hybrids, the indole based fluorinated compound with a methoxy substituent at the *meta*-position of the aryl ring exhibited the utmost potent AChE and BChE inhibition with IC_{50} values of 1.97 ± 0.19 μM and 7.08 ± 0.20 μM, respectively (Scheme 34).[81]

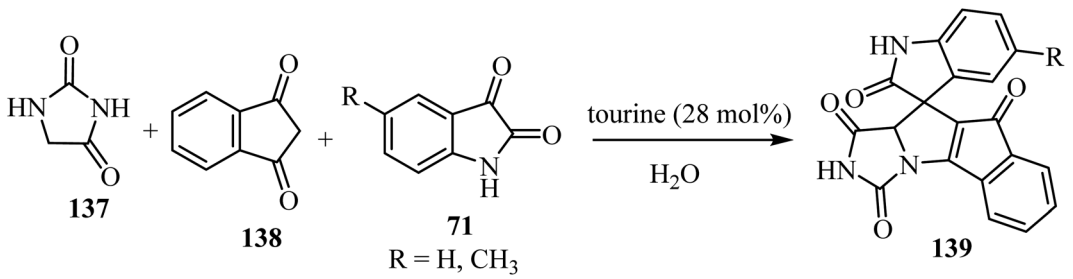
The three-component domino reaction of isatin derivatives **71**, 1,3-diketone (**138**), and hydantoin (**137**) without catalyst did not succeed either in the absence of solvent, or in water or EtOH as solvents: the desired product **139** was not obtained after stirring for 12 h (no result).[82] However, using either piperidine, 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or taurine (2-aminoethanesulfonic acid) as a catalyst in H_2O as solvent, the desired products **139** were obtained in appreciably good yield (Scheme 35). But when the reaction was carried out in the presence of L-proline as a catalyst using H_2O as a solvent, comparatively better yield of the desired



Scheme 33 Synthesis of spiroindoles **134**.



Scheme 34 Synthesis of dispiro[indene-2,3′-pyrrolidine-2′,3″-indoline]-1,2″(3*H*)-diones **136**.



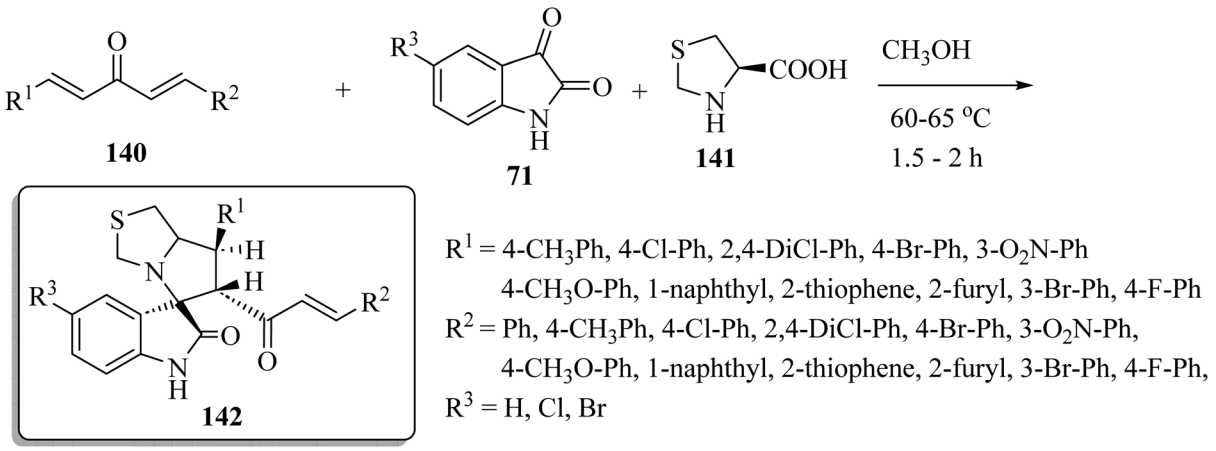
Scheme 35 Synthesis of spiro[indeno[2′,1′:4,5]pyrrolo[1,2-*c*]imidazole-10,3′-indoline]-tetraone derivatives **139**.

product was obtained.[82] An excellent yield of **139** was obtained when taurine (28 mol%) was used as a catalyst using H_2O as a solvent (Scheme 35).[82]

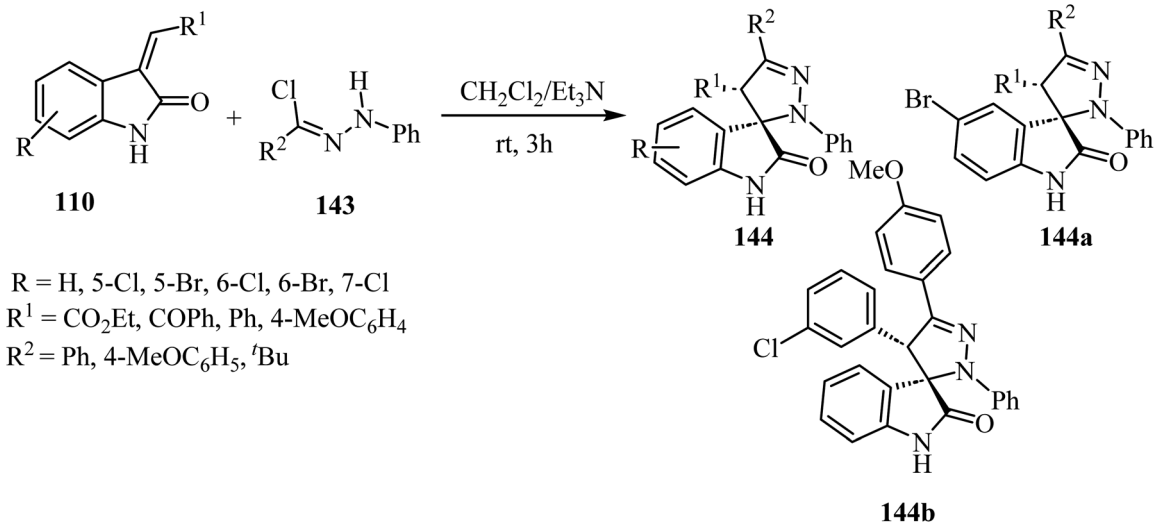
Spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazol]-2-one (**142**) was synthesized as shown in Scheme 36. One-pot multi-component condensation of *α*,*β*-unsaturated dienones **140** with the isatin derivatives **71** and amino acid derivatives **141** (L-4-thiazolidinecarboxylic acid) in CH_3OH at reflux produced the spirooxindole series **142** (Scheme 36).[83] The anticancer activities of compounds **142** were tested against colon (HCT-116), prostate (PC-3), and hepatocellular (HepG-2) cancer cell lines; some compounds inhibited colony formation, cell migration, arrested cancer cell growth at G2/M, and induced apoptosis through intrinsic and extrinsic pathways.[83]

The synthesis of racemic spiro(2-oxindolo)pyrazolines **144** was accomplished by treating hydrazonoyl chlorides **143** with 3-alkenyl-2-oxindoles **110** in the presence of triethylamine (Et_3N) as the organic basic agent and CH_2Cl_2 as a solvent. The regioselective cycloaddition of the dipolar intermediate gave 19 examples of the spiro cycloadducts with 80–90% yield (Scheme 37).[84] Other examples were provided similarly.[85,86] Biological evaluation of the so-obtained spiro(2-oxindolo)pyrazoline library showed antiproliferative activity in HCT-116p53(+/+) human colorectal cancer cell line with two derivatives displaying good activities (**144a**: $IC_{50} = 13.1 \pm 1.0$ μM, **144b**: $IC_{50} = 10.9 \pm 0.8$ μM), see Scheme 37. Both spiro(indolo)pyrazolines **144a**,**b** were able to induce apoptosis and cell cycle arrest. Cytotoxic effects induced by **144a** occurred in cancer cells without eliciting cells death in non-malignant human colon fibroblasts. Furthermore, it was demonstrated that the combination of **144a** with subtoxic concentrations of the chemotherapeutic agent 5-fluorouracil exerted a synergistic inhibitory effect on HCT-116 colon cancer cell proliferation.[84]

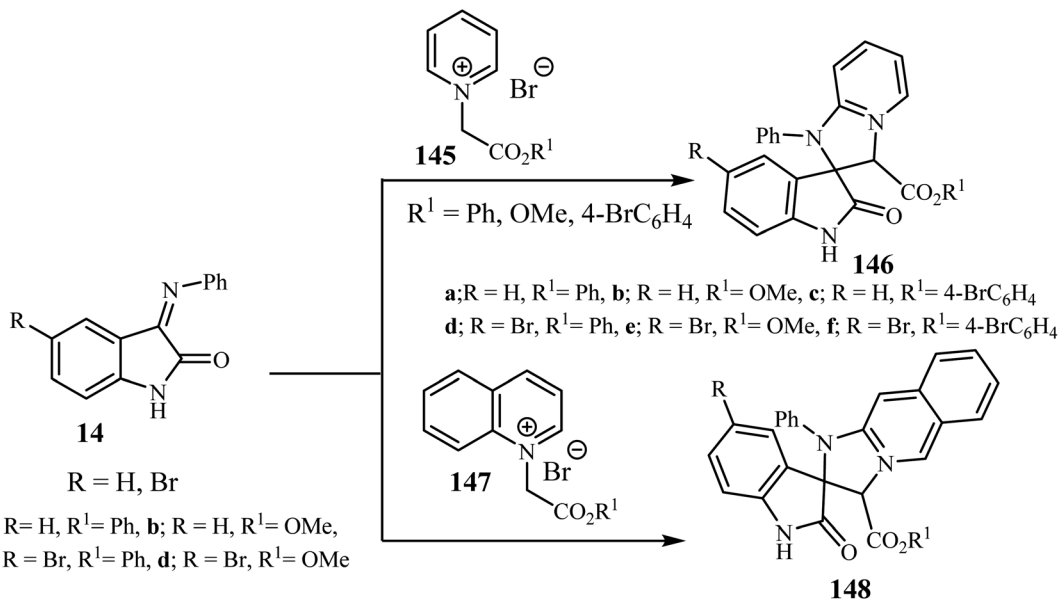
Sheibani and co-workers[87] reported that cycloaddition between isatin-3-imines **14** and pyridinium or isoquinolinium salts gave racemic spiro(2-oxindolo) imidazolines **146**/**148** in 90–95% yield. Mild conditions, operational simplicity and easily accessible starting materials were features of these



Scheme 36 Synthesis of spiro[indoline-3,5′-pyrrolo[1,2-*c*]thiazol]-2-ones **142** with four stereogenic centers.



Scheme 37 Nitrilimine cycloaddition to 3-alkylidene-2-oxindoles **110** hydrazonoyl chloride **143**.



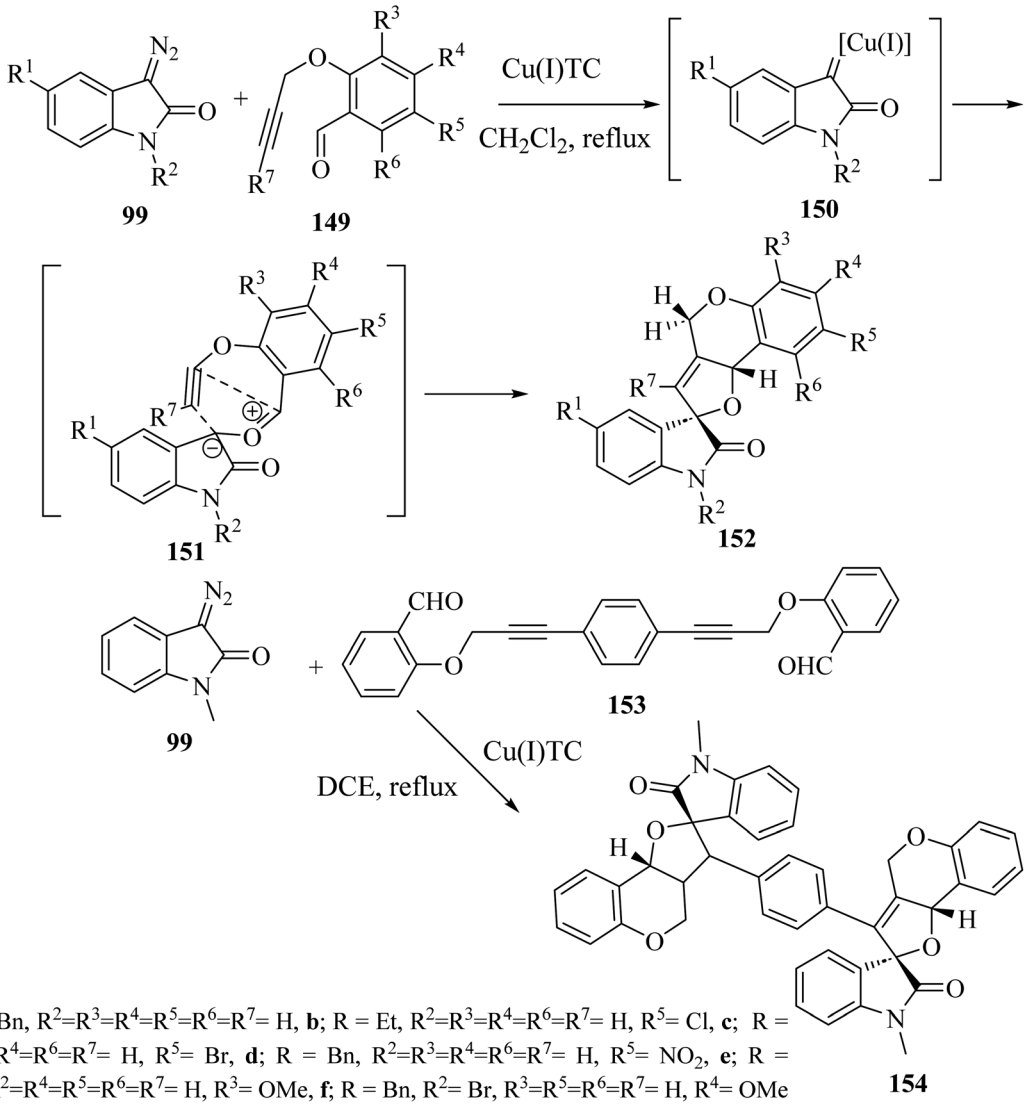
Scheme 38 Cycloaddition between isatin-3-imines **14** and pyridinium or isoquinolinium ylides **145** and **147**.

cycloadditions (Scheme 38).[87] The cycloaddition reactions involved the nucleophilic attack by the isoquinolinium-ylides on isatin-3-imines **14** which act as a dipolarophile.[87]

Addition of 3-diazoisatins **99** to *O*-propargyl salicylaldehydes **149** in the presence of copper(I) thiophenecarboxylate [(Cu(I)TC] in dichloromethane (CH_2Cl_2) as solvent gave the spiro(furo[3,2-*c*]chromene)-2-oxindoles **152** (ref. 88) (Scheme 39). Mechanistically, the reaction between 3-copper(I)carbene-diazoisatins and salicylaldehydes involved the generation of the carbonyl ylide intermediates **151**, whose subsequent stereoselective intramolecular cycloaddition gave products **152** in 61–84% yield as single diastereoisomers (Scheme 39).[88] In the same reaction conditions, a bis-propargylated salicylaldehyde **153** reacted with diazoisatin **99** giving the complex bis-cycloadduct **154** as single diastereoisomer.[88]

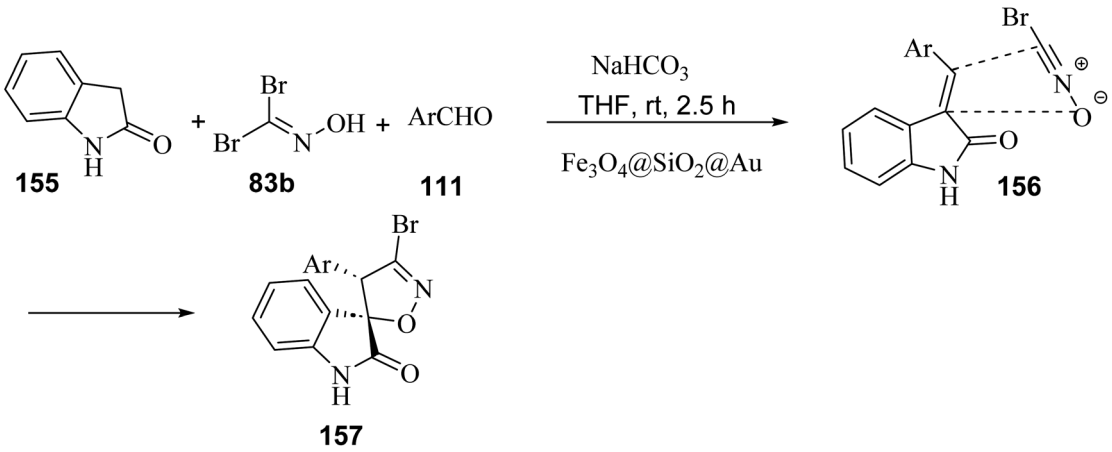
A regio- and diastereo-selective three-component reaction between aldehydes **111**, dibromoformaldoxime (**83b**) and 2-oxindole (**155**) has been pursued in the presence of ferrite-silica nanoparticles decorated with Au(0) nanoparticles (Fe_3O_4@SiO_2@Au) as the nano-catalyst (Scheme 40). From the synthetic standpoint, a sequential Knoevenagel condensation-nitrile oxide cycloaddition led to the formation of spiro(2-oxindolo) isoxazolines **157** under mild reaction conditions in 78–85% yield.[89] Both bromonitrile oxide and 3-alkylidene-2-oxindole, were generated *in situ*, the former by action of sodium hydrogen carbonate ($NaHCO_3$) on dibromoformaldoxime, the latter by Knoevenagel condensation between 2-oxindole and aromatic aldehydes. The spiro(2-oxindolo) isoxazoline cycloadducts apparently result from the regioselective attack of bromonitrile oxide on the carbon–carbon double bond of the 3-alkylidene-2-oxindole. From the mechanistic standpoint, Au(0) nanoparticles act as efficient catalysts by activating bromonitrile oxide through the lanthanide contraction effect.[90]

The synthesis of spirooxindole-δ-lactams from oxoindole-derived α-aryl-β-amino acids has been described.[91] Oxoindole derivatives **159** were obtained stereoselectively by an organo-catalyzed asymmetric Mannich reaction between homophthalic anhydrides **158** and isatin-derived *N*-Boc imines **14** with

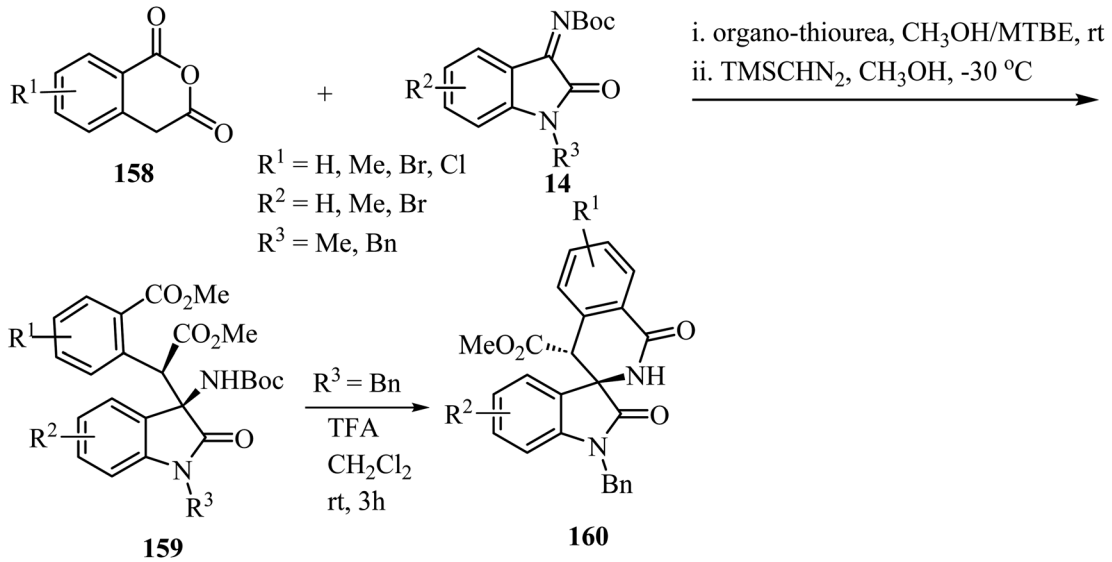


152, a: R = Bn, R^2=R^3=R^4=R^5=R^6=R^7= H, **b**; R = Et, R^2=R^3=R^4=R^6=R^7= H, R^5= Cl, **c**; R = Pr, R^2=R^3=R^4=R^6=R^7= H, R^5= Br, **d**; R = Bn, R^2=R^3=R^4=R^6=R^7= H, R^5= NO_2, **e**; R = propargyl, R^2=R^4=R^5=R^6=R^7= H, R^3= OMe, **f**; R = Bn, R^2= Br, R^3=R^5=R^6=R^7= H, R^4= OMe

Scheme 39 Intramolecular cycloaddition of the indolic carbonyl ylide **151**.



Scheme 40 Fe_3O_4@SiO_2@Au-catalyzed three component reactions between 2-oxindole, aromatic aldehydes and dibromoaldoxime.



Scheme 41 TFA-mediated *N*-Boc deprotection/intramolecular *N*-acylation reaction of oxoindole-derived α-aryl-β-amino acids.

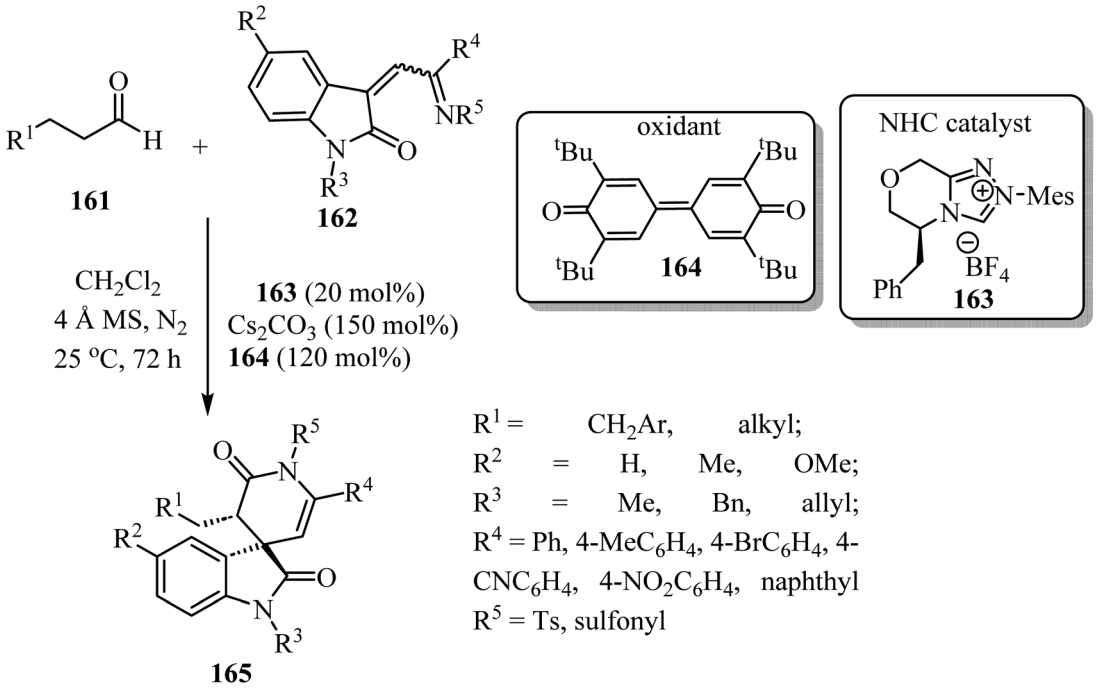
trimethylsilyldiazomethane ($TMSCHN_2$) as methylating agent (Scheme 41). Treatment of oxindoles **159** with trifluoroacetic acid (TFA) provided spiro-δ-lactams **160** in good yields (65–75%) with retention of the stereochemistry of the two adjacent carbon chiral centers. The reaction proceeds through deprotection of the amino group followed by intramolecular *N*-acylation to afford the spiro-δ-lactams.[91]

Spiro-oxindole-δ-lactams **165** were synthesized *via* an NHC-catalyzed oxidative [4 + 2] annulation of aliphatic aldehydes **161** with oxindole-derived α,β-unsaturated imines **162** using chiral pre-NHC catalyst **163** (Scheme 42).[92] The target spirocyclic lactams **165** were obtained in good yields (up to 94%) and good to excellent enantioselectivities (87–97% ee). The reaction exhibited good functional group tolerance although attempts to carry out the reaction with *N*-Boc-imine or *N*-Ac-imine derivatives did not lead to the formation of the desired products.[92]

The synthesis of chiral spiro-δ-lactams with antimalarial activity was reported *via* two different strategies using bicyclic δ-lactam **166**, derived from *S*-tryptophanol, as building block (Scheme 43).[93] Compound **166** reacted with 2,4-dinitrofluorobenzene *via* aromatic nucleophilic substitution to afford compound **167**. Next, reduction with H_2/Pd–C followed by $TiCl_4$/triethylsilyl hydride promoted spiro-cyclization led to spiro oxindole-δ-lactams **168** and **169** (Scheme 43).

The three-component approach to the synthesis of spiro indoline δ-lactams **172**, used 2-bromobenzyl bromides **171** as the third reaction component along with α-isocyano δ-lactams **170** and benzylamine (**51**), in the presence of a Pd/Cu catalytic system (Scheme 44).[94]

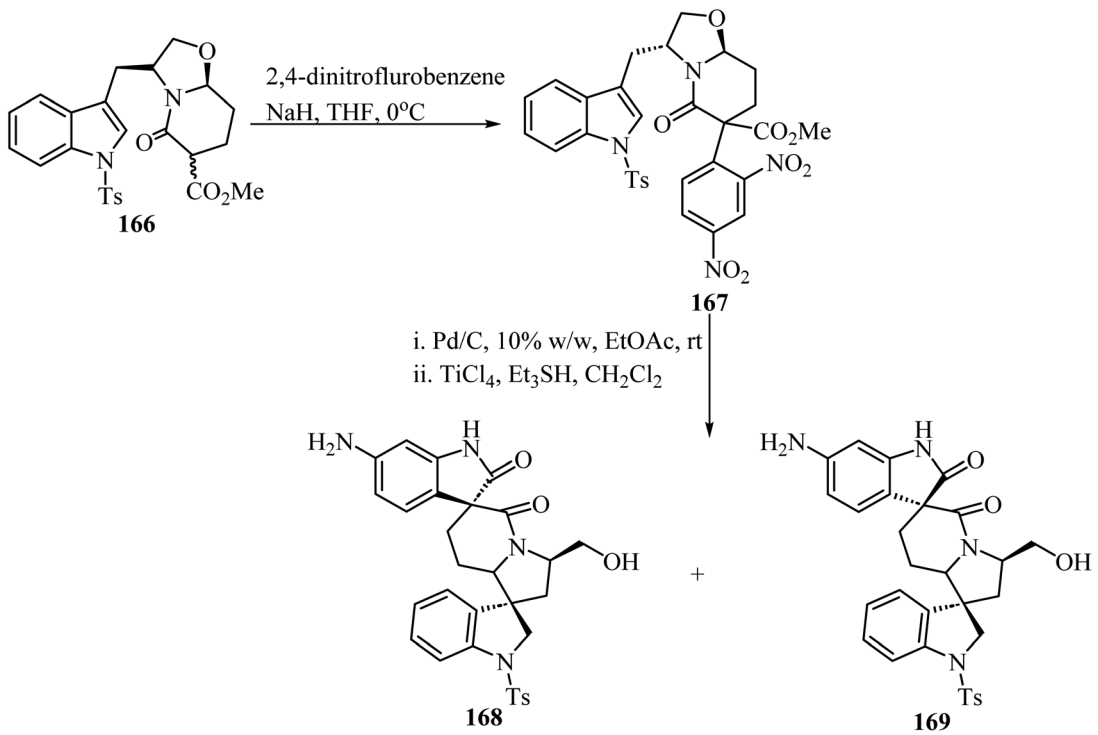
The proposed mechanism for this multicomponent reaction involves initial Pd-catalyzed benzylation of α-isocyano δ-lactams **170** to give intermediate **173** which undergoes a copper-



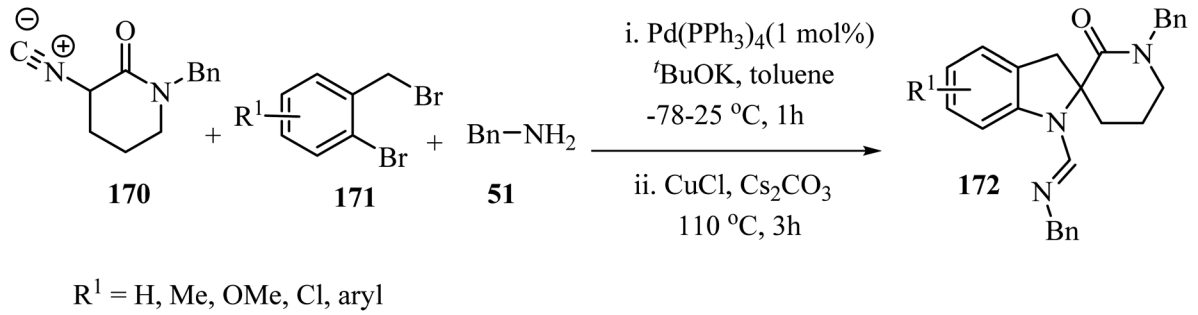
Scheme 42 NHC-catalyzed [2 + 4] spiroannulation of aliphatic aldehydes **161** with oxoindole-derived α,β-unsaturated imines **162**.

mediated *in situ* amine addition to the isocyanide moiety and finally isomerization to generate **174**.[94] In the final step, the intramolecular *N*-arylation of palladium complex **175** *via* Pd/Cu catalysis generates the indoline core, affording spirocyclic δ-lactams **172** in moderate to good yields (51–73%) (Scheme 45).[94]

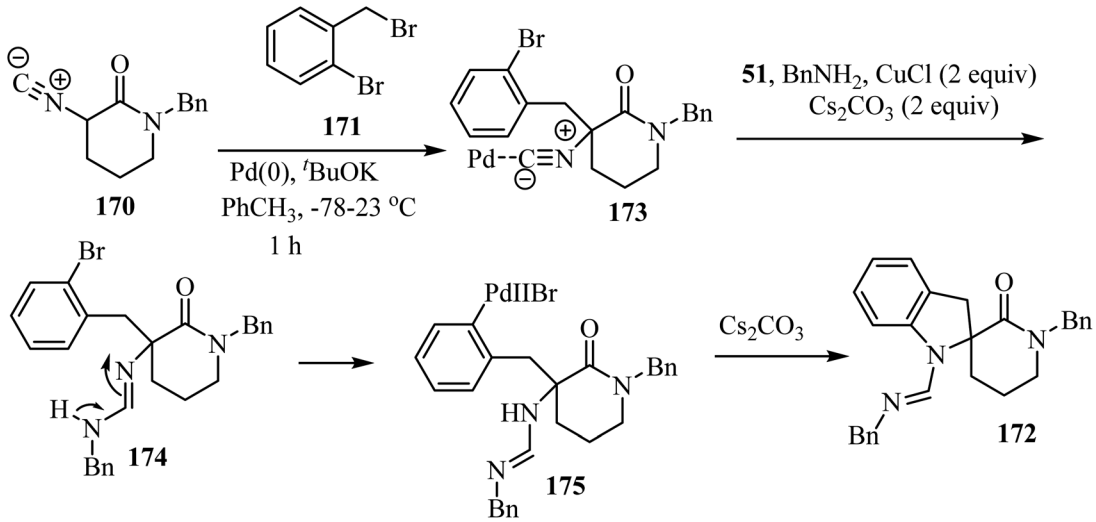
Recently, an efficient catalytic asymmetric three-component reaction of isoquinolines **76**, allene dicarboxylates **176** and methylene indolinones **110** was realized for the synthesis of spiroindolino-pyrido[2,1-*a*]isoquinolines **178**.[95] In the presence of the chiral *N*,*N*′-dioxide/$Mg(OTf)_2$ catalytic system, the reaction proceeded *via* the nucleophilic addition and [4 + 2] cycloaddition/



Scheme 43 Cyclization of a *S*-tyrptophanol derived chiral bicyclic spiro δ-lactam **166**.



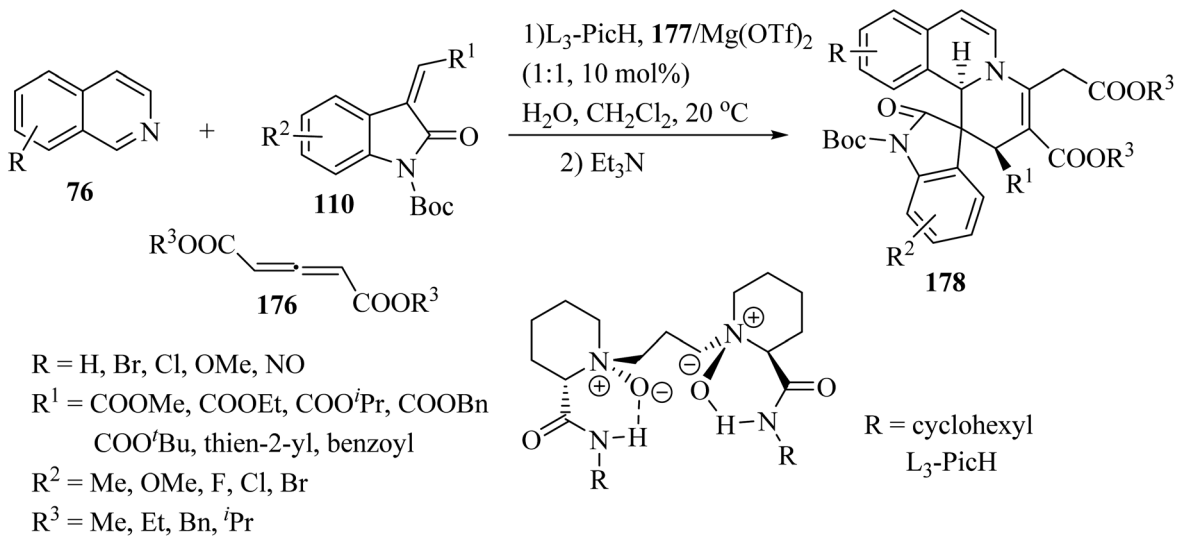
Scheme 44 Cooperative Pd/Cu-catalyzed tandem three-component reaction involving δ-lactams **170**, amines **51** and 2-bromobenzyl bromides **171**.



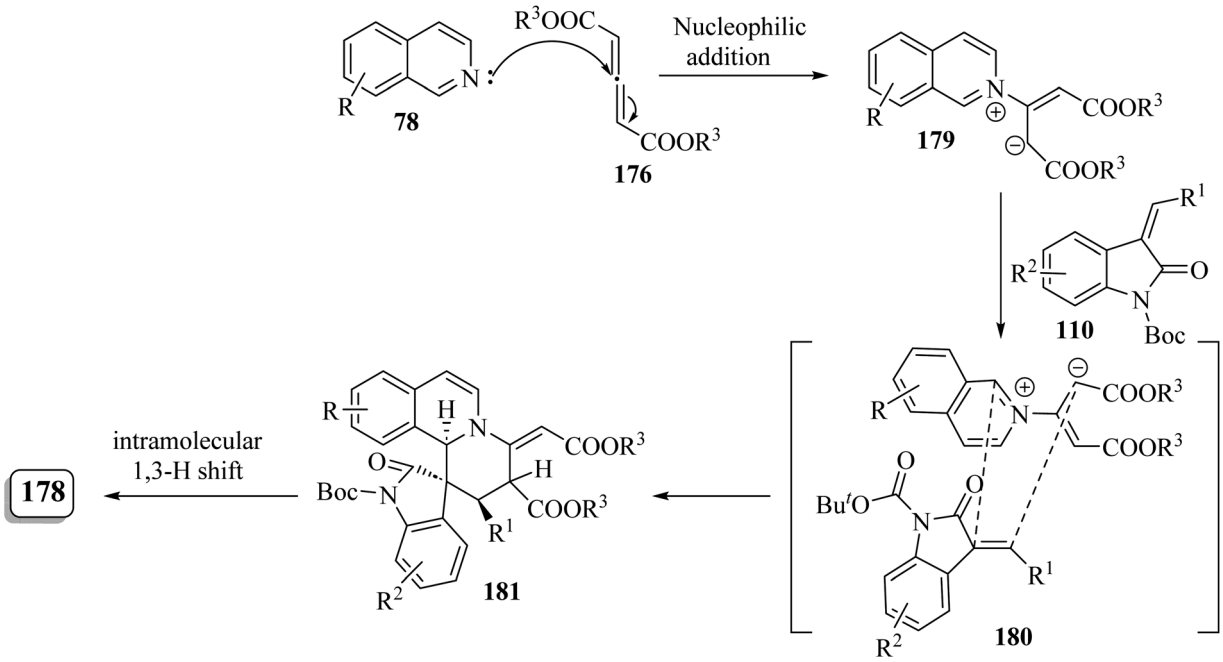
Scheme 45 The proposed mechanism for the formation of **172**.

isomerization sequence. The tandem reaction enabled rapid access to the spiro-products with good to excellent stereoselectivities under mild reaction conditions (Scheme 46).

It is conceivable that initially the 1,4-dipole **179** was generated *in situ* through the nucleophilic attack of isoquinoline **78** on the allene dicarboxylate **176** (ref. 95) (Scheme 47). Subsequently, the [4 + 2] cycloaddition of **110** with intermediate **179**



Scheme 46 Synthesis of spiro-indolino-pyrido[2,1-*a*]isoquinolines **178**.



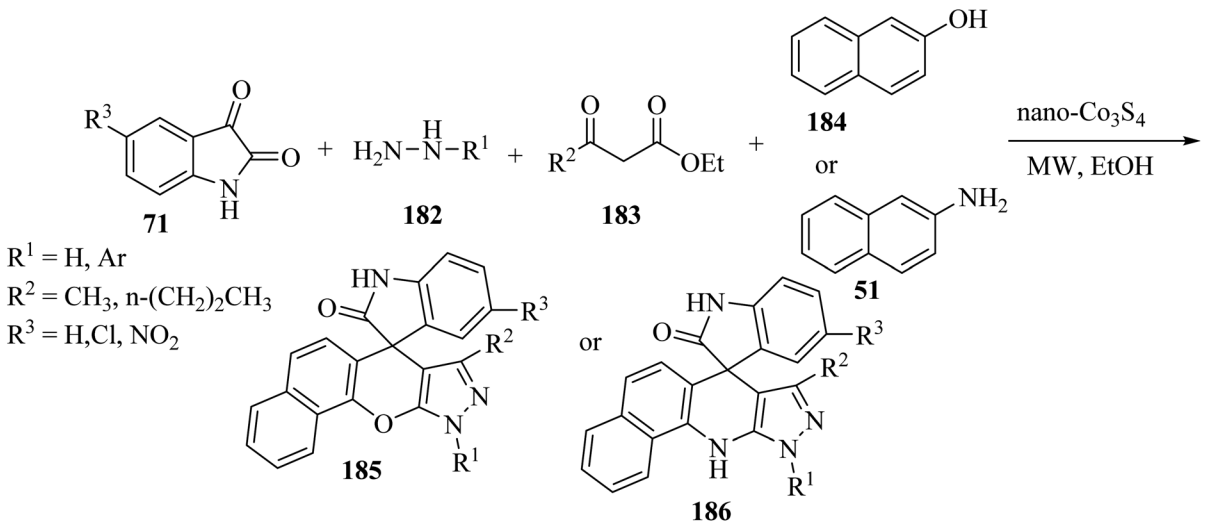
Scheme 47 Rational pathway for the formation of **178**.

proceeded *via* the simultaneous Si/*β-Re* face attack, affording the exocyclic alkene intermediate **180.** Finally, intramolecular [1,3]-hydrogen shift resulted in the isomerized product **178** (Scheme 47).[95]

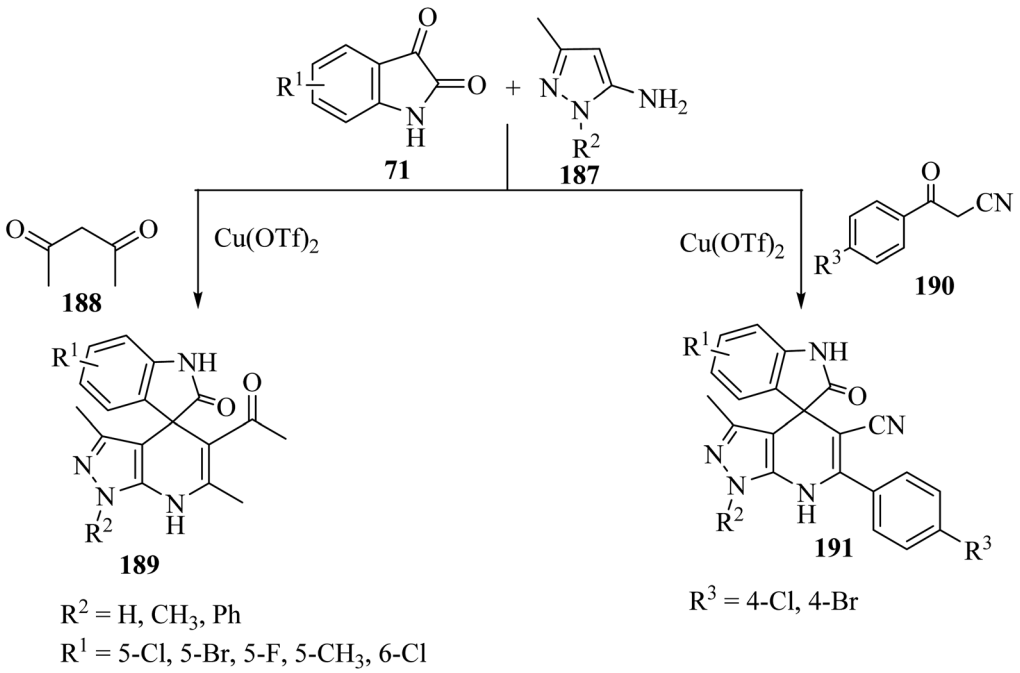
Khojasteh-Khosro and Shahbazi-Alavi[96] developed an efficient and rapid procedure for the formation of spiro[benzo[5,6]chromeno[2,3-*c*]pyrazole-11,3′-indol]-2′(1′*H*)-ones **185** and dihydrospiro[pyrazolo-[3,4-*b*]benzo[*H*]quinolin-7,3′-indol]-2′(1′*H*)-ones **186** through a four-component reaction of hydrazines **182**, isatins **71**, ketoesters **183**, and 2-naphthol (**184**) or naphthylamine (**51**) in the presence of nano-Co_3S_4 under MW-assisted reaction conditions (Scheme 48).[96]

Wu *et al.*[97] have developed a facile, efficient and environmentally benign method to produce the structurally diverse spiro-oxindole scaffolds named spiro[indole-[4*H*]pyrazolo[3,4-*b*]quinolines] **189** and spiro[indoline pyrazolo[3,4-*b*]pyridine]carbonitrile (**191**) through a three-component condensation of isatin derivatives **71**, 5-aminopyrazole (**187**), and 1,3-dicarbonyl compound such as pentane-2,4-dione (**188**) or *β*-oxobenzenepropanenitriles **190** catalyzed by copper triflate [$Cu(OTf)_2$] in EtOH (Scheme 49).[97]

Choudhury and co-workers[98] have described a medium-dependent, metal-free three-component condensation of isatin derivatives **71**, 4-hydroxycoumarin (**192**) and aminopyrazole



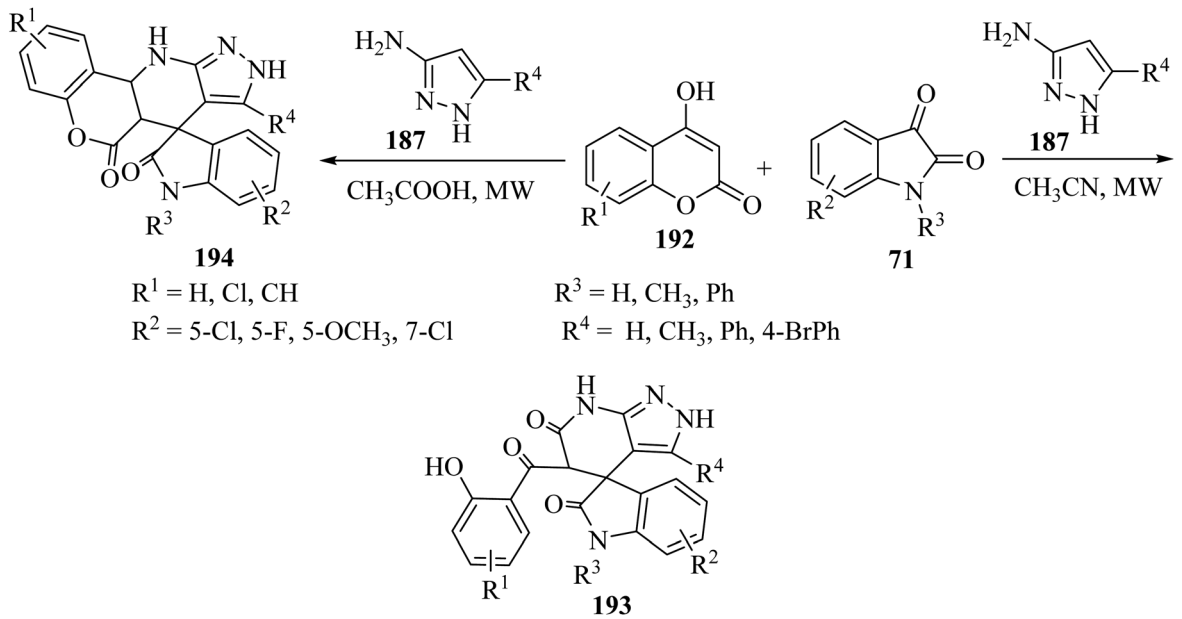
Scheme 48 Synthesis of spirooxindoles **185** and **186** under microwave (MW) irradiation.



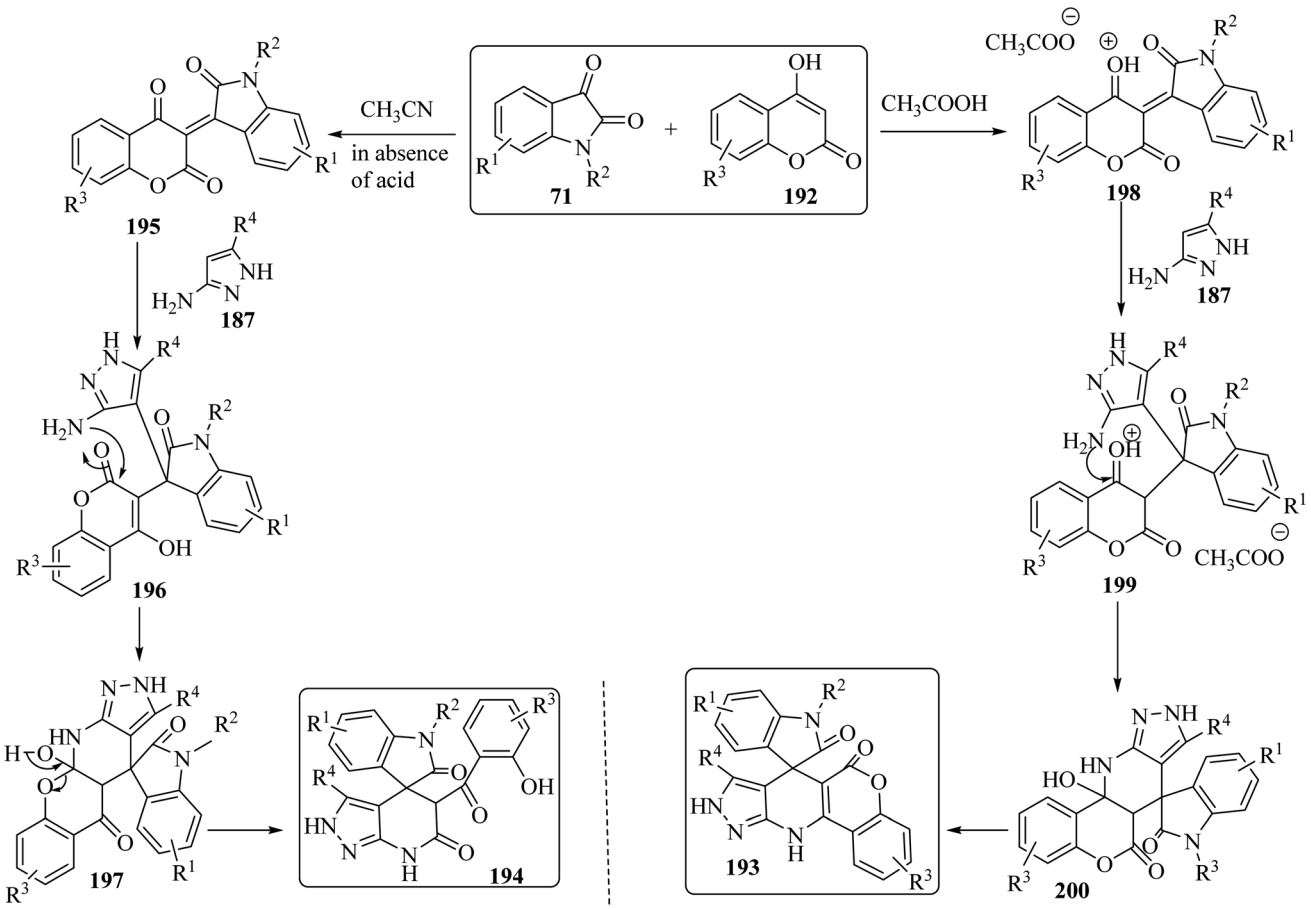
Scheme 49 Synthesis of spiro compounds **189** and **191**.

(**187**) under MW-assisted conditions for the formation of two diverse kinds of fused spirooxindoles **193** and **194**. Isatin derivatives **71**, 4-hydroxycoumarins **192** and aminopyrazole **187** reacted together under MW-assisted conditions in acetonitrile (CH_3CN) solvent and produced spirooxindoles fused with pyrazolo-tetrahydropyridinones **193** *via* opening the ring of the hydroxycoumarin core (Scheme 50). But when acidic conditions are used as the reaction medium, related fused spirooxindoles containing a tetracyclic coumarin dihydropyridine-pyrazole scaffold **194** were obtained. This medium-dependent three component condensation led to the production of a class of pharmaceutically important spiro-oxindoles under metal-free conditions (Scheme 50).[98]

The proposed reaction mechanism for the synthesis of **193** or **194** is illustrated in Scheme 51.[98] It is expected that 4-hydroxycoumarin **192** first reacts with isatin derivatives **71** to form intermediate **195**; then amino pyrazole **187** underwent 1,4-addition to obtain tri-substituted methane **196**. In non-acidic



Scheme 50 Synthesis of fused spirooxindooles **193** and **194** *via* the reaction of 4-hydroxy coumarin derivatives **192** and amino pyrazole **187**.

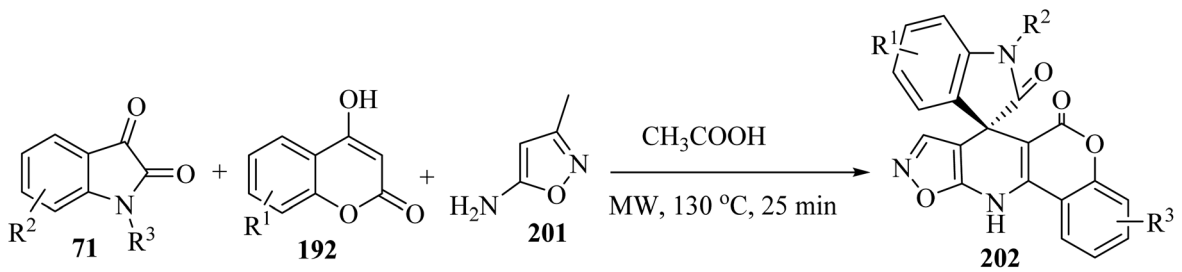


Scheme 51 A rational mechanism for the formation of **193** and **194**.

conditions, **196** 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 **197**, and eventually stable compound **194** forms *via* ring-opening of the coumarin. On the other hand, by using acid, tri-substituted methane intermediate **196** remains as protonated form **199**, containing the active protonated carbonyl group (ketone) **200**, so ring closure happens intramolecularly by involving the ketone group of the coumarin instead of the ester group, and product **193** was formed (Scheme 51).[98]

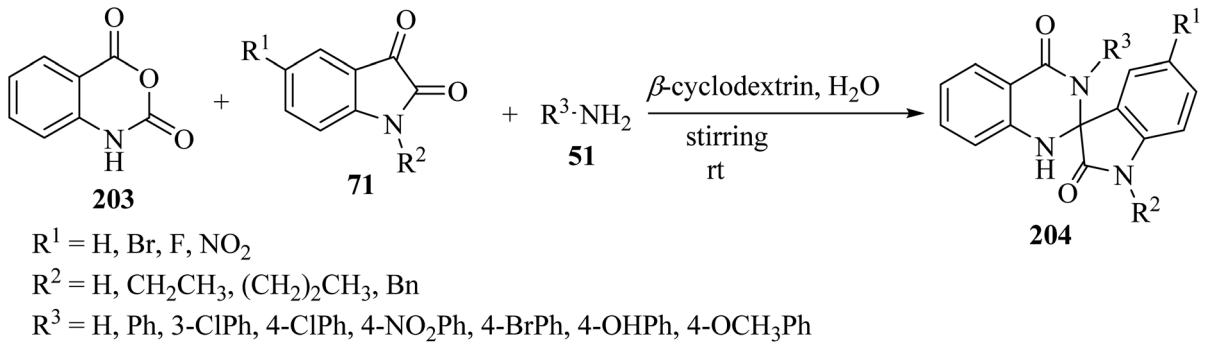
In order to expand the substrate scope, the same authors have prepared another spiro-oxindole fused with coumarin-dihydropyridine-isooxazole tetracycle **202** by applying 5-amino-3-methylisoxazole (**201**) (Scheme 52).[98]

Tripathi[99] has introduced an efficient multicomponent synthetic method for the formation of spiro[indoline-3,2′-quinazoline]-2,4′(3′*H*)-diones **204** from isatoic anhydride (**203**),



R^1 = H, CH_3
R^2 = 5-Cl, 5-F, 5-OCH_3, 5-NO_2, 7-Cl
R^3 = H, CH_3

Scheme 52 Formation of spirooxindole scaffolds **202** containing coumarin-dihydropyridine-isoxazol tetracycles.

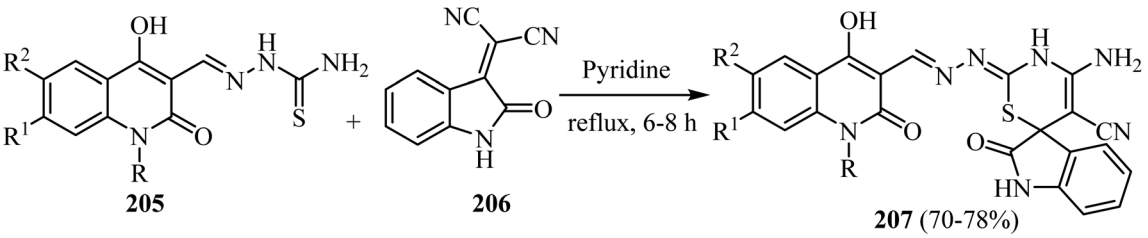


Scheme 53 Synthesis of various spiroindole quinazoline derivatives **204**.

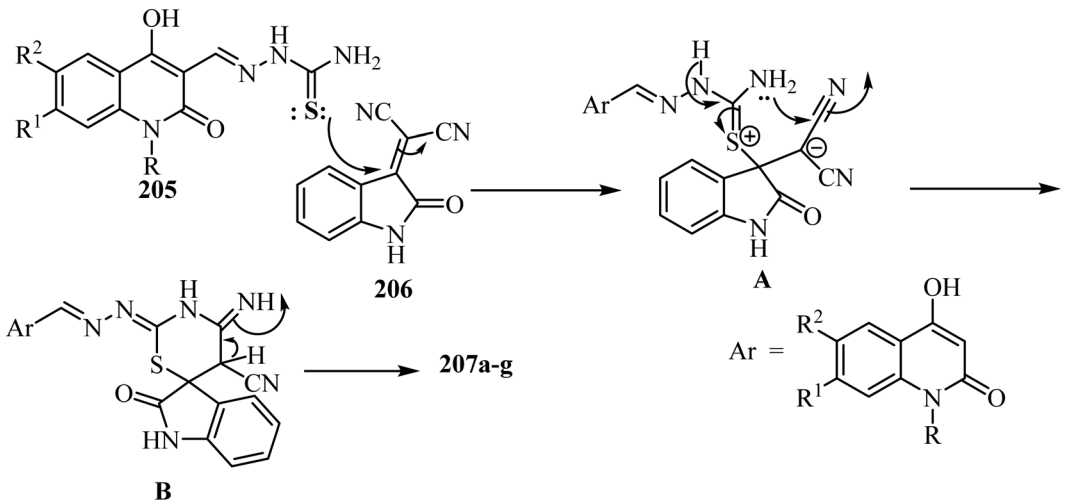
isatin derivatives **71**, and primary amines **51**, which was catalyzed by β-cyclodextrin in an aqueous medium (Scheme 53). Due to the use of environmentally friendly catalysts and green solvents, this is a green method to produce valuable spiroheterocycles.[99]

Aly *et al.*[100] prepared a series of spiro[indoline-3,6′-[1,3]thiazines] **207** in modest yields by refluxing substituted (1,2-dihydroquinolin-3-yl)methylene)hydrazine-carbothioamides **205** with 2-(2-oxoindolin-3-ylidene)malononitrile (**206**) in pyridine as a solvent (Scheme 54).[100] The suggested mechanism for the formation of spiro indolothiazines **207** was based upon attack by the thione-lone pair in **205** on the olefinic C=C in **206** leading to the formation of salt **A** as an intermediate (Scheme 53). Attack of the amino lone pair on the electrophilic carbon in the nitrile group leads to the formation of adduct **B** (Scheme 54). Finally, the products **207a–g** were formed after proton transfer in **B** as shown in Scheme 54.[100]

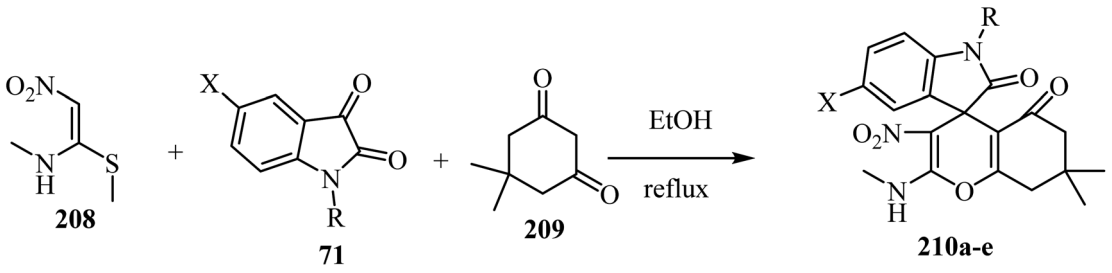
(*E*)-*N*-Methyl-1-(methylthio)-2-nitroethenamine (NMSM) (**208**) has drawn significant attention as an important synergistic building block due to the presence of push–pull skeleton for the synthesis of various O/N-heterocyclic ring systems *via* multicomponent reactions (MCRs).[101,102] By using an MCR



a; R = C_2H_5, R^1 = R^2 =H, **b**; R = R^1 = R^2 =H, **c**; R = R^1 = H, R^2 = CH_3
d; R = R^1 = H, R^2 = OCH_3, **e**; R = R^1 = H, R^2 = Cl, **f**; R = R^2 = H, R^1 = Cl, **g**; R = R^2 = H, R^1 = Br

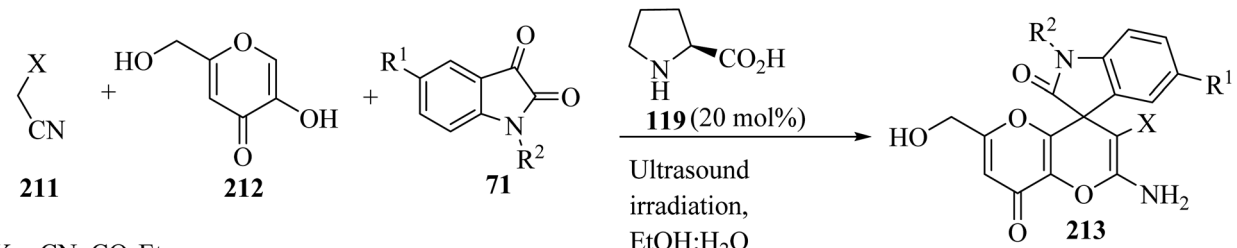


Scheme 54 Formation of spiro [indoline-3,6′-[1,3]thiazine]-5′-carbonitriles **207a–g** and the mechanism describes their formation.



a; R = X = H, **b**; R = H, X = Cl, **c**; R = H, X = Br,
d; R = H, X = NO_2, **e**; R = Me, X = H

Scheme 55 Utility of NMSM for the one-pot synthesis of fused spiro 4*H*-pyrans **210**.

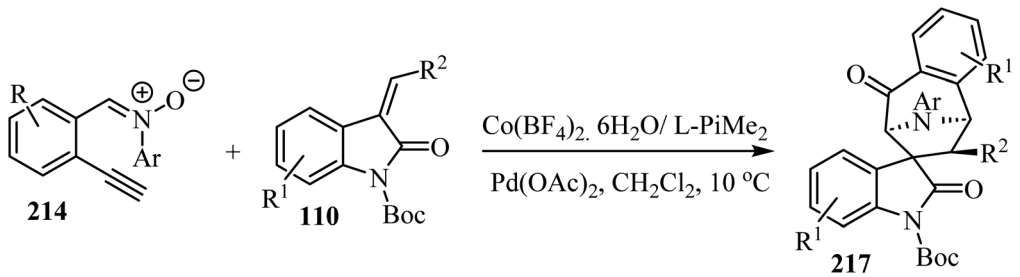


X = CN, CO_2Et

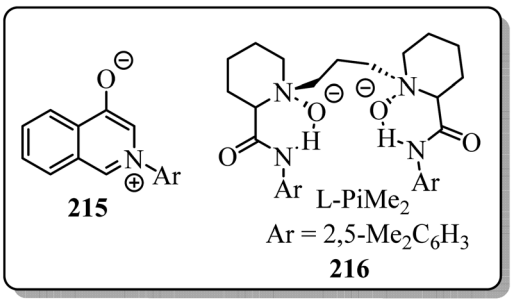
R^1 = H, Cl, Br; R^2 = H, Me, allyl, Bn

Scheme 56 Ultrasound-assisted organocatalytic domino synthesis of spiro[indoline-3,4′-pyrano[3,2-*b*]pyran **213**.

strategy and NMSM as a building block, spiro-4*H*-pyrans were synthesized using oxygen containing 1,3-dinucleophilic sources (cyclic-1,3-diketone, **209**), isatin derivatives **71**, and 1*N*-methyl-1*S*-methyl-2-nitroethylene (NMSM) **208** under catalyst-free conditions to furnish compounds **210** (Scheme 55).[102] These compounds were initially screened for *in vitro* antibacterial



a: R = R^1=H, R^2= $CO_2{}^tBu$; **b**: R =H, R^1= 5-CH_3, R^2= $CO_2{}^tBu$; **c**: R = H, R^1= 5-OCH_3, R^2= $CO_2{}^tBu$; **d**: R =H, R^1= 5-Cl, R^2= $CO_2{}^tBu$; **e**: R =H, R^1= 5-F, R^2= $CO_2{}^tBu$; **f**: R =H, R^1=6-Cl, R^2= $CO_2{}^tBu$; **g**: R =H, R^1= 6-OCH_3, R^2= $CO_2{}^tBu$; **h**: R = R^1=H, R^2= CO_2Me



Scheme 57 Synthesis of spiro-tropanyl oxindoles **217**.

activity against two Gram-positive and three Gram-negative bacterial strains, and all the compounds exhibited moderate to potent antibacterial activity.[102]

Spiro[indoline-3,4′-pyrano[3,2-*b*]pyran]-3′-carbonitrile/carboxylate derivatives **213** were formed from a domino three-component reaction of active methylene compounds **211**, kojic acid **212**, and isatin derivatives **71** in aqueous ethanolic solution by employing secondary amine, L-proline (**119**), as a catalyst at ambient temperature (Scheme 56).[103]

An asymmetric tandem cycloisomerization and intramolecular [5 + 2] cycloaddition reaction of 2-ethynylphenyl substituted nitrones **214** with arylideneindolinones **110** by dual metallic relay catalysis was investigated by Feng's group (Scheme 57). The reaction comprises the palladium(II)-promoted *in situ* formation of the isoquinolinium salt **215** followed by the chiral *N*,*N*′-dioxide-Co(II) complex-catalyzed regio-, diastereo-, and enantio-selective [5 + 2] cycloaddition. The desired spiro-tropanyl oxindoles **217** (ref. 104) containing four contiguous chiral centers were produced in good yields. Generally, arylideneindolinones **110** bearing either electron-donating or electron-withdrawing groups at the 5- or 6-position provided good yields. Furthermore, electron-donating groups led to better diastereoselectivity. The synthetic potential of this catalytic system was confirmed by the gram-scale production of the products (Scheme 57).[104]

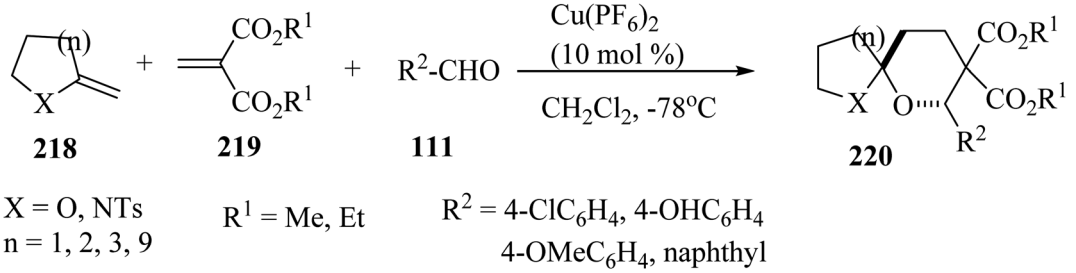
2.4. Synthesis of spiro pyran

Spiroketals **220** were synthesized in an excellent yield by the reaction of exocyclic enol ether **218**, methylene malonate (**219**), and aldehydes **111**. The reaction was carried out with 10 mol% of $Cu(PF_6)_2$ as a catalyst in dichloromethane (CH_2Cl_2) at −78 °C (Scheme 58).[105]

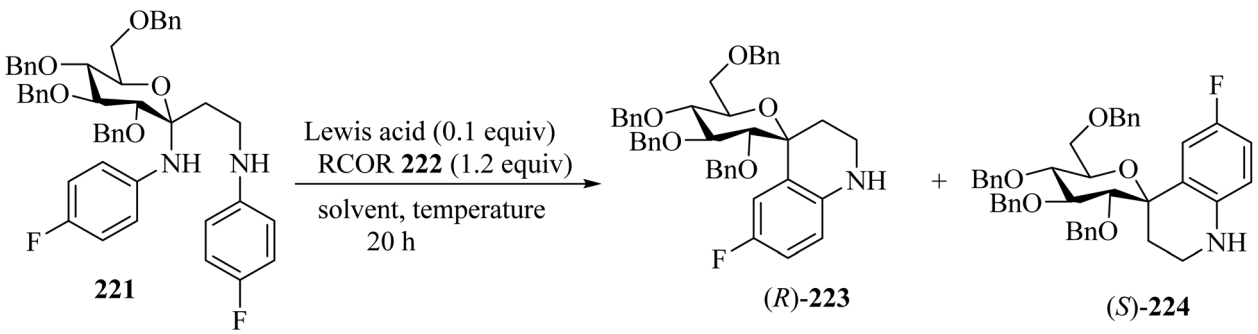
Mixing of *C*,*N*-glucoside **221** with benzophenones **222** in the presence of $InCl_3$ (0.1 equiv.) in dichloroethane (DCE) at 60 °C for 20 h resulted in the formation of spiro[pyran-4-quinoline] **223**/**224** in 59% yield as a mixture of diastereomers (ratio of (*R*)-**223**/(*S*)-**224** = 2.5/1). The reaction did not occur in the absence of benzophenone, indicating that the ketone is essential for promoting the elimination of *N*-aryl group (Scheme 59).[106]

For the synthesis of compound **231**, the cage dione **225** was treated with allyl magnesium bromide (**226**) in dry ether to deliver the diallyl cage diol **227** along with another hemiketal derivative **228** by transannular cyclization. Next, the cage diol **227**, on allylation with the NaH in the presence of allyl bromide (**229**) in dry DMF, gave the triallyl cage compound **230** (ref. 107) (Scheme 60). Subsequent, ring-closing metathesis of triallyl compound **230** with the Grubbs catalysts (or G-I catalysts) produced at room temperature condition, the cage derivative **231** (ref. 107) (Scheme 60). Grubbs catalysts[108] are a series of transition metal carbene complexes used as catalysts for olefin metathesis. Finally, hydrogenation of the compound **231** with hydrogen in the presence of 10% palladium on activated charcoal in dry EtOAc gave the saturated cage system **232** with a 90% yield (Scheme 60).[107]

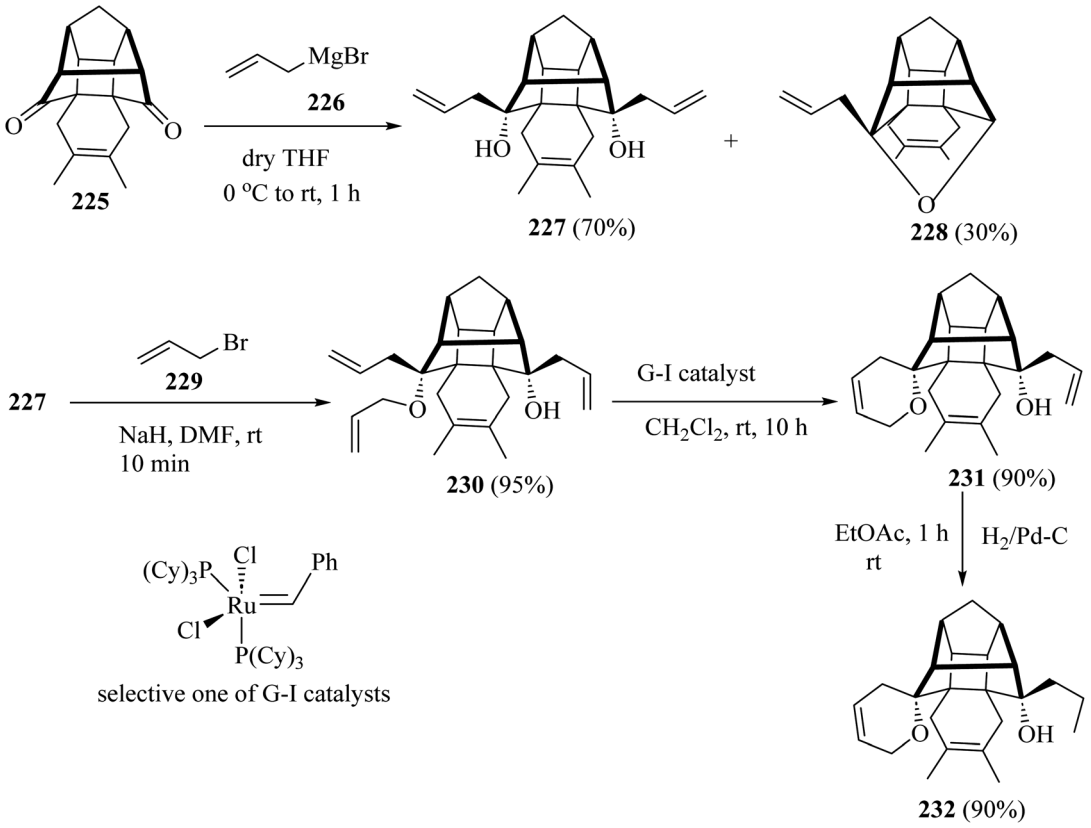
Several amino-substituted 2′-amino-6′-(hydroxymethyl)-8′-oxo-8′*H*-spiro[indeno[1,2-*b*]-quinoxaline-11,4′-pyrano[3,2-*b*]pyran]-3′-carbonitrile/carboxylate derivatives **233** were



Scheme 58 Synthesis of spiroketals **220**.



Scheme 59 Conversion of *C*,*N*-glycosides to spiro[pyran-4-quinolines] (*R*)-**223** and (*S*)-**224**.



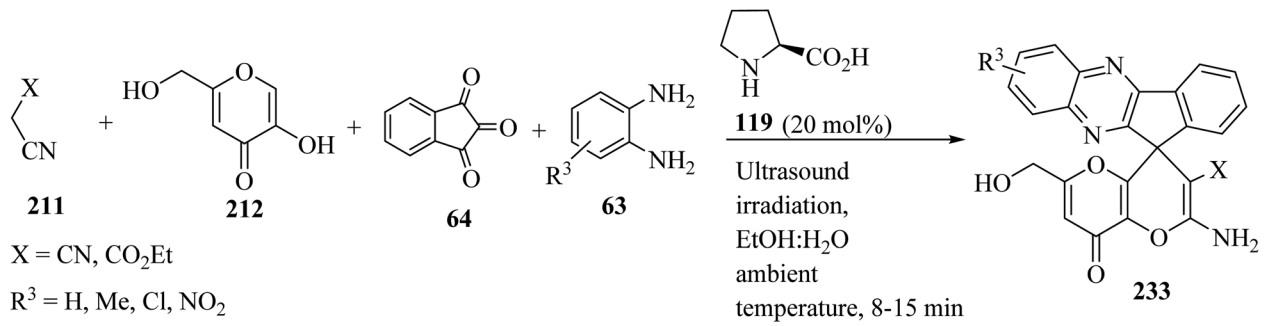
Scheme 60 Synthesis of spiro-pyrano-cage framework **231** and **232**.

synthesized *via* ultrasound-assisted organocatalytic domino, four-component reactions of active methylene compounds **211**, kojic acid (**212**), ninhydrin (**64**), and 1,2-diamines **63** in the presence of L-proline (**119**) in aqueous ethanolic solution at ambient temperature (Scheme 61).[103]

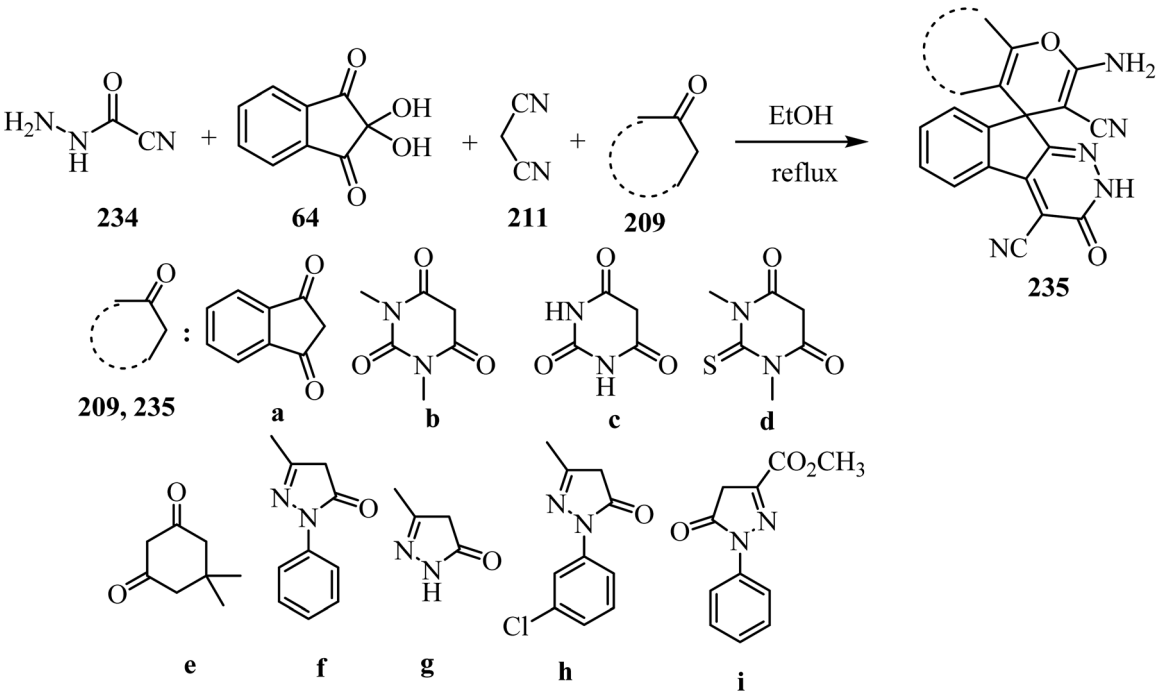
As shown in Scheme 62, spiro[indeno[2,1-*c*]pyridazine-9,4′-pyran]-3′,4′-dicarbonitrile derivatives **235** were synthesized by refluxing a mixture of cyanoacetohydrazide (**234**), ninhydrin (**64**), malononitrile (**211**) and various cyclic CH-acids **209** in EtOH under catalyst-free conditions in a one-pot procedure (Scheme 62).[109]

A proposed mechanism for the construction of spiroindenopyridazines **235** is shown in Scheme 63. Initially, condensation of cyanoacetohydrazide **234** and ninhydrin **64** leads to intermediate **236**, which undergoes intramolecular cyclization to give the corresponding indeno[2,1-*c*]pyridazine **237**. Subsequent addition of malononitrile **211** to indeno[2,1-*c*]pyridazine **237** affords intermediate **238**. Michael addition of CH-acid **209** to Knoevenagel adduct **238** leads to intermediate **239**, which undergoes keto–enol tautomerization followed by *O*-cyclization *via* nucleophilic addition of oxygen to a nitrile group to produce intermediate **240**. Finally, imine–enamine tautomerization of **240** afforded the desired structures **235**[109] (Scheme 63).

Oxa-Pictet–Spengler reaction between stoichiometric amounts of the nitroketone **241** with the indole derivatives **242**



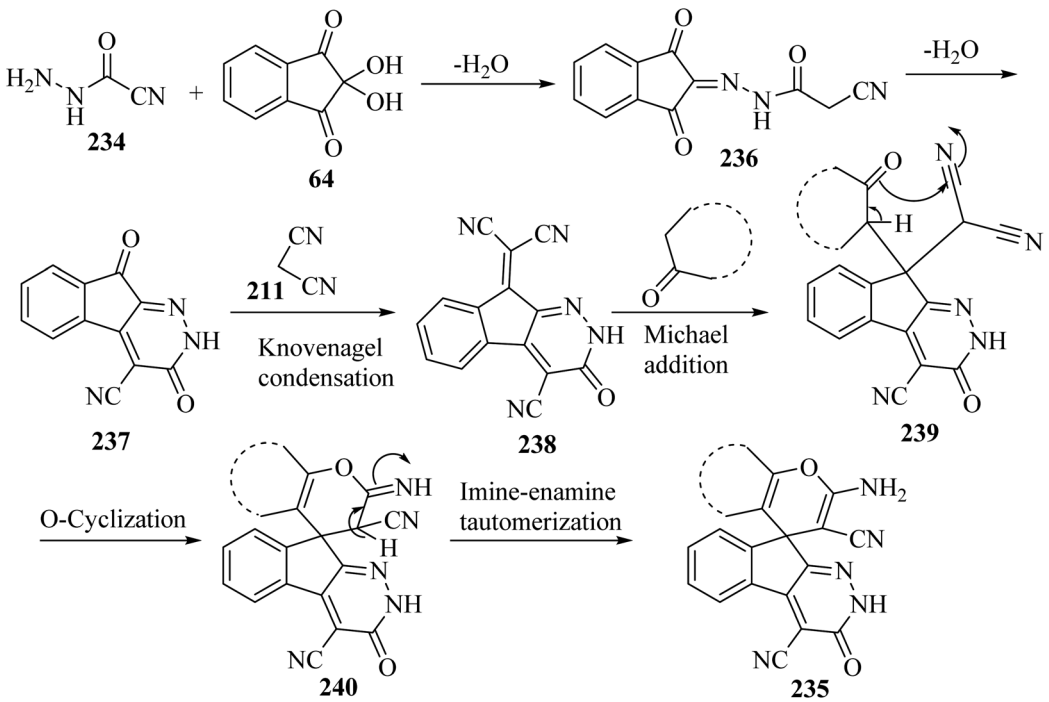
Scheme 61 Ultrasound-assisted organocatalytic domino synthesis of 2′-amino-6′-(hydroxymethyl)-8′-oxo-8′*H*-spiro[indeno[1,2-*b*]quinoxaline-11,4′-pyrano[3,2-*b*]pyran]-3′-carbonitrile/carboxylate derivatives **233**.



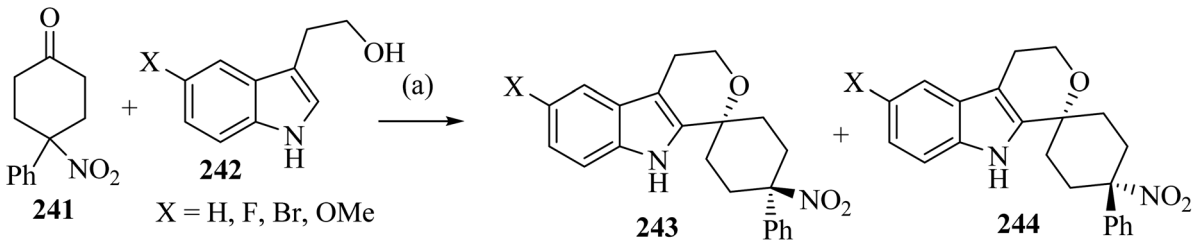
Scheme 62 Synthesis of spiroindenopyridazine-4*H*-pyran derivatives 235a–i.

in TFA–CH_2Cl_2 proceeded straightforwardly (Scheme 64).[110] In general, the *trans* diastereoisomers **243** were precipitated from the reaction mixture and were collected by filtration. The supernatants contained the *cis*-diastereo-isomers **244** together with residual amounts of the *trans*-isomers **243**, which were separated and purified by chromatography.[110]

Synthesis of spiro-pyran **246** [111] was established as shown in Scheme 64. The relative configuration of one representative was established by the *trans*-isomer **243**; it was subsequently submitted to the reduction of the nitro group with zinc to furnish the primary amine **245** (89%) (Scheme 65). Formic acid was chosen because it was also used in the next step, the

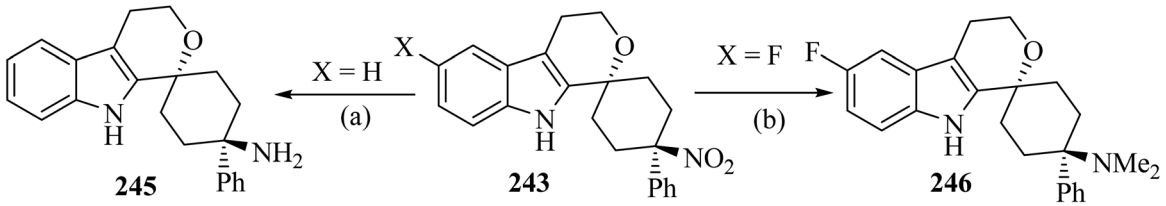


Scheme 63 Proposed mechanism for the formation of products 235.



(a) (1) 1.2 equiv of TFA, CH_2Cl_2, 50 °C,16 h.
(2) NaOH (1 mol/L in H_2O), 0 °C, 0.5 h.

Scheme 64 Spirocyclization by oxa-Pictet–Spengler reaction furnishing separable *trans*-isomers **243** and *cis*-isomers **244**.



(a) 40 equiv of Zn, 40 equiv of HCO_2H, CH_3OH, 50 °C, 16 h. **(b)** (1) As (a), (2) + 40 equiv of HCO_2H, 40 equiv of H_2CO (37% M in H_2O), 70 °C, 16 h.

Scheme 65 Synthesis of spiro-pyran **246**.

reductive amination with formaldehyde according to an Eschweiler–Clarke protocol,[112] which gave the corresponding dimethylamino derivative **246**.[111]

3. Conclusion

This review summarizes various methodologies used to synthesize spiro-azetidine-2-one, spiro-pyrrolidine, spiro-indol(one), and spiro-pyran compounds with enormous scope in pharmaceutics. During the past two decades, ample attention has gone into replacing the age-old methods associated with volatile solvents, harsh reaction conditions, and poor yield of products. New methods have been developed to mitigate these shortcomings as well as increase quantitative yields. In this review, new methods have been systematically catalogued for the convenience of readers. In addition, we focused light on some spots dealing with biological activity of the aforementioned spiro heterocycles.

Author contributions

M. B. Alshammari (writing and revision), A. A. Aly (conceptualization, writing, edit, revision, and submitting), A. Ahmed (editing), A. H. Mohamed (writing and editing), A. B. Brown (editing). All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors thank the Deanship of Scientific Research at Prince Sattam bin Abdulaziz University under research project No. 2021/01/18104. We also acknowledge support from the KIT-Publication Fund of the Karlsruhe Institute of Technology.

References

1 Y. Zheng, C. M. Tice and S. B. Singh, The use of spirocyclic scaffolds in drug discovery, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673–3682.
2 Y.-J. Zheng and C. M. Tice, The utilization of spirocyclic scaffolds in novel drug discovery, *Expert Opin. Drug Discovery*, 2016, **11**, 831–834.
3 K. I. Molvi, N. Haque, B. Z. S. Awen and M. Zameeruddin, Synthesis of spiro compounds as medicinal agents; New opportunities for drug design and discovery. Part I: A Review, *World J. Pharm. Pharm. Sci.*, 2014, **3**, 536–563.
4 L.-M. Zhou, R.-Y. Qu and G.-F. Yang, An overview of spirooxindole as a promising scaffold for novel drug discovery, *Expert Opin. Drug Discovery*, 2020, **15**, 603–625.
5 A. J. S. Alves, N. G. Alves, M. I. L. Soares and T. M. V. D. Pinho e Melo, Strategies and methodologies for the construction of spiro-γ-lactams: An update, *Org. Chem. Front.*, 2021, **8**, 3543–3593.
6 K. Acosta-Quiroga, C. Rojas-Pena, L. S. Nerio, M. Gutiérrez and E. Polo-Cuadrado, Spirocyclic derivatives as antioxidants: A review, *RSC Adv.*, 2021, **11**, 21926–21954.

7 A. J. Boddy and J. A. Bull, Stereoselective synthesis and applications of spirocyclic oxindoles, *Org. Chem. Front.*, 2021, **8**, 1026–1084.
8 *Vicinal Diaryl Substituted Heterocycles: A Gold Mine for the Discovery of Novel Therapeutic Agents*, ed. M. R. Yadav, P. R. Murumkar and R. B. Ghuge, Elsevier, 2018.
9 R. J. Shah, N. R. Modi, M. J. Patel, L. J. Patel, B. F. Chauhan and M. M. Patel, Design, synthesis and *in vitro* antibacterial and antifungal activities of some novel piro[azetidine- 2,3′-indole]-2,4(1′*H*)-dione, *Med. Chem. Res.*, 2011, **20**, 587–594.
10 P. Mondal and S. Mondal, Synthesis, characterization and SAR studies of Novel Series of Spiro *β*-Lactam of 5-methylindole-2,3-dione derivatives as a potential antibacterial and anthelmintic agent, *Curr. Chem. Lett.*, 2022, **11**, 403–414.
11 A. Jarrahpour, E. Ebrahimi, E. De Clercq, V. Sinou, C. Latour, L. Djouhri Bouktab and J. M. Brunel, Synthesis of mono-, bis-spiro- and dispiro-β-lactams and evaluation of their antimalarial activities, *Tetrahedron*, 2011, **67**, 8699–8704.
12 M. Esmaeilpour, A. R. Sardarian, A. Jarrahpour, E. Ebrahimi and J. Javidi, Synthesis and characterization of β-lactam functionalized superparamagnetic Fe_3O_4@SiO_2 nanoparticles as an approach for improvement of antibacterial activity of β-lactams, *RSC Adv.*, 2016, **6**, 43376–43387.
13 A. Bhalla, G. Modi, S. S. Bari, A. Kumari, S. Berry and G. Hundal, Stereoselective synthesis of novel C-3 functionalized 3-sulfonyl-β-lactams: Promising biologically active heterocyclic scaffolds, *Tetrahedron Lett.*, 2017, **58**, 1160–1165.
14 P. S. Sukhramani, P. S. Sukhramani, S. R. Tirthani, S. A. Desai and M. P. Suthar, Biological cytotoxicity evaluation of spiro[azetidine-2, 3'-indole]-2',4(1'*H*)-dione derivatives for anti-lung and anti-breast cancer activity, *Pharm. Lett.*, 2011, **3**, 236–243.
15 A. Bhalla, P. Venugopalan and S. S. Bari, A New Synthetic Approach to Novel Spiro-β- lactams, *Eur. J. Org Chem.*, 2006, 4943–4950.
16 B. S. Santos, S. C. C. Nunes, A. A. C. C. Pais and T. M. V. D. Pinho e Melo, Chiral spiro-β- lactams from 6-diazopenicillanates, *Tetrahedron*, 2012, **68**, 3729–3737.
17 B. S. Santos, C. S. B. Gomes and T. M. V. D. Pinho e Melo, Synthesis of chiral spiropyrazoline-β-lactams and spirocyclopropyl-β-lactams from 6-alkylidenepenicillanates, *Tetrahedron*, 2014, **70**, 3812–3821.
18 B. S. Santos and T. M. V. D. Pinho e Melo, Synthesis of chiral spirocyclopentenyl-β-lactams through phosphane-catalyzed [3+2] annulation of allenoates with 6-alkylidene-penicillanates, *Eur. J. Org Chem.*, 2013, 3901–3909.
19 G. Morrison, M. N. Asiedu, J. M. Priebe, J. Dunning, N. Ghoreishi-Haack, R. A. Kroes, M. S. Bowers, A. L. Barth, C. N. Cearley and J. R. Moskal, The NMDAR modulator NYX- 2925 alleviates neuropathic pain *via* a Srcdependent mechanism in the mPFC, *Neurobiol. Pain*, 2020, **7**, 100039.
20 A. El-Shazly and M. Wink, Diversity of pyrrolizidine alkaloids in the Boraginaceae: structures, distribution, and biological properties, *Diversity*, 2014, **6**, 188–282.
21 J. Robertson and K. Stevens, Pyrrolizidine alkaloids, *Nat. Prod. Rep.*, 2014, **31**, 1721–1788.
22 C. E. Puerto Galvis and V. V. Kouznetsov, Regio- and stereoselective synthesis of spirooxindole 1′-nitro pyrrolizidines with five concurrent stereocenters under aqueous medium and their bioprospection using the zebrafish (Danio rerio) embryo model, *Org. Biomol. Chem.*, 2013, **11**, 7372–7386.
23 R. J. Nash, A. A. Watson and N. Asano, in *Alkaloids: Chemical and Biological Perspectives*, Elsevier, 1996, vol. 11, pp. 345–376.
24 M. A. Abou-Gharbia and P. H. Doukas, Synthesis of tricyclic arylspiro compounds as potential antileukemic and anticonvulsant agents, *Heterocycles*, 1979, **12**, 637–640.
25 M. J. Kornet and A. P. Thio, Oxindole-3-spiropyrrolidines and -piperidines: Synthesis and local anesthetic activity, *J. Med. Chem.*, 1976, **19**, 892–898.
26 R. Schobert and A. Schlenk, Tetramic and tetronic acids: An update on new derivatives and biological aspects, *Bioorg. Med. Chem.*, 2008, **16**, 4203–4221.
27 J. Liu, C.-J. Li, Y.-Q. Du, L. Li, H. Sun, N.-H. Chen and D.-M. Zhang, Bioactive compounds from the stems of Clausena lansium, *Molecules*, 2017, **22**, 2226.
28 S.-f. Chu and J.-t. Zhang, Recent advances in the study of (–) clausenamide: chemistry, biological activities and mechanismof action, *Acta Pharm. Sin. B*, 2014, **4**, 417–423.
29 X. R. Tian, H. F. Tang, X. L. Tian, J. J. Hu, L. L. Huang and K. R Gustafson, Review of bioactive secondary metabolites from marine bryozoans in the progress of new drugs discovery, *Future Med. Chem.*, 2018, **10**, 1497–1514.
30 S. S. Panda, A. S. Girgis, M. N. Aziz and M. S. Bekheit, Spirooxindole: a versatile biologically active heterocyclic scaffold, *Molecules*, 2023, **28**, 618.
31 J. Bariwal, L. G. Voskressensky and E. V. Van der Eycken, Recent advances in spiro- cyclization of indole derivatives, *Chem. Soc. Rev.*, 2018, **47**, 3831–3848.
32 M. Sapnakumari, B. Narayana, K. S. Shashidhara and B. K. Sarojini, Multicomponent synthesis, biological evaluation and molecular docking of new spiro-oxindole derivatives, *J. Taibah Univ. Sci.*, 2017, **11**, 1008–1018.
33 S. Yagnam, A. M. Akondi, R. Trivedi, B. Rathod, R. S. Prakasham and B. Sridhar, Spirooxindole-fused pyrazolo pyridine derivatives: NiO–SiO2 catalyzed one-pot synthesis and antimicrobial activities, *Synth. Commun.*, 2018, **48**, 255–266.
34 L. Kortekaas and W. R. Browne, The evolution of spiropyran: fundamentals and progress of an extraordinarily versatile photochrome, *Chem. Soc. Rev.*, 2019, **48**, 3406–3424.
35 B. S. Lukyanov and M. B. Lukyanova, Spiropyrans: Synthesis, properties, and application, *Chem. Heterocycl. Compd.*, 2005, **41**, 281–311.
36 H. E. Prypsztejn and R. M. Negri, An experiment on photochromism and kinetics for the undergraduate laboratory, *J. Chem. Educ.*, 2001, **78**, 645–648.
37 G. Such, R. A. Evans, L. H. Yee and T. P. Davis, Factors influencing photochromism of spiro-compounds within

polymeric matrices, *J. Macromol. Sci., Part C*, 2003, **43**, 547–579.

38 A. K. Chibisov and H. Görner, Photochromism of spirobenzopyranindolines and spironaphthopyranindolines, *Phys. Chem. Chem. Phys.*, 2001, **3**, 424–431.

39 F. Maurel, J. Aubard, M. Rajzmann, R. Guglielmetti and A. Samat, A quantum chemical study of the ground state ring opening/closing of photochromic 1,3,3-trimethyl-spiro[indoline-2,3′-naphtho[2,1-*b*][1,4]oxazine], *J. Chem. Soc., Perkin Trans. 2*, 2002, 1307–1315.

40 C. Lenoble and R. S. Becker, Photophysics, photochemistry, kinetics, and mechanism of the photochromism of 6′-nitroindolinospiropyran, *J. Phys. Chem.*, 1986, **90**, 62–65.

41 M. Gehrtz, C. Bräuchle and J. Voitländer J, Photochromic forms of 6-nitrobenzo- spiropyran. Emission spectroscopic and ODMR investigations, *J. Am. Chem. Soc.*, 1982, **104**, 2094–2101.

42 L. D. Weis, T. R. Evans and P. A. Leermakers, Electronic spectra and photochemistry of adsorbed organic molecules. VI. Binding effects of silica as a mechanistic probe in systems of photochemical interest, *J. Am. Chem. Soc.*, 1968, **90**, 6109–6118.

43 H. Xia, K. Xie and G. Zou, Advances in spiropyrans/spirooxazines and applications based on fluorescence resonance energy transfer (FRET) with fluorescent materials, *Molecules*, 2017, **22**, 2236.

44 M. Ramadan, Y. A. M. M. Elshaier, A. A. Aly, M. Abdel-Aziz, H. M. Fathy, A. B. Brown, J. R. Pridgen, K. N. Dalby and T. S. Kaoud, Design and synthesis of 2′-amino-spiro[pyrano[3,2-c]quinoline]-3′-carbonitrile derivatives as ATP-non-competitive Src inhibitors that suppress breast cancer cell migration and proliferation, *Bioorg. Chem.*, 2021, **116**, 105344.

45 H. Staudinger, Ketenes. 1. Diphenylketene, *Adv. Cycloaddit.*, 1907, **356**, 51–123.

46 N. Fu and T. T. Tidwell, Preparation of β-lactams by [2+2] cycloaddition of ketenes and imines, *Tetrahedron*, 2008, **64**, 10465–10496.

47 L. Jiao, Y. Liang and J. Xu, Origin of the relative stereoselectivity of the β-lactam formation in the Staudinger reaction, *J. Am. Chem. Soc.*, 2006, **128**, 6060–6069.

48 C. Palomo, J. M. Aizpurua, I. Ganboa and M. Oiarbide, Asymmetric synthesis of β- lactams by Staudinger ketene-imine cycloaddition reaction, *Eur. J. Org Chem.*, 1999, 3223–3235.

49 R. Heiran, S. Sepehri, A. Jarrahpour, C. Digiorgio, H. Douafer, J. M. Brunel, A. Gholami, E. Riazimontazer and E. Turos, Synthesis, docking and evaluation of in vitro anti-inflammatory activity of novel morpholine capped β-lactam derivatives, *Bioorg. Chem.*, 2020, **102**, 104091.

50 A. A. Golubev, I. A. Smetanin, A. V Agafonova, N. V. Rostovskii, A. F. Khlebnikov, G. L. Starova and M. S. Novikov, [2 + 1 + 1] Assembly of spiro β-lactams by Rh(ii)- catalyzed reaction of diazocarbonyl compounds with azirines/isoxazoles, *Org. Biomol. Chem.*, 2019, **17**, 6821–6830.

51 J.-H. Jin, J. Zhao, W.-L. Yang and W.-P. Deng, Asymmetric synthesis of spirooxindole β-lactams *via* isothiourea-catalyzed Mannich/lactamization reaction of aryl acetic acids with isatin-derived ketimines, *Adv. Synth. Catal.*, 2019, **361**, 1592–1596.

52 N. F. Kirillov, E. A. Nikiforova, D. V Baibarodskikh, T. A. Zakharova and L. S. Govorushkin, Synthesis of new bis(spiro-β-lactams) *via* interaction of methyl 1-bromo-cycloalkanecarboxylates with zinc and *N,N′*-bis(arylmethylidene)benzidines, *J. Chem.*, 2019, 7496512.

53 L. Wallbaum, D. Weismann, D. Löber, C. Bruhn, P. Prochnow, J. E. Bandow and U. Siemeling, Stable and persistent acyclic diaminocarbenes with cycloalkyl substituents and their transformation to β-lactams by uncatalysed carbonylation with CO, *Chem.–Eur. J.*, 2019, **25**, 1488–1497.

54 Y. Fang, G. Liao, H. Guo, B. Yu and H.-M. Liu, Synthesis of biologically relevant steroidal spiro β-lactams from dienamides through the cascade 4-endo *N*- cyclization/aerobic oxidation sequence, *Steroids*, 2020, **159**, 108635.

55 Y. Nakane, A. Nakazaki and T. Nishikawa, Studies toward the synthesis of chartelline C, *J. Org. Chem.*, 2020, **85**, 7534–7542.

56 N. G. Alves, I. Bártolo, A. J. S. Alves, D. Fontinha, D. Francisco, S. M. M. Lopes, M. I. L. Soares, C. J. V. Simões, M. Prudêncio, N. Taveira and T. M. V. D. Pinho e Melo, Synthesis and structure-activity relationships of new chiral spiro-β-lactams highly active against HIV-1 and Plasmodium, *Eur. J. Med. Chem.*, 2021, **219**, 113439.

57 S.-Q. Luo, W. Liu, B.-F. Ruan, S.-L. Fan, H.-X. Zhu, W. Tao and H. Xiao, $P(NMe_2)_3$ mediated cyclopropanation of α-methylene-β-lactams for rapid syntheses of spirocyclopropyl β-lactams, *Org. Biomol. Chem.*, 2020, **18**, 4599–4603.

58 F. Golmohammadi, S. Balalaie, V. Fathi Vavsari, M. U. Anwar and A. Al-Harrasi, Synthesis of Spiro-β-lactam-pyrroloquinolines as Fused Heterocyclic Scaffolds through Post- transformation Reactions, *J. Org. Chem.*, 2020, **85**, 13141–13152.

59 N. Arumugam, A. I. Almansour, R. S. Kumar, V. S. Krishna, D. Sriram and R. Padmanaban, A stereo, regioselective synthesis and discovery of anti-mycobaterium tuberculosis activity of novel β-lactam grafted spirooxindolopyrrolidine hybrid heterocycles, *Arabian J. Chem.*, 2021, **14**, 102938.

60 M.-X. Zhao, Q. Liu, K.-M. Yu, X.-L. Zhao and M. Shi, Organocatalyzed asymmetric formal [3 + 2] cycloaddition of isocyanoacetates with N-itaconimides: facile access to optically active spiropyrroline succinimide derivatives, *Org. Chem. Front.*, 2019, **6**, 3879–3884.

61 N. Arumugam, A. I. Almansour, R. Suresh Kumar, S. Ibrahim Alaqeel, V. Siva Krishna and D. Sriram, Anti-tubercular activity of novel class of spiropyrrolidine tethered indenoquinoxaline heterocyclic hybrids, *Bioorg. Chem.*, 2020, **99**, 103799.

62 S. Boudriga, S. Haddad, M. Askri, A. Soldera, M. Knorr, C. Strohmann and C. Golz, Highly diastereoselective construction of novel dispiropyrrolo[2,1-*a*]isoquinoline derivatives *via* multicomponent 1,3-dipolar cycloaddition of cyclic diketones-based tetra- hydroisoquinolinium *N*-ylides, *RSC Adv.*, 2019, **9**, 11082–11091.

63 F. M. Moghaddam, A. Moafi, B. Jafari, A. Vilinger and P. Langer, Regio- and diastereoselective synthesis of novel polycyclic pyrrolo[2,1-*a*]isoquinolines bearing indeno[1,2-*b*]quinoxaline moieties by a three-component [3+2]-cycloaddition reaction, *Synlett*, 2020, **31**, 267–271.

64 S. Das, Recent applications of ninhydrin in multicomponent reactions, *RSC Adv.*, 2020, **10**, 18875–18906.

65 S. Das and A. Dutta, Ninhydrin adducts as valid synthon in organic synthesis: a review, *ChemistrySelect*, 2020, **5**, 11361–11377.

66 S. Das, P. Das, S. Maity, P. Ghosh and A. Dutta, Supramolecular self-assembly of structurally diversified ninhydrin-based molecules, *J. Mol. Struct.*, 2021, **1224**, 129033.

67 D. Liu, J. Sun, Y. Zhang and C.-G. Yan, Diastereoselective synthesis of spirocyclic isoxazolo[5,4-c]pyrrolo[2,1-a] isoquinolines via cascade double [3 + 2]cycloadditions, *Org. Biomol. Chem.*, 2019, **17**, 8008–8013.

68 J. Bariwal, L. G. Voskressensky and E. V. Van der Eycken, Recent advances in spiro- cyclization of indole derivatives, *Chem. Soc. Rev.*, 2018, **47**, 3831–3848.

69 J. Xu, L. Liang, H. Zheng, Y. R. Chi and R. Tong, Green oxidation of indoles using halide catalysis, *Nat. Commun.*, 2019, **10**, 4754.

70 R. Raju, R. Raghunathan, N. Arumugam, A. I. Almansour and R. S. Kumar, Regio- and stereoselective synthesis of novel β-lactam engrafted spiroheterocyclic hybrids *via* one- pot three component cycloaddition strategy, *Tetrahedron Lett.*, 2020, **61**, 152661.

71 T. Zha, X. Tong, Y. Deng, F. Peng and Z. Shao, Catalytic asymmetric and divergent synthesis of tricyclic and tetracyclic spirooxindoles: Controllable site-selective electrophilic halocyclization of 1,6-enynes, *Org. Lett.*, 2019, **21**, 6068–6073.

72 B. Ma, P. Wu, X. Wang, Z. Wang, H.-X. Lin and H.-X. Dai, Efficient synthesis of spirooxindole pyrrolones by a rhodium(III)-catalyzed C–H activation/carbene insertion/Lossen rearrangement sequence, *Angew. Chem., Int. Ed.*, 2019, **58**, 13335–13339.

73 S. Chen, G.-L. Wang, S.-W. Xu, M.-Y. Tian, M. Zhang, X.-L. Liu and W.-C. Yuan, Regio- and stereoselective [3 + 2] cycloaddition reaction: access to isoxazole-dispirobisoxindoles featuring three contiguous stereocenters, *Org. Biomol. Chem.*, 2019, **17**, 6551–6556.

74 Y. Huang, H.-L. Fang, Y.-X. Huang, J. Sun and C.-G. Yan, Synthesis of 7′- arylidenespiro[indoline-3,1′-pyrrolizines] and 7′-arylidenespiro[indene-2,1′-pyrrolizines] *via* [3 + 2] cycloaddition and β-C–H functionalized pyrrolidine, *J. Org. Chem.*, 2019, **84**, 12437–12451.

75 K. E. Treurne Balazs, M. Molnár, Z. Madarász and M. Nyerges, A facile synthesis of novel polycyclic spiropyrrolidine oxindoles incorporating the 1,3-dipolar cycloaddition of azomethine ylides, *Synth. Commun.*, 2020, **50**, 3245–3255.

76 V. D. Tripathi, A. K. Shukla and H. S. Mohammed, Regioselective three component domino synthesis of polyhydrospiro[indoline-3,3′-pyrrolizine]-2-one *via* [3+2] cycloaddition reaction, *Asian J. Chem.*, 2019, **31**, 613–616.

77 N. Satish Kumar, M. S. Reddy, V. R. Bheeram, S. B. Mukkamala, L. Raju Chowhan and L. Chandrasekhara Rao, Zinc oxide nanoparticles as efficient catalyst for the synthesis of novel di-spiroindolizidine bisoxindoles in aqueous medium, *Environ. Chem. Lett.*, 2019, **17**, 455–464.

78 A. I. Almansour, N. Arumugam, S. M. Soliman, B. S. Krishnamoorthy, J.-F. Halet, R. V. Priya, J. Suresh, D. M. Al-thamili, F. A. Al-aizari and R. S. Kumar, Stereoselective synthesis, structure and DFT studies on fluoro- and nitro- substituted spirooxindole-pyrrolidine heterocyclic hybrids, *J. Mol. Struct.*, 2021, **1237**, 130396.

79 C. Wang, D. Wen, H. Chen, Y. Deng, X. Liu, X. Liu, L. Wang, F. Gao, Y. Guo, M. Sun, K. Wang and W. Yan, The catalytic asymmetric synthesis of CF_3-containing spiro-oxindole–pyrrolidine–pyrazolone compounds through squaramide-catalyzed 1,3-dipolar cycloaddition, *Org. Biomol. Chem.*, 2019, **17**, 5514–5519.

80 A. Ghosh, S. Kolle, D. S. Barak, R. Kant and S. Batra, Multicomponent reaction for the synthesis of 5,6-dihydropyrrolo[2,1-*a*]isoquinolines, *ACS Omega*, 2019, **4**, 20854–20867.

81 R. S. Kumar, A. I. Almansour, N. Arumugam, D. Kotresha, T. S. Manohar and S. Venketesh, Cholinesterase inhibitory activity of highly functionalized fluorinated spiropyrrolidine heterocyclic hybrids, *Saudi J. Biol. Sci.*, 2021, **28**, 754–761.

82 K. Verma, Y. K. Tailor, S. Khandelwal, E. Rushell, M. Agarwal and M. Kumar, Efficient and environmentally sustainable domino protocol for the synthesis of diversified spiroheterocycles with privileged heterocyclic substructures using bio-organic catalyst in aqueous medium, *Mol. Diversity*, 2020, **24**, 1355–1365.

83 A. Barakat, M. S. Islam, H. M. Ghawas, A. M. Al-Majid, F. F. El-Senduny, F. A. Badria, Y. A. M. M. Elshaier and H. A. Ghabbour, Design and synthesis of new substituted spirooxindoles as potential inhibitors of the MDM2–p53 interaction, *Bioorg. Chem.*, 2019, **86**, 598–608.

84 Â. Monteiro, L. M. Gonçalves and M. M. M. Santos, Synthesis of novel spiropyrazoline oxindoles and evaluation of cytotoxicity in cancer cell lines, *Eur. J. Med. Chem.*, 2014, **79**, 266–272.

85 C. J. A. Ribeiro, R. C. Nunes, J. D. Amaral, L. M. Gonçalves, C. M. P. Rodrigues, R. Moreira and M. M. M. Santos, Spirotriazoline oxindoles: A novel chemical scaffold with *in vitro* anticancer properties, *Eur. J. Med. Chem.*, 2017, **140**, 494–509.

86 R. C. Nunes, C. J. A. Ribeiro, Â. Monteiro, C. M. P. Rodrigues, J. D. Amaral and M. M. M. Santos, *In vitro* targeting of colon cancer cells using spiropyrazoline oxindoles, *Eur. J. Med. Chem.*, 2017, **139**, 168–179.

87 T. S. Mokhtari, M. Seifi, V. Saheb and H. Sheibani, Polar [3 + 2] cycloaddition of isatin-3-imines with electrophilically activated heteroaromatic *N*-ylides: Synthesis of spirocyclic imidazo[1,2-*a*]pyridine and isoquinoline derivatives, *Arab. J. Chem.*, 2019, **12**, 2937–2942.

88 S. Muthusamy, A. Prabu and E. Suresh, Copper-catalyzed synthesis of spiro-indolofuro-benzopyrans: tandem reactions of diazoamides and *O*-propargyl salicylaldehydes, *Org. Biomol. Chem.*, 2019, **17**, 8088–8093.

89 H. Yazdani, S. Pardis, M. Loni and A. Bazgir, Gold nanoparticle as a Lewis acid catalyst in 1,3-dipolar cycloaddition reaction, *Catal. Commun.*, 2020, **134**, 105844.

90 H. Li, G. Li, B. A. Berg and W. Yang, Finite reservoir replica exchange to enhance canonical sampling in rugged energy surfaces, *J. Chem. Phys.*, 2006, **125**, 144902.

91 Z. Chang, C. Ye, J. Fu, P. Chigumbu, X. Zeng, Y. Wang, C. Jiang and X. Han, Enantioselective synthesis of oxindole-derived α-aryl-β-amino acid derivatives and δ-Lactams with homophthalic anhydrides, *Adv. Synth. Catal.*, 2019, **361**, 5516–5520.

92 C. He, Z. Li, J. Xu and H. Ren, Asymmetric synthesis of spirocyclic oxindole δ-Lactams *via* NHC-catalyzed formal [2+4] annulation of aliphatic aldehydes with oxindole-derived *α,*β-unsaturated ketimines, *J. Org. Chem.*, 2019, **84**, 12177–12186.

93 N. G. Alves, A. J. S. Alves, M. I. L. Soares and T. M. V. D. Pinho e Melo, Recent advances in the synthesis of spiro-β-lactams and spiro-δ-lactams, *Adv. Synth. Catal.*, 2021, **363**, 2464–2501.

94 J. George, H. Y. Kim and K. Oh, Cooperative Pd/Cu catalysis to spiro[indoline-2,3′-pyrrolidin]-2′-ones: Tandem benzylation of α-isocyano lactams, amine addition, and *N*-arylation, *Org. Lett.*, 2019, **21**, 5747–5752.

95 G. Pan, C. He, M. Chen, Q. Xiong, W. Cao and X. Feng, Synthesis of dihydroisoquinoline and dihydropyridine derivatives *via* asymmetric dearomative three-component reaction, *CCS Chem.*, 2022, **4**, 2000–2008.

96 S. Khojasteh-Khosro and H. Shahbazi-Alavi, Preparation of spirooxindoles catalyzed by nano-Co_3S_4 under microwave irradiations, *J. Chem. Res.*, 2019, **43**, 107–111.

97 C. Wu, J. Liu, D. Kui, Y. Lemao, X. Yingjie, X. Luo, X. Meiyang and R. Shen, Efficient multicomponent synthesis of spirooxindole derivatives catalyzed by copper triflate, *Polycyclic Aromat. Compd.*, 2022, **42**, 277–289.

98 R. Mishra, A. Jana, A. K. Panday and L. H. Choudhury, Synthesis of spirooxindoles fused with pyrazolo-tetrahydropyridinone and coumarin-dihydropyridine-pyrazole tetracycles by reaction medium dependent isatin-based multicomponent reactions, *New J. Chem.*, 2019, **43**, 2920–2932.

99 V. D. Tripathi, β-Cyclodextrin mediated multicomponent synthesis of spiroindole derivatives in aqueous medium, *Asian J. Chem.*, 2020, **32**, 293–296.

100 A. H. Mohamed, M. B. Alshammari, E. M. El-Sheref and A. A. Aly, Novel series of dihydroquinolindihydro-spiro [indoline-3,6'-[1,3]thiazine]-5′-carbonitrile derivatives, *J. Mol. Struct.*, 2020, **1219**, 128618.

101 Saigal, S. Khan, H. Rahman, Shafiullah and M. M. Khan, Nitroketene N,S-acetals: synergistic building blocks for the synthesis of heterocycles, *RSC Adv.*, 2019, **9**, 14477–14502.

102 Saigal, M. Irfan, P. Khan, M. Abid and M. M. Khan, Design, synthesis, and biological evaluation of novel fused spiro-4*H*-pyran derivatives as bacterial biofilm disruptor, *ACS Omega*, 2019, **4**, 16794–16807.

103 B. Borah, J. Bora, P. Ramesh and L. R. Chowhan, Sonochemistry in an organocatalytic domino reaction: an expedient multicomponent access to structurally functionalized dihydropyrano[3,2-*b*]pyrans, spiro-pyrano [3,2-*b*]pyrans, and spiro-indenoquinoxaline-pyranopyrans under ambient conditions, *RSC Adv.*, 2022, **12**, 12843–12857.

104 B. Hu, X. Zhang, Y. Mo, J. Li, L. Lin, X. Liu and X. Feng, Catalytic asymmetric tandem cycloisomerization [5+2] cycloaddition reaction of *N*-aryl nitrone alkynes with methylene-indolinones, *Org. Lett.*, 2020, **22**, 1034–1039.

105 L. Zhou, S.-Y. Yu, Y. Tang and L. Wang, Facile stereoselective approach to diverse spiroheterocyclic tetrahydropyrans: concise synthesis of (+)-broussonetine G and H, *Angew. Chem., Int. Ed.*, 2019, **58**, 15016–15020.

106 P.-Y. Chen, Y.-T. Chiang, M.-T. Hsieh, Y.-C. Hseu, C.-H. Lin and H.-C. Lin, Expeditious and stereoselective synthesis of (1*S*)-spiro[pyran-4-quinolines], *Eur. J. Org Chem.*, 2022, e202201116.

107 S. Kotha, M. Salman and S. R. Cheekatla, Synthesis of pentacycloundecane (PCUD) based spiro-pyrano-cage framework via ring-closing metathesis, *Molbank*, 2023, M1567.

108 R. H. Grubbs, *Handbook of Metathesis*, Wiley-VCH, Weinheim, 1st edn, 2003, ISBN 978-3-527-30616-9.

109 F. Safari, H. Hosseini, M. Bayat and A. Ranjbar, Synthesis and evaluation of antimicrobial activity, cytotoxic and pro-apoptotic effects of novel spiro-4*H*-pyran derivatives, *RSC Adv.*, 2019, **9**, 24843–24851.

110 K. R. Campos, J. C. S. Woo, S. Lee and R. D. Tillyer, A General synthesis of substituted indoles from cyclic enol ethers and enol lactones, *Org. Lett.*, 2004, **6**, 79–82.

111 D. Wachtendorf, M. Schmidtmann and J. Christoffers, Improved and flexible synthetic access to the spiroindole backbone of cebranopadol, *Org. Lett.*, 2020, **22**, 6420–6423.

112 C. Zhao, S. B. Chen and D. Seidel, Direct formation of oxocarbenium ions under weakly acidic conditions: catalytic enantioselective oxa-Pictet–Spengler reactions, *J. Am. Chem. Soc.*, 2016, **138**, 9053–9056.