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

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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 $\mu\text{g mL}^{-1}$. 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*

Spiro- β -lactams (Spiroazetidin-2-ones)

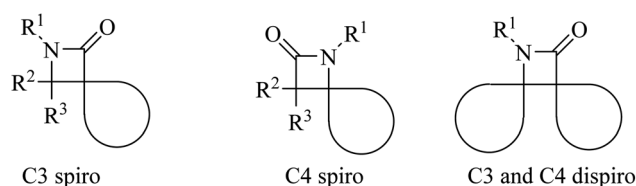


Fig. 1 Different structures of spiroazetidin-2-ones.

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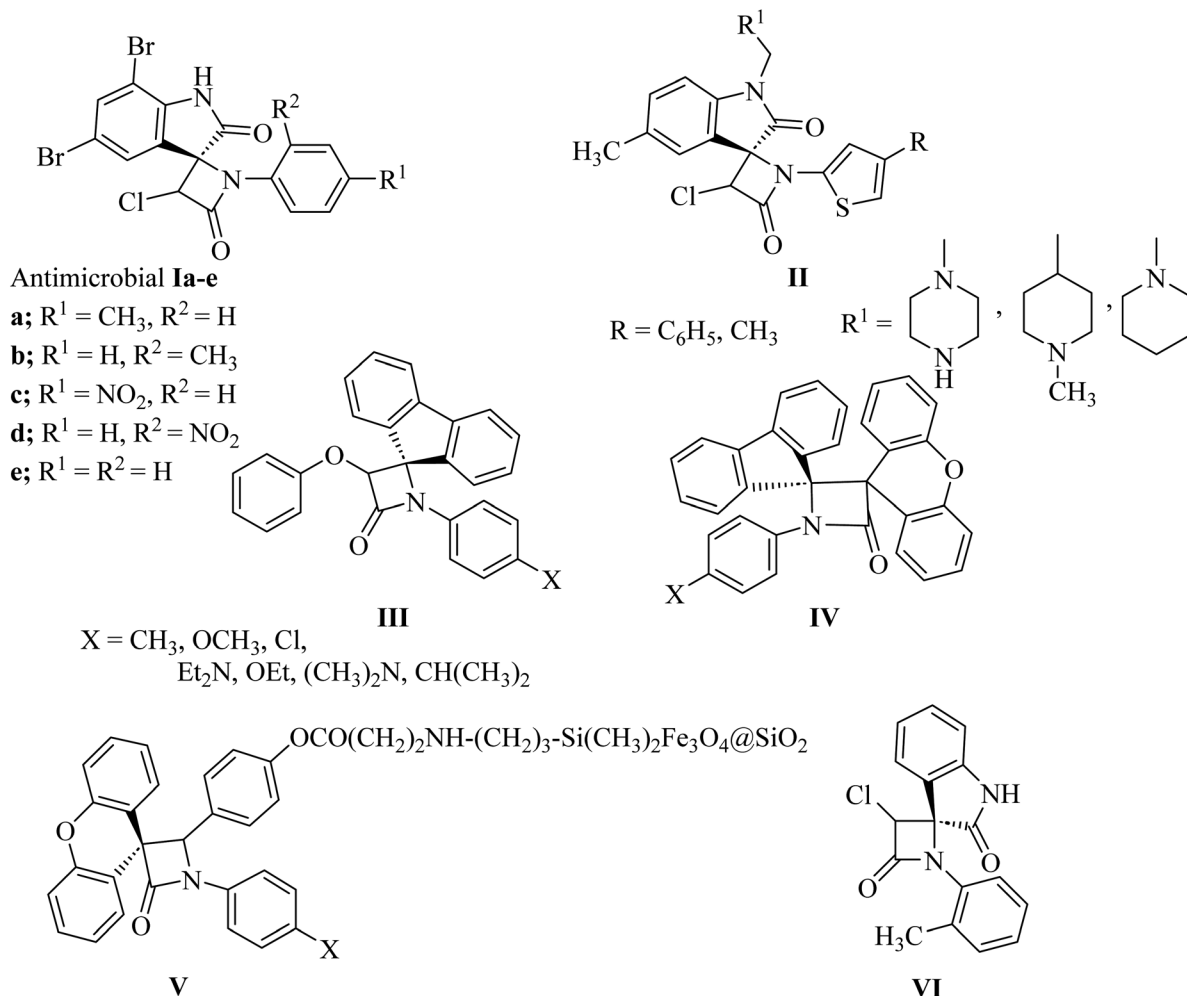


Fig. 2 Biologically active spiro azetidin-2-one derivatives I–VI.

K14 strain with IC_{50} varying from 5 to 32.2 mM.¹¹ The spirocyclic β -lactam **V** (Fig. 2), supported on superparamagnetic $\text{Fe}_3\text{O}_4@\text{SiO}_2$ 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 $\text{Fe}_3\text{O}_4@\text{SiO}_2/\beta$ -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 ($\text{IC}_{50} = 22.75\text{--}25.18 \mu\text{M}$) 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 **IV**,^{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 casuarina²³ (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 (**XIV**) showed microtubule assembly inhibition, whereas pteropodine (**XX**) and isopteropodine (**XXI**) damped the operation of muscarinic serotonin receptors (Fig. 6).^{32,33}

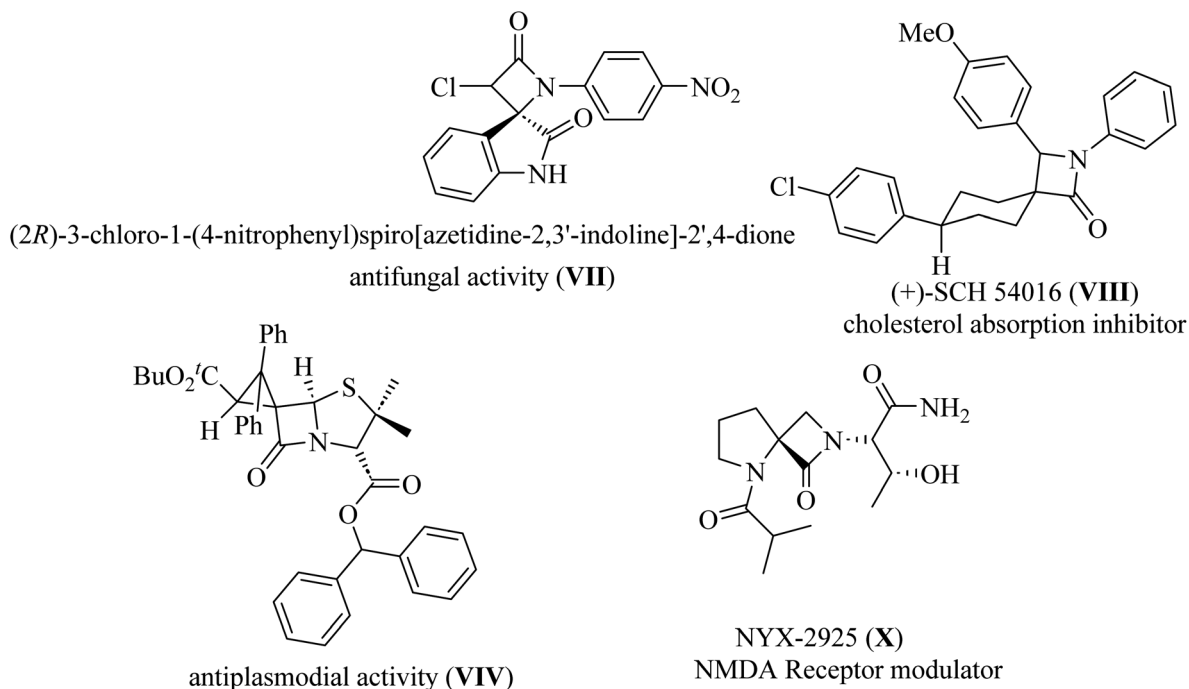


Fig. 3 Representative examples of biologically active spiro cyclic β -lactam VII–X.

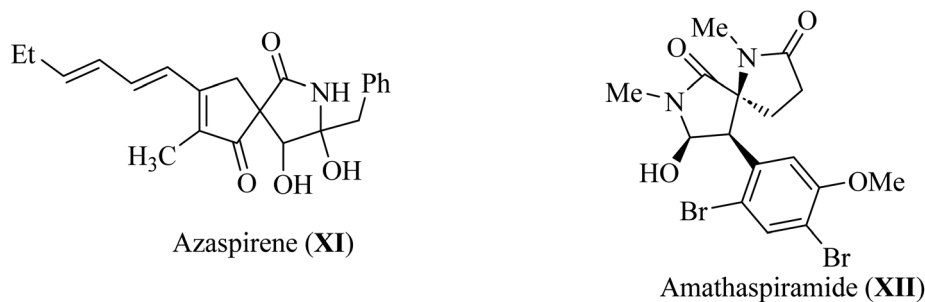


Fig. 4 Alkaloids naturally occurring pyrrolidin-2-ones XI–XII.

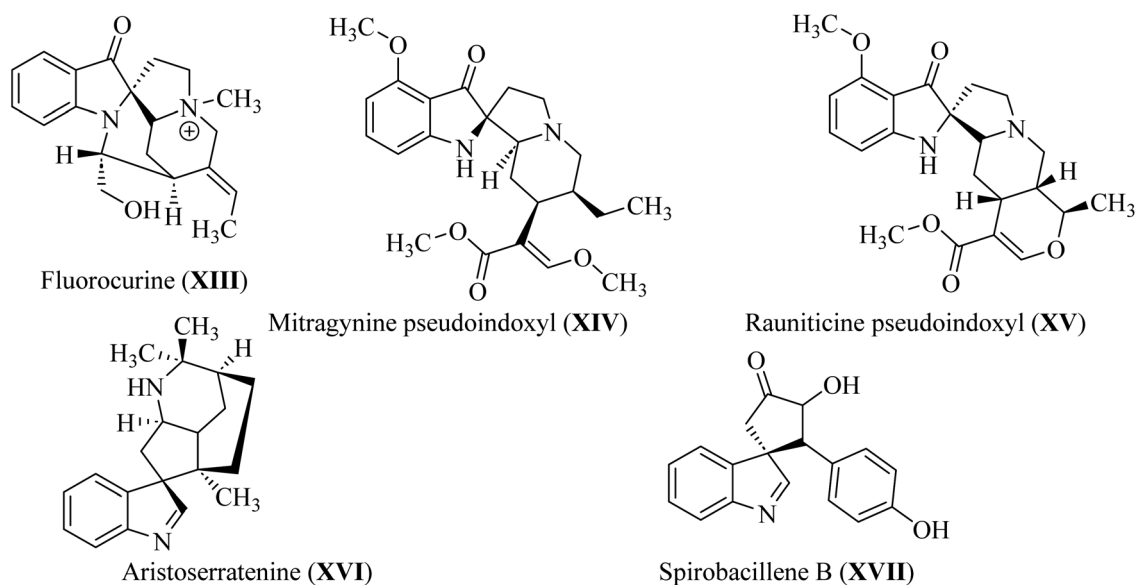


Fig. 5 Natural C-2 and C-3 spiroindol and spiroindol(one) containing compounds XIII–XVII.



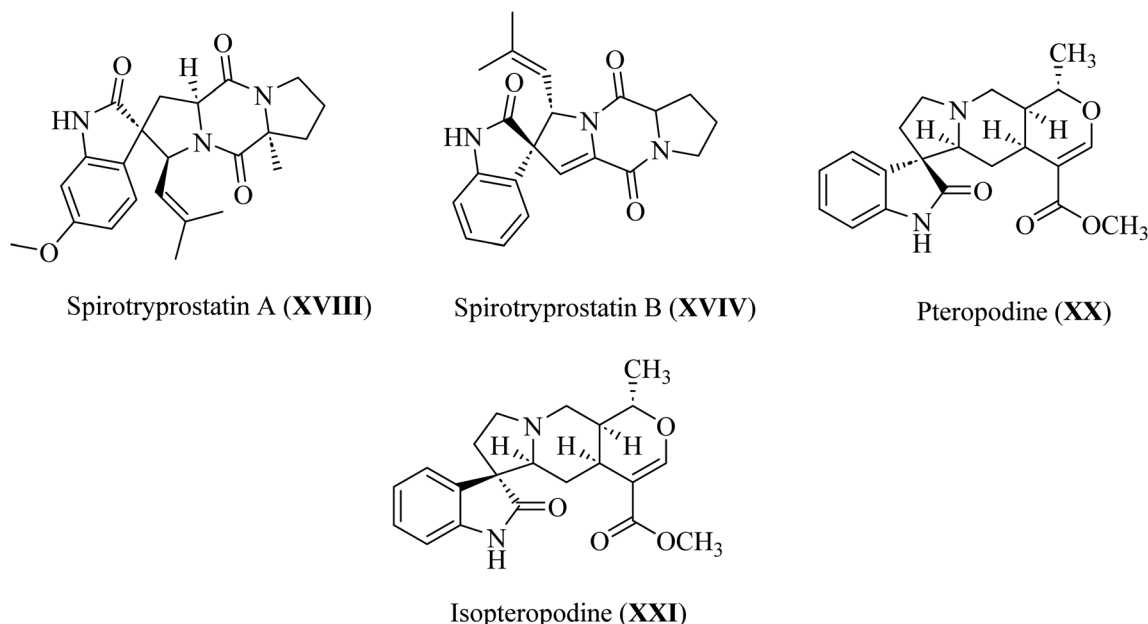


Fig. 6 Selected pharmaceutical structures containing spiro indol(one) scaffolds XVIII–XXI.

1.4. Spiro-pyran derivatives

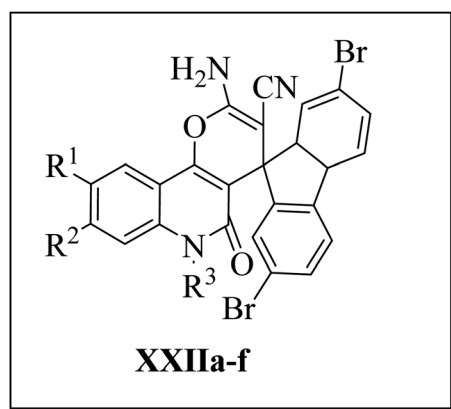
Spiropyrans were discovered in the early twentieth century.³⁴ In the 1920s, Fisher and Hirshberg observed their photochromic characteristics and reversible reaction.³⁴ Studies on photochromic compounds that have continued up to the present.^{35,36}

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 IC₅₀'s of 4.9, 5.9, and 0.9 μ M, 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 Src tyrosine phosphorylation by **XXIId** revealed a mechanism of ATP-non-competitive inhibition. 1 μ M 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:** R¹ = R² = R³ = H
- b:** R¹ = Cl, R² = R³ = H
- c:** R¹ = CH₃, R² = R³ = H
- d:** R¹ = R³ = H, R² = CH₃
- e:** R¹ = Br, R² = R³ = H
- f:** R¹ = OCH₃, R² = R³ = 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

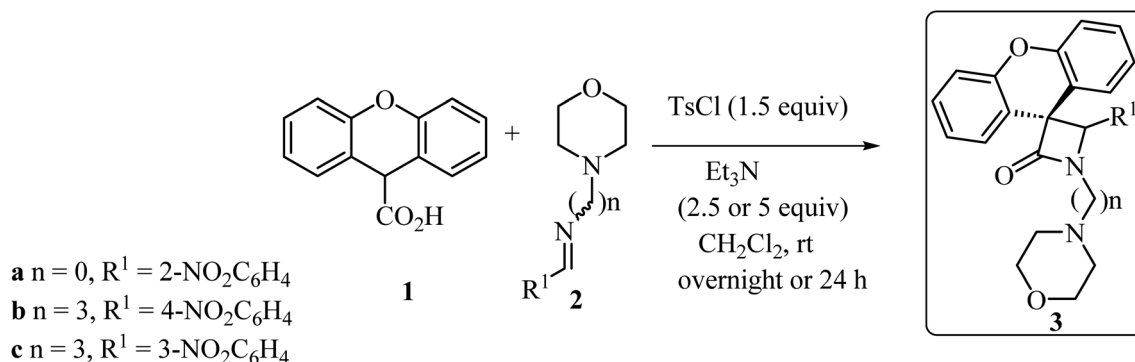
With the discovery and structural elucidation of the antibiotic penicillin, the Staudinger synthesis became of major importance in medicinal chemistry, as it allowed the synthesis of penicillin derivatives in the laboratory. Although several alternative methods have been developed, the Staudinger reaction 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 (Et₃N) in dichloromethane (CH₂Cl₂).

In 2019, Novikov and co-workers⁵⁰ 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 Rh₂(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).

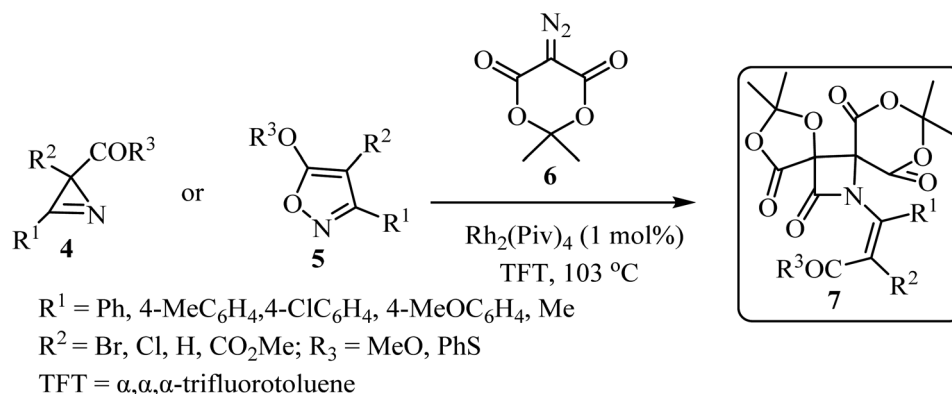
Concerning the reaction mechanism, the rhodium carbenoid **8** obtained from the Meldrum's acid derived diazo-compound **6**, adds to the azirines **4** or isoxazoles **5** forming adducts **9** or **12**, respectively (Scheme 3). Both pathways lead to the same 2-azabuta-1,3-diene **13** product. A parallel 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

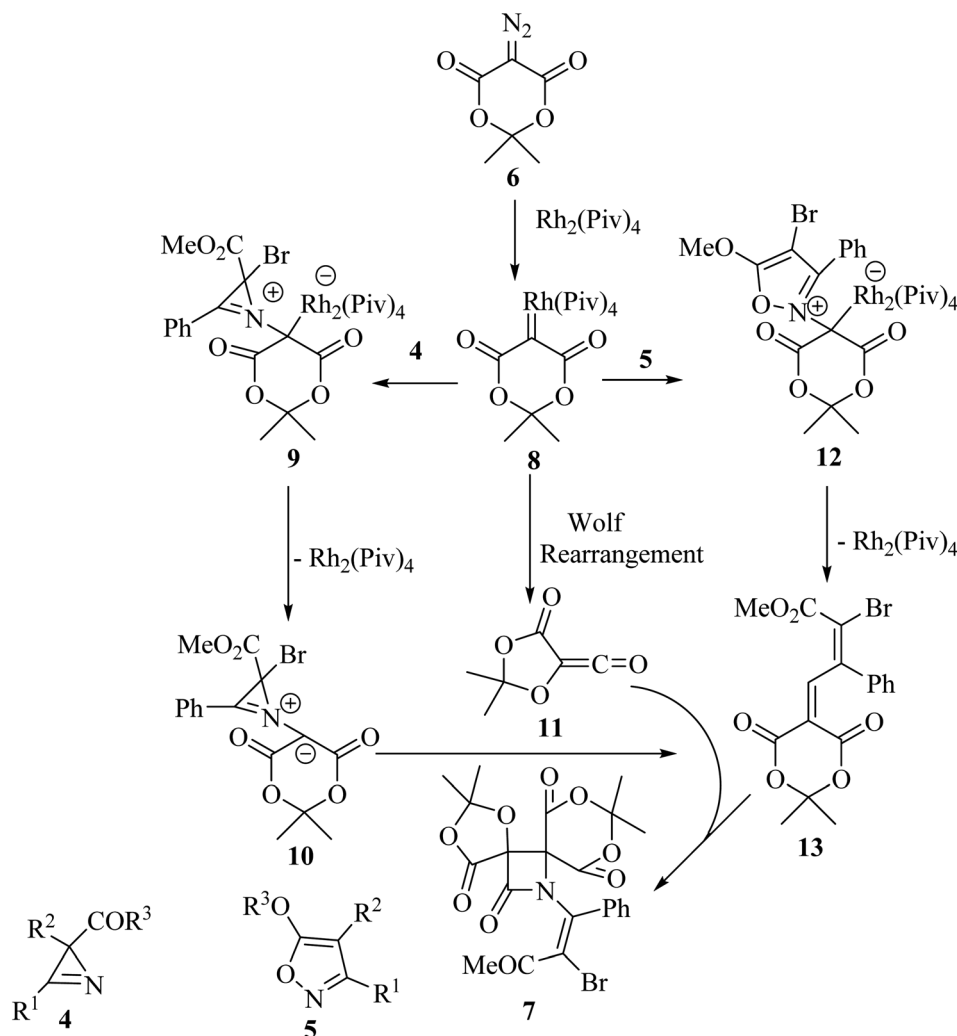
Concerning the proposed reaction mechanism,⁵¹ the first step of the reaction involves a reaction between the aryl acetic acid **15** and pivaloyl chloride which generates a mixed anhydride **18**, responsible for the HBTM acylation which afforded intermediate **19** (Scheme 5). Deprotonation of intermediate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



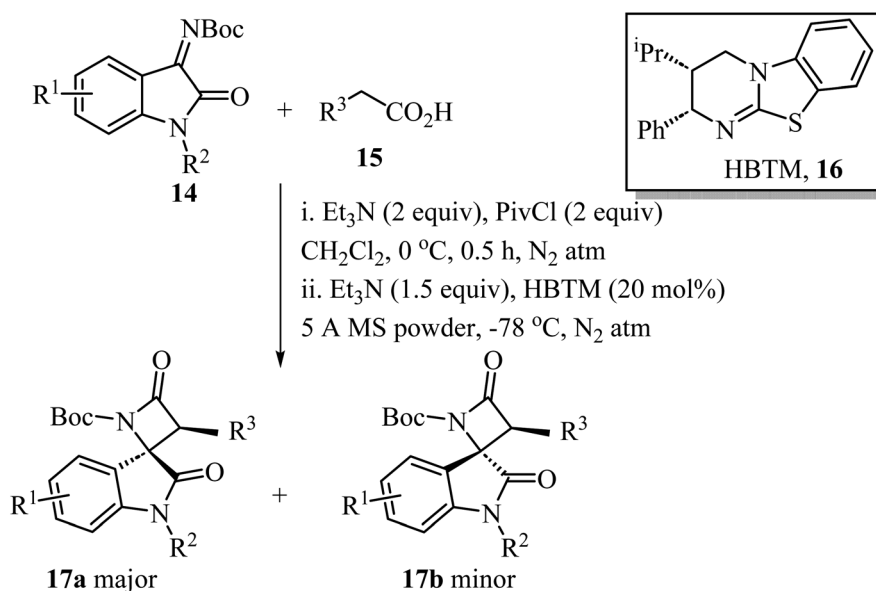
Scheme 1 Staudinger synthesis of spiro- β -lactams **3** containing the xanthene moiety.

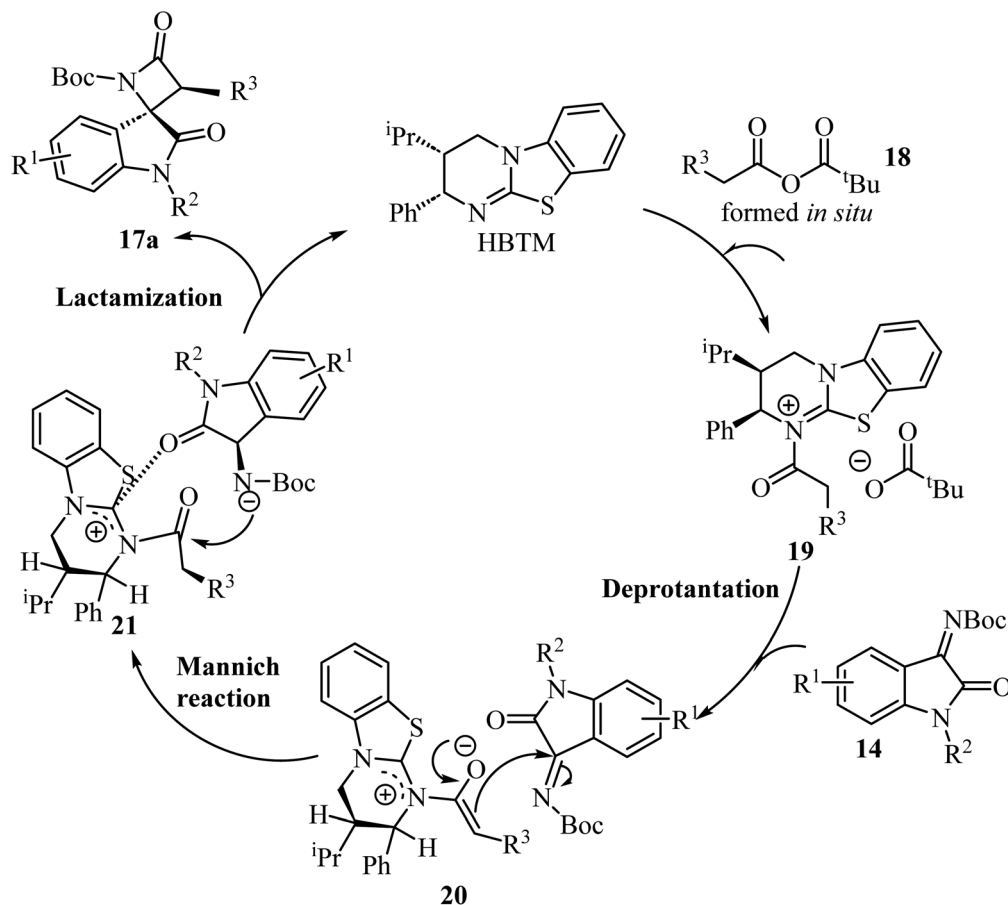


Scheme 2 Synthesis of dispirocyclic *N*-vinyl- β -lactam **7** from diazo Meldrum's acids (**6**) and 2*H*-azirines or 5-alkoxyisoxazoles **5**.



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**.



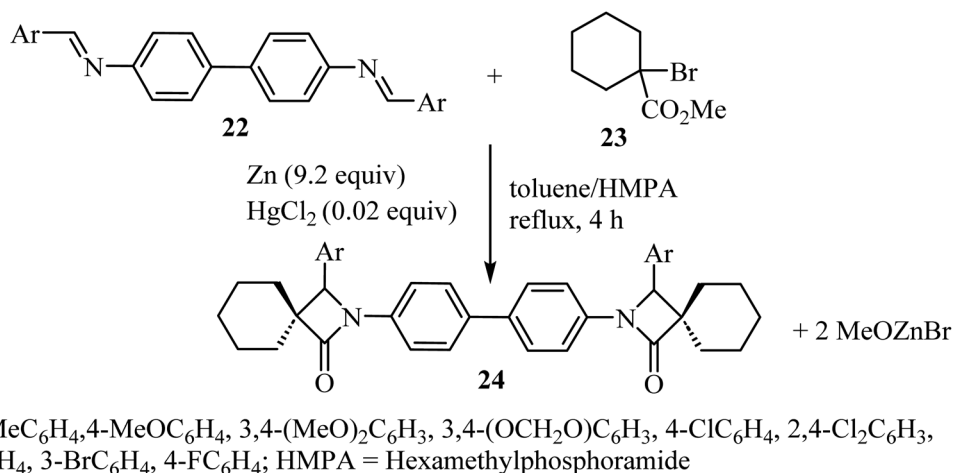
Scheme 5 A plausible mechanism for the formation of 17a.

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-

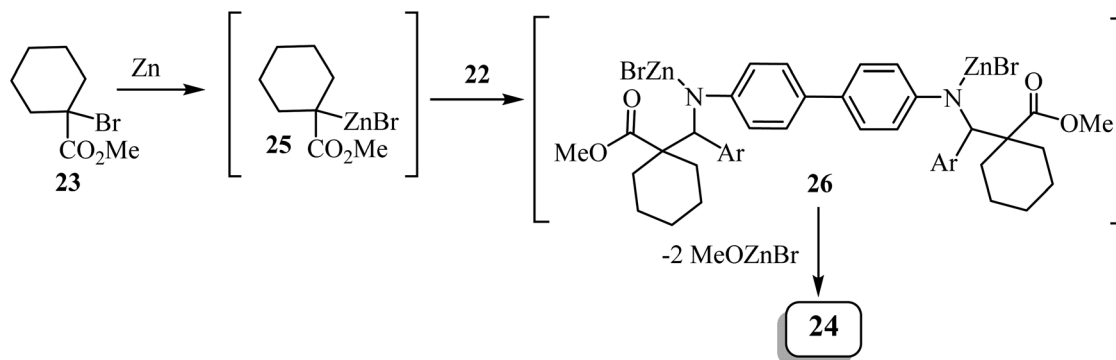
bromo-cyclohexanecarboxylate (23) and *N,N*-bis-(arylmethylidene)benzidines 22 as the first step (Scheme 6).⁵²

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



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





Scheme 7 Rationale for the formation of compound 24.

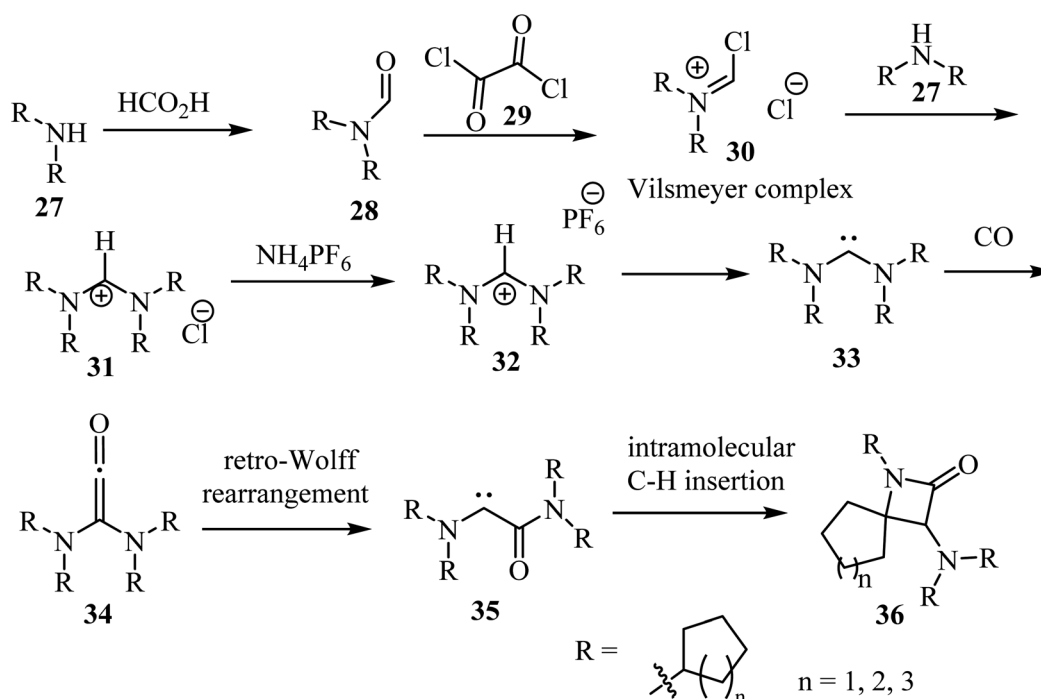
with elimination of bromo-zinc methoxide. Bis(spiro- β -lactams) **24** were isolated in good yields (69–84%) (Scheme 7). The reaction was also expanded to synthesize nine spiro-cyclopentane-containing β -lactams by using methyl 1-bromocyclopentanecarboxylate as the starting carboxylate, in yields ranging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

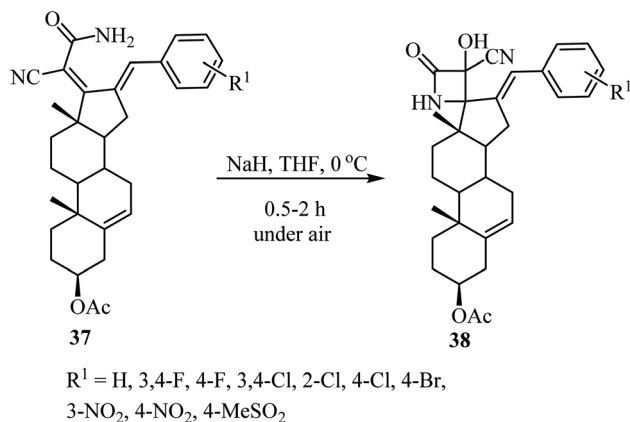
Siemeling *et al.*,⁵³ reported a metal-free synthesis of racemic spiro- β -lactam derivatives **36** by exploring the reactivity of acyclic diaminocarbenes **33**, containing cycloalkyl substituents and using carbon monoxide as building block (Scheme 8). Compounds **33** were synthesized from secondary 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 $\text{NaN}(\text{SiMe}_3)_2$. 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

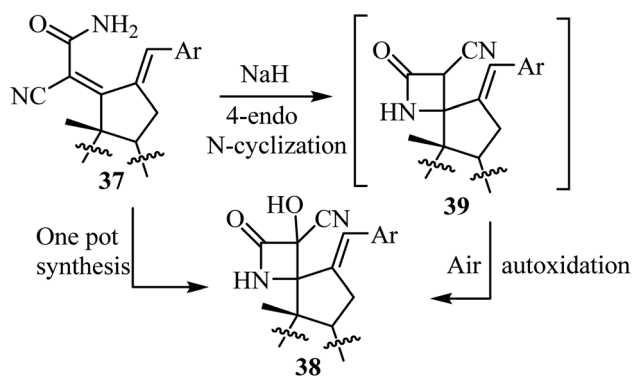
The proposed mechanism involves an intramolecular lactamization of steroidal dienamides **37** *via* a selective 4-*endo* *N*-

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).



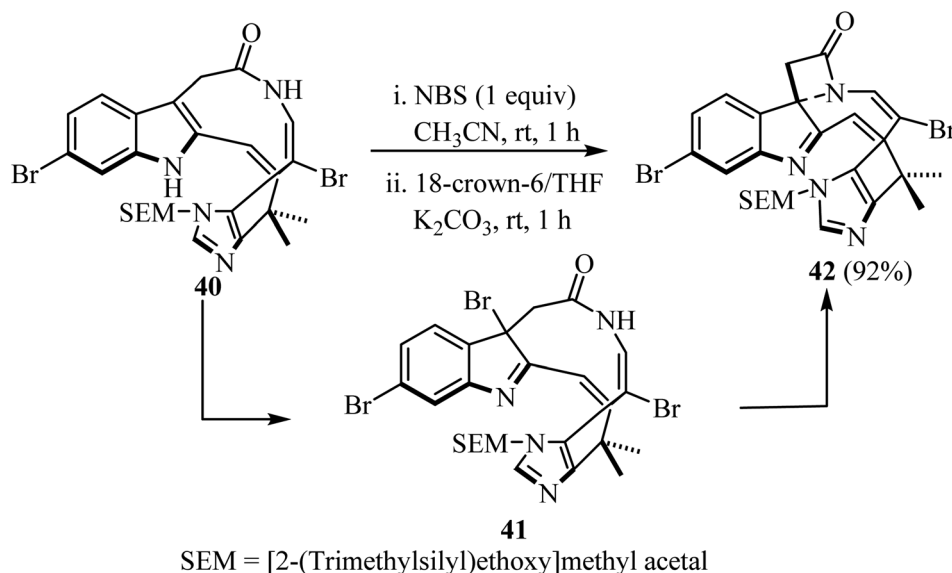
Scheme 10 Plausible mechanism for the formation of compound **38**.

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 $\text{K}_2\text{CO}_3/\text{CH}_3\text{CN}$. 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 nitron 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**.

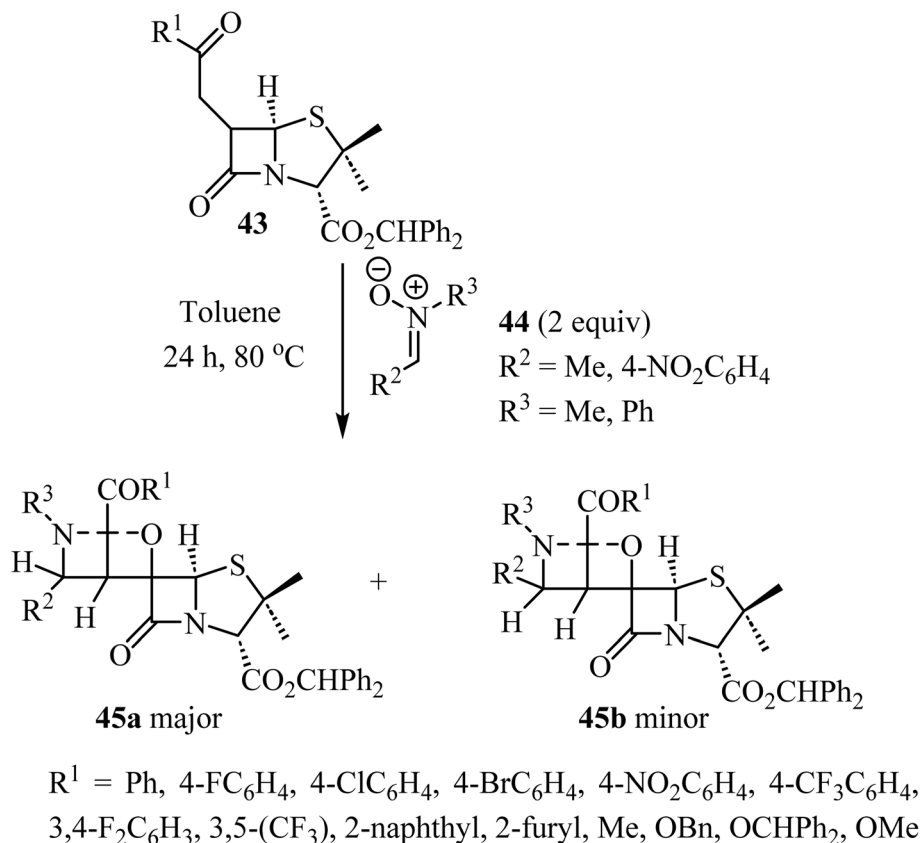
Recently Luo *et al.* reported a phosphine-mediated reductive cyclopropanation reaction of α -keto esters **46** with α -methylene- β -lactams **47** (Scheme 13).⁵⁷ That metal-free protocol provided the efficient *syn* synthesis of highly functionalized spirocyclopropyl β -lactams **48** through a mechanism 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 spirocyclization of a bromoenamide.





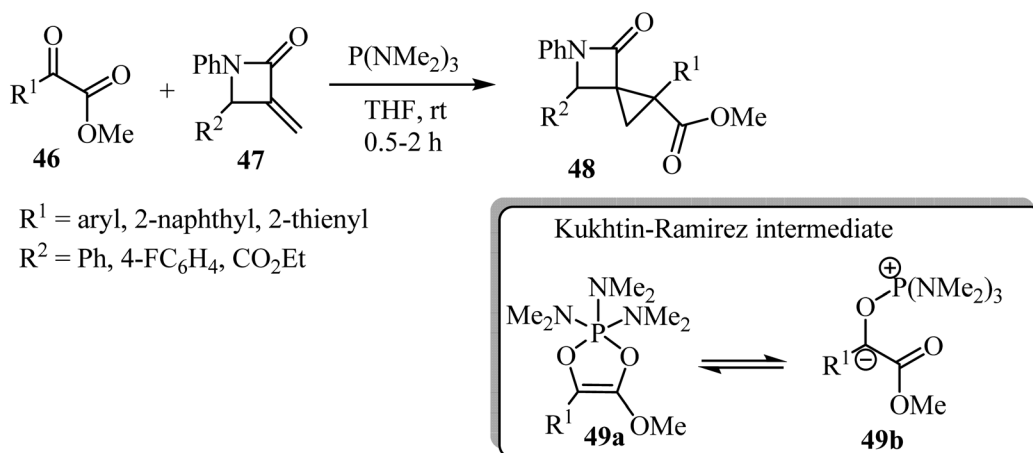
Scheme 12 1,3-Dipolar cycloaddition between 6-alkylidene penicillanates **43** and nitrones **44**.

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

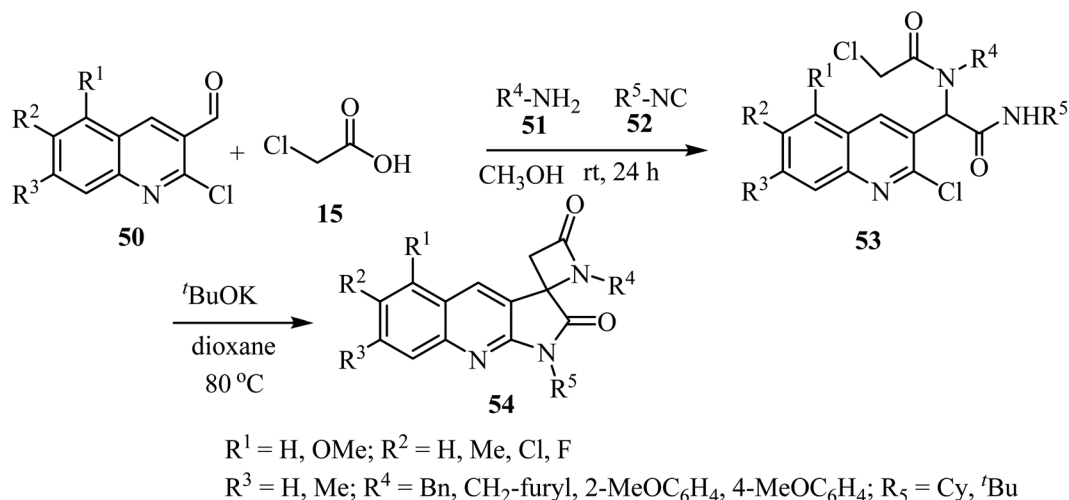
by formation of the β -lactam ring through a nucleophilic acyl substitution.⁵⁸

2.2. Synthesis of spiro pyrrolidine derivatives

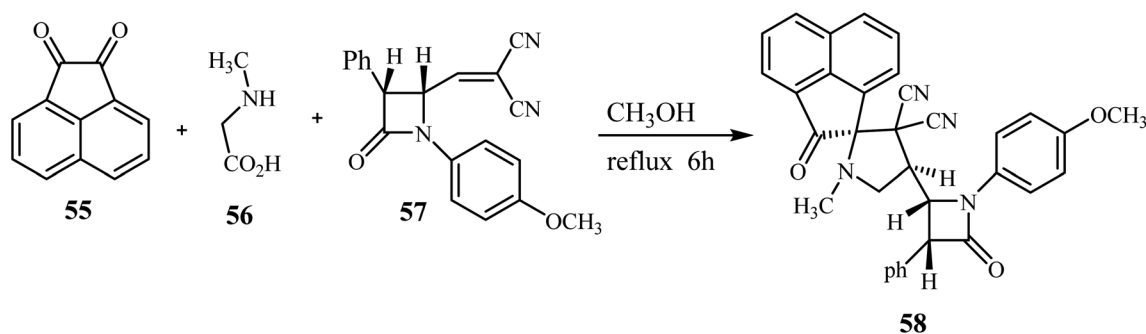
The azomethine ylide generated *in situ* by the condensation of acenaphthenequinone (**55**) with sarcosine (**56**) underwent smooth cycloaddition reaction with **57** regio- and stereo-selectively in refluxing CH_3OH for 6 h affording exclusively the single diastereomer **58** in excellent yield (Scheme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



Scheme 13 $\text{P(NMe}_2)_3$ -mediated cyclopropanation of α -methylene- β -lactams **48**.



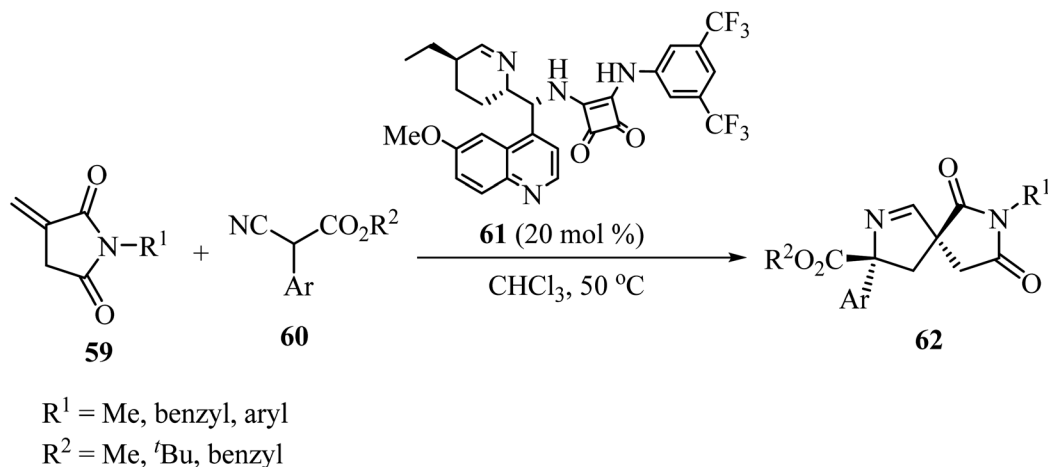
Scheme 14 Synthesis of spirocyclic-bis-β-lactams-lactams **54** from four-component Ugi-adducts precursors.



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

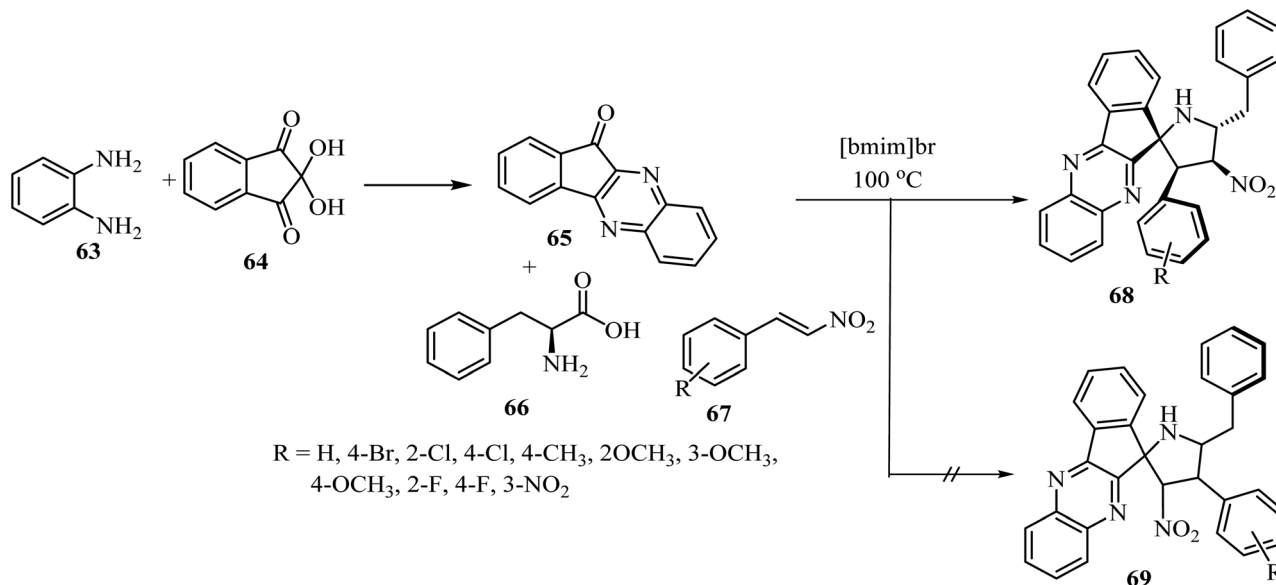
In 2019, Zhao and coworkers described the asymmetric synthesis of spiro pyrrolines **62** from isocyanoacetates **60** and nitaconimides **59** as Michael acceptors (Scheme 16).⁶⁰ The process was catalyzed by squaramide **61** derived from dihydroquinine and provided the corresponding spirocyclic compounds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



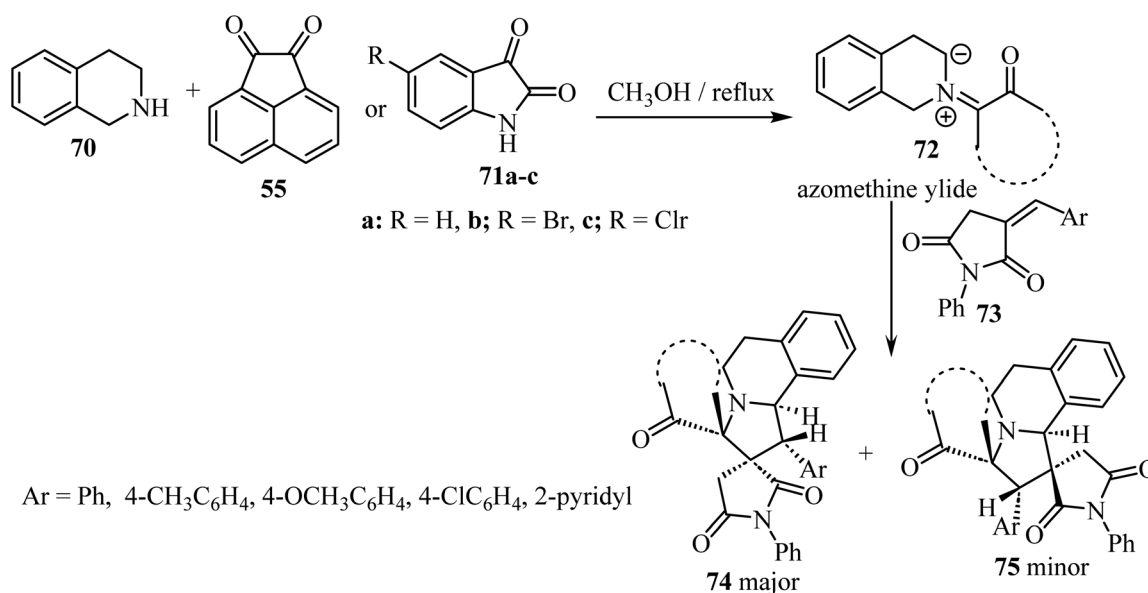
Scheme 17 Synthesis of spiro-pyrrolidine tethered indenoquinoloxaline **68**.

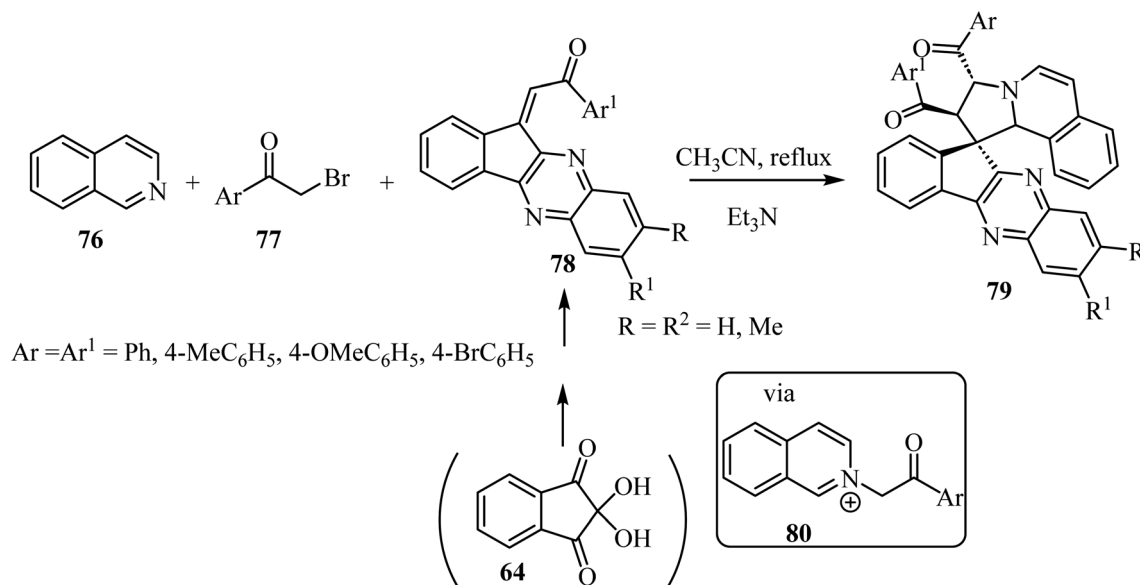
(Scheme 17).⁶¹ *In vitro* activity of these spiroheterocyclic hybrids against *Mycobacterium tuberculosis* H37Rv, using MABA assay, revealed that the compound with nitro group on the phenyl ring is the most active candidate (1.56 $\mu\text{g mL}^{-1}$) of the series and has an activity similar to that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

A diastereoselective approach⁶² 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

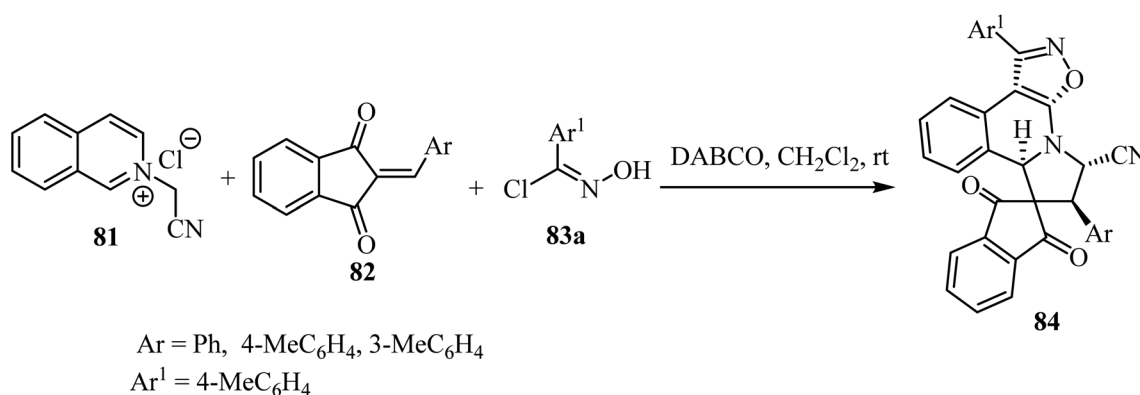
solvents (such as CH₃OH, EtOH, CH₃CN, and toluene), methanol (CH₃OH) was selected as the most effective solvent and an unprecedented regioselectivity was observed in this cycloaddition reaction resulting in two products **74/75**.⁶²

The construction of spiropyrrolo[2,1-*a*]isoquinolines containing the indenoquinoloxaline 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 Et₃N, 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 CH₂Cl₂ 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 literature⁶⁸ 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 (H₂O₂, Oxone, O₂) is highly favorable, Tong and co-workers⁶⁹ 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



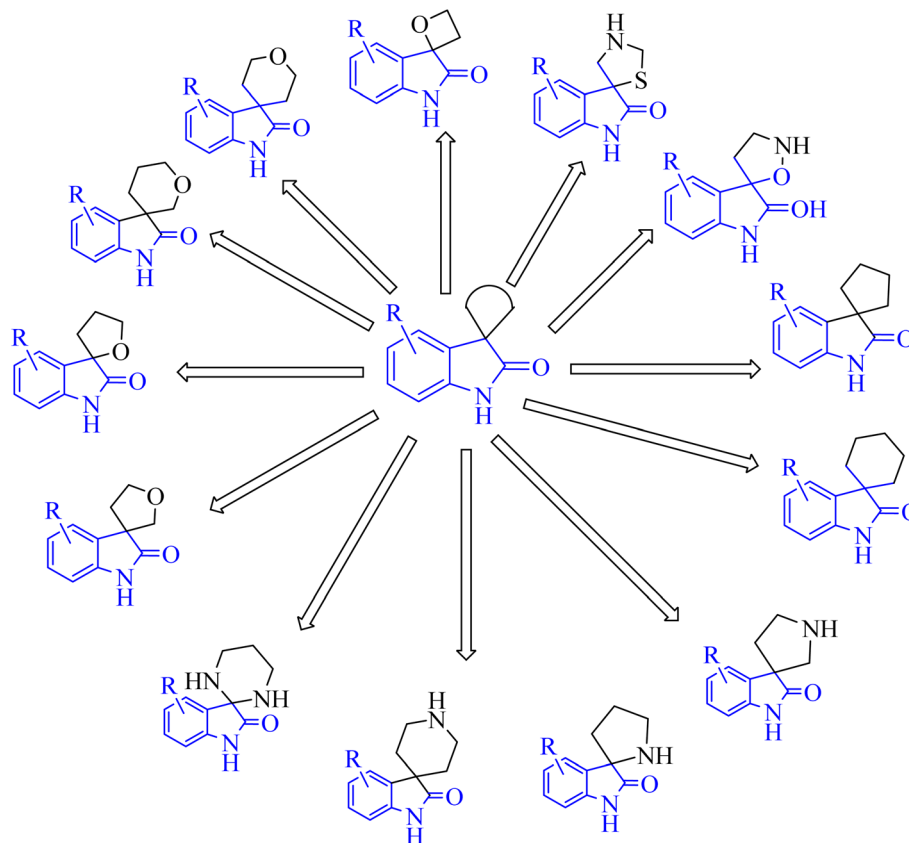
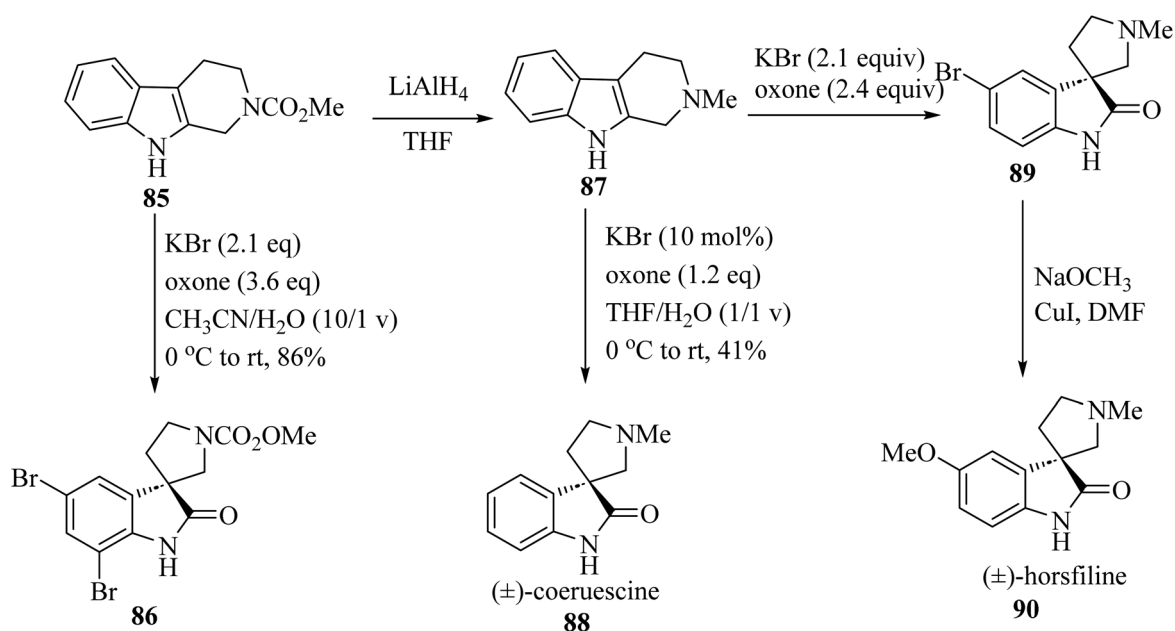


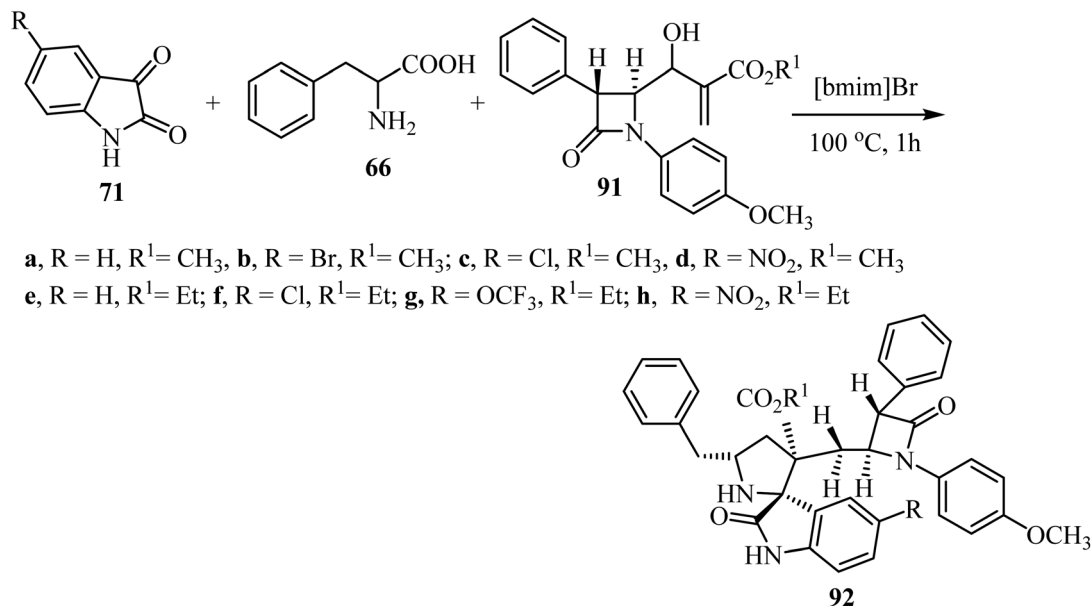
Fig. 8 Diagram showed different spiro indol(ene) derivatives.

$\mu\text{g mL}^{-1}$ and $1.56 \mu\text{g mL}^{-1}$, respectively, which were two-fold and equal activity than the standard drug, Ethambutol ($\text{MIC} = 1.56 \mu\text{g mL}^{-1}$).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



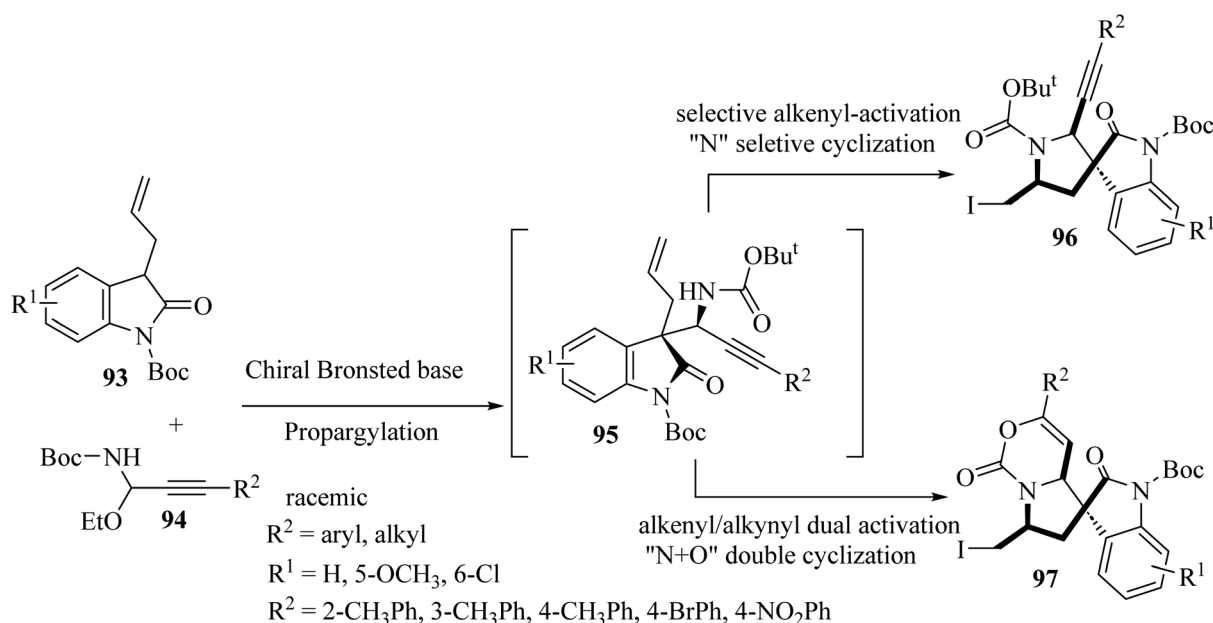
Scheme 21 Oxidative rearrangement of tetrahydro-β-carbolines for the formation of spirooxindole natural compounds **86**, **88** and **90**.

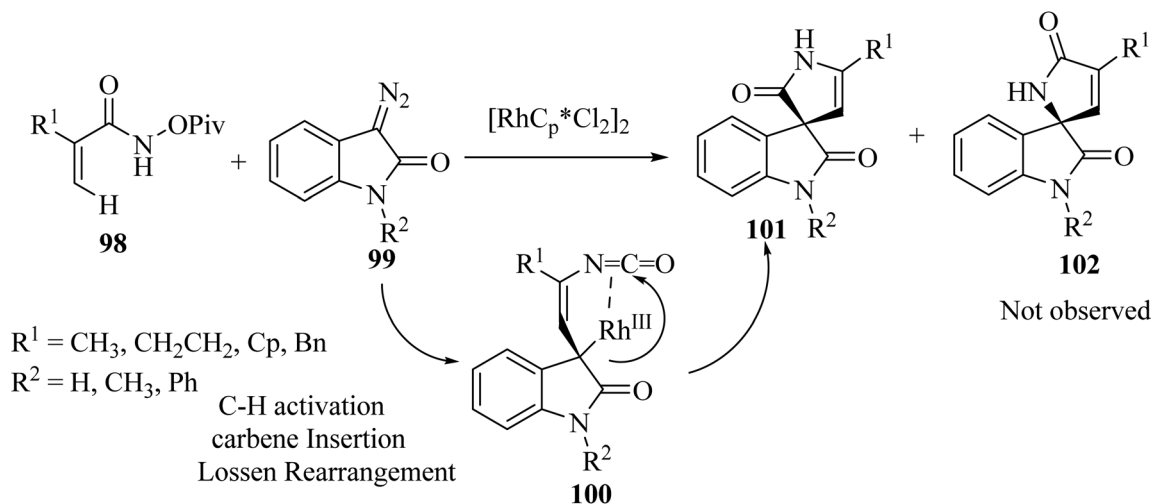
Scheme 22 Synthesis of spiro oxindolopyrrolidine **92**.

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 IC₅₀'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**.



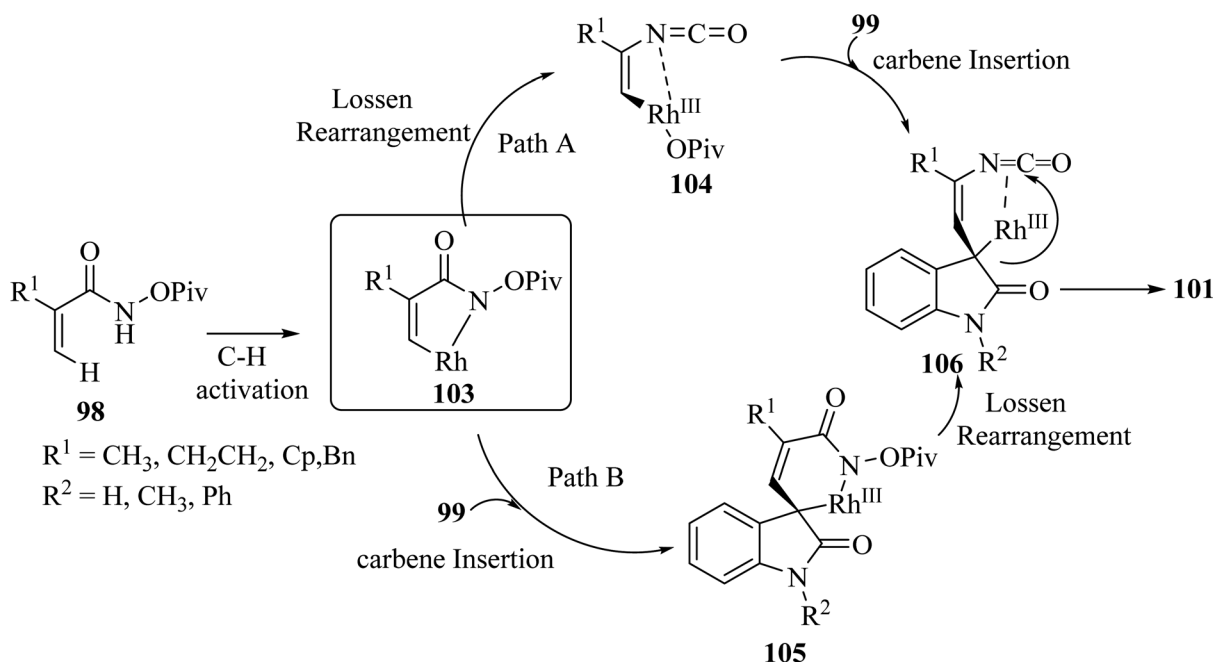
Scheme 24 C(sp²)-H activation/annulation on to synthesis spiro oxindole pyrrolone scaffolds **101**.

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

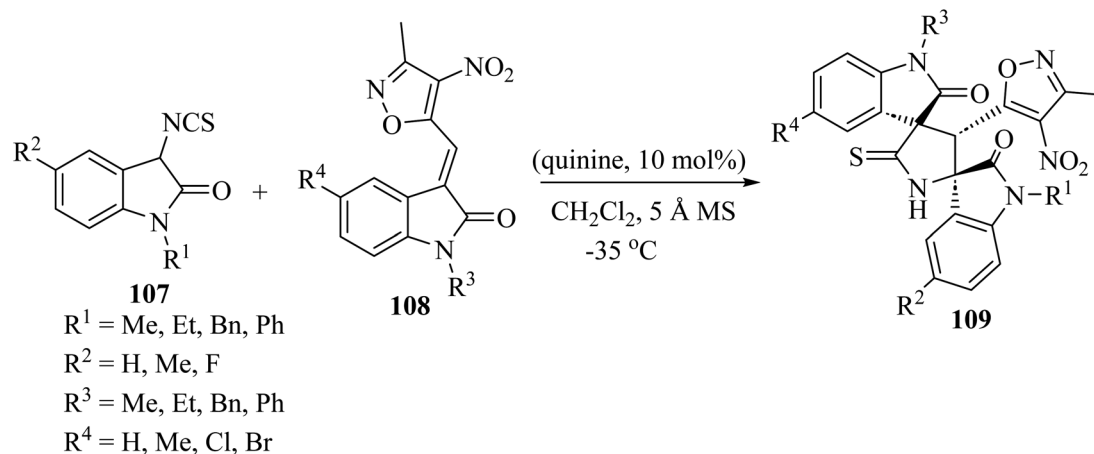
Providing an electron-withdrawing moiety for alkylideneloxindoles acting as dipolarophiles, the asymmetric Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles **107** and 3-methyl-4-nitro-5-isatylidenyl isoxazoles **108**, catalyzed by quinine, yielded enantiomerically enriched 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

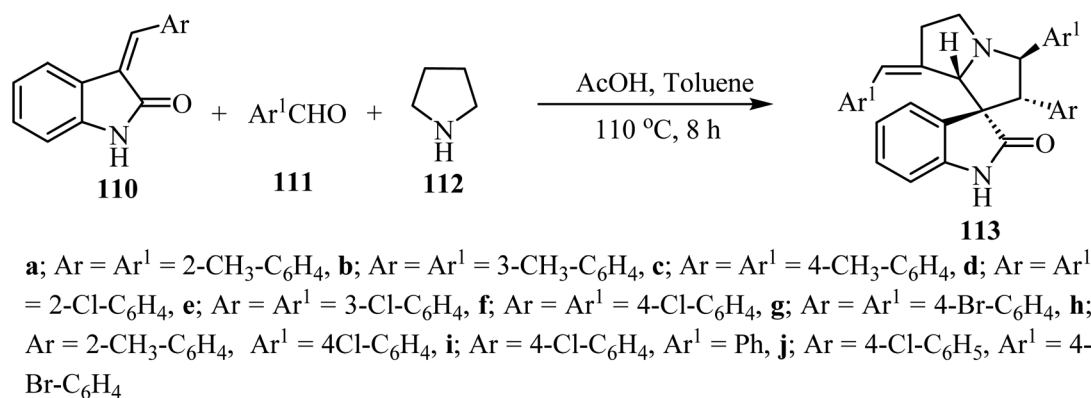
The synthesis of complex spiro heterocyclic compounds **113** has been pursued, by cycloaddition of *in situ* generated azomethine ylides with 3-alkylidene-2-oxindoles **110** as dipolarophiles. This acetic acid-promoted three component reaction **110**, aldehydes **111** and pyrrolidine (**112**) gives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

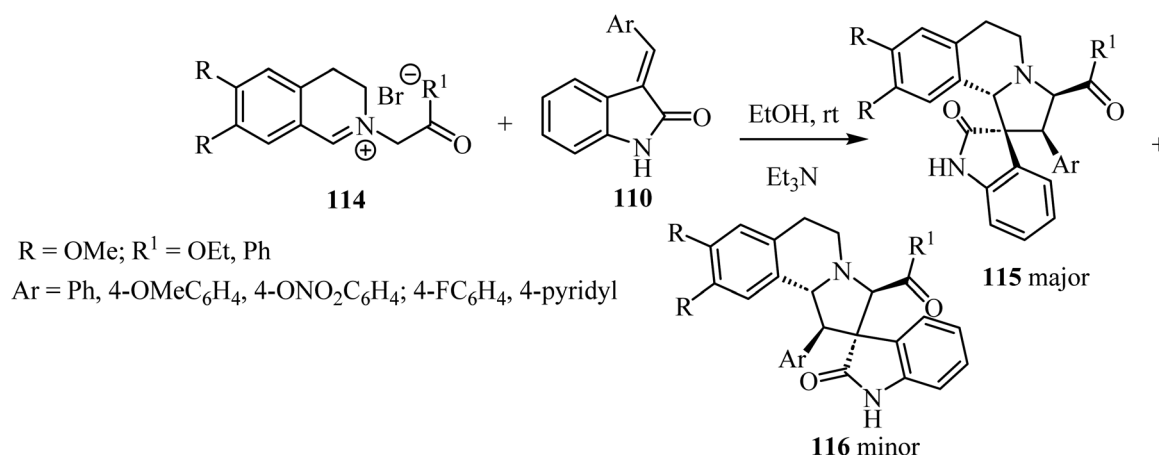


Scheme 27 Synthesis of spiroindoles **113**.

yields, single diastereomer). The reaction mechanism involved $\beta\text{-C-H}$ 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

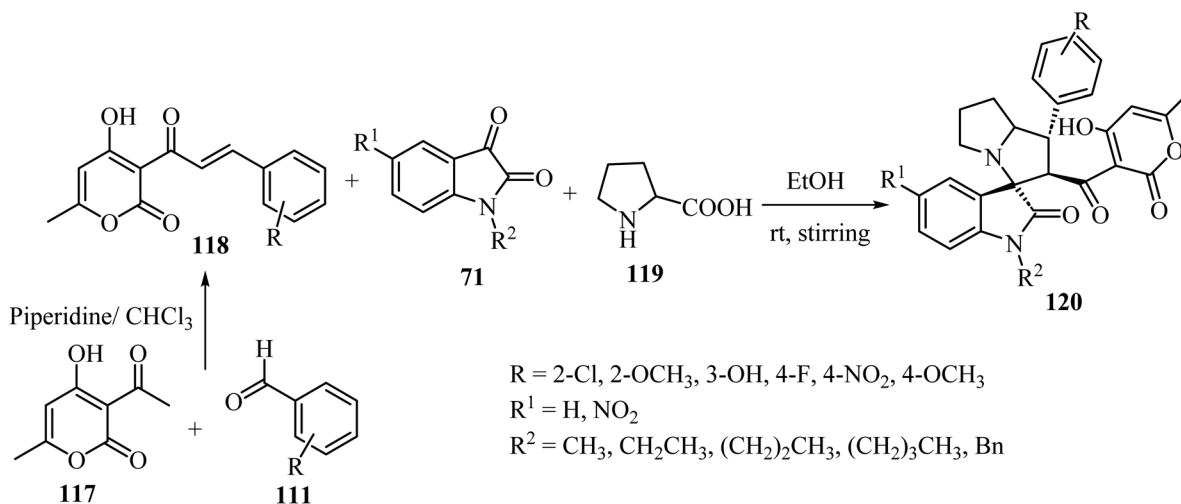
Tripathi *et al.*⁷⁶ have described the regioselective synthesis of hexahydrospiro[indoline-3,3'-pyrrolizine]-2-ones **120** in good-to-excellent efficiencies through [3 + 2] cycloaddition. The products were obtained *via* reaction of substituted 3-pyran-2-ones **118**, isatin derivatives **71**, and 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-2H-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** skeleton⁷⁷ 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

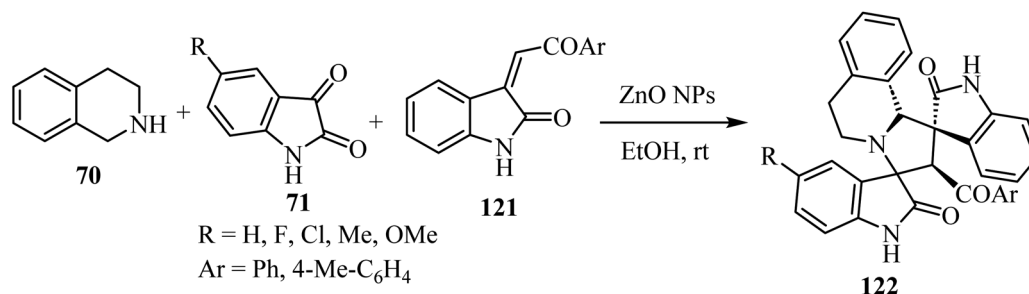
nanoparticles (NPs) were tested in order to determine their recyclability. Unfortunately, the efficiency of the nano-catalyst declined at every cycle, and after the third one the nanoparticles resulted as aggregates⁷⁷ (Scheme 30).

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

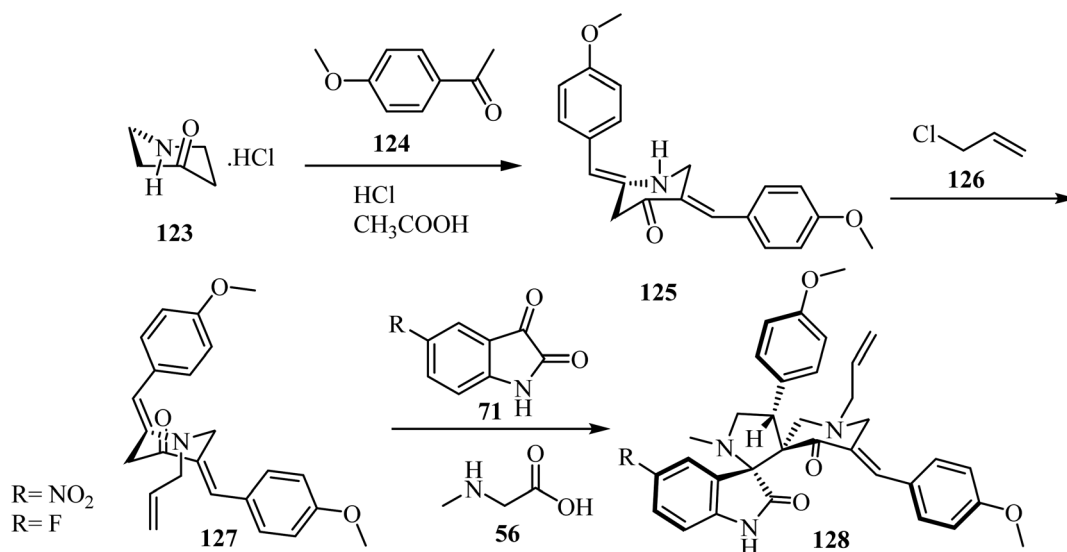
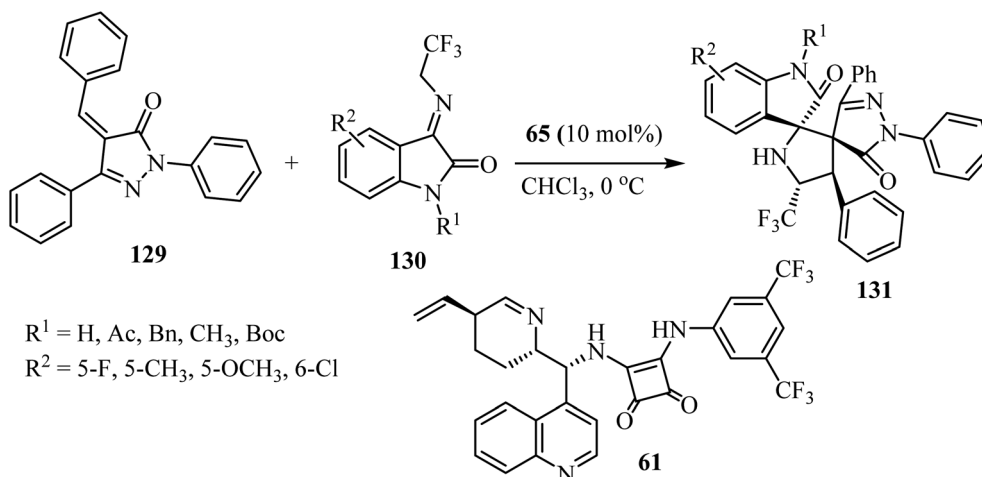
Yan's group⁷⁹ have described a procedure for the formation of CF_3 -containing spiro-oxindole-pyrrolidinepyrazolone compounds **131** *via* organo-catalytic [3 + 2] cycloaddition. This reaction involves the cycloaddition of α,β -unsaturated pyrazolones **129** with *N*-2,2,2-trifluoroethylisatin ketimines **130** in CHCl_3 at ambient temperature in the presence of a cinchonine-derived squaramide **65** catalyst to produce a pyrrolidine spiro-



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



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**.

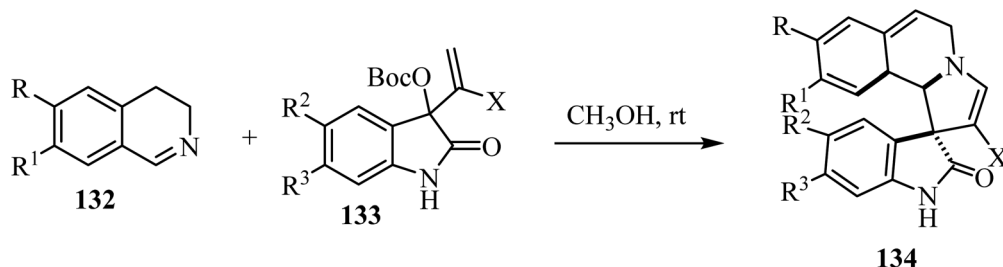
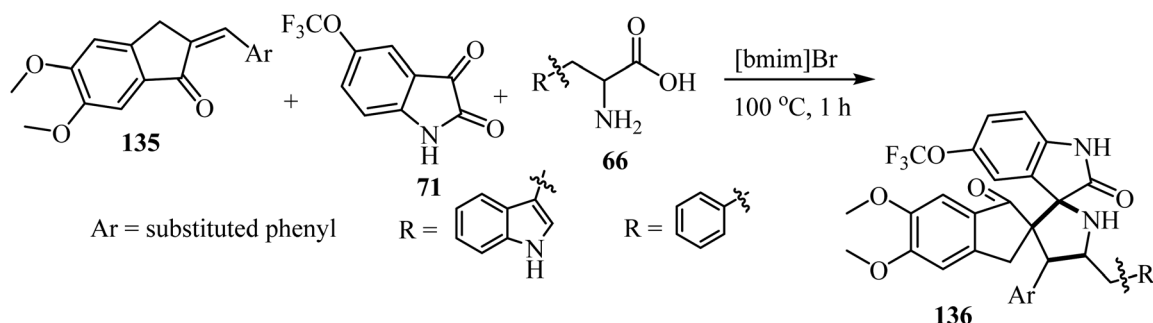
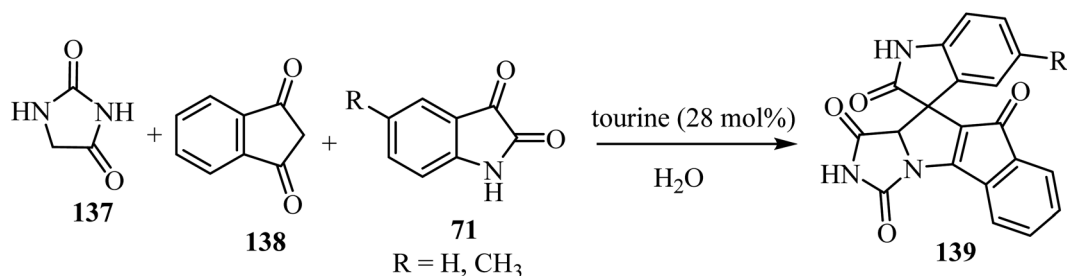
fused with both oxindole and pyrazolone (**131**) with four adjacent stereocenters and two adjacent spiro-quaternary chiral centers, in high efficiencies and stereoselectivities (Scheme 32).⁷⁹

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 IC₅₀ 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 H₂O 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 H₂O 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''(3H)-diones **136**.Scheme 35 Synthesis of spiro[indeno[2',1':4,5]pyrrolo[1,2-c]imidazole-10,3'-indoline]-tetraone derivatives **139**.

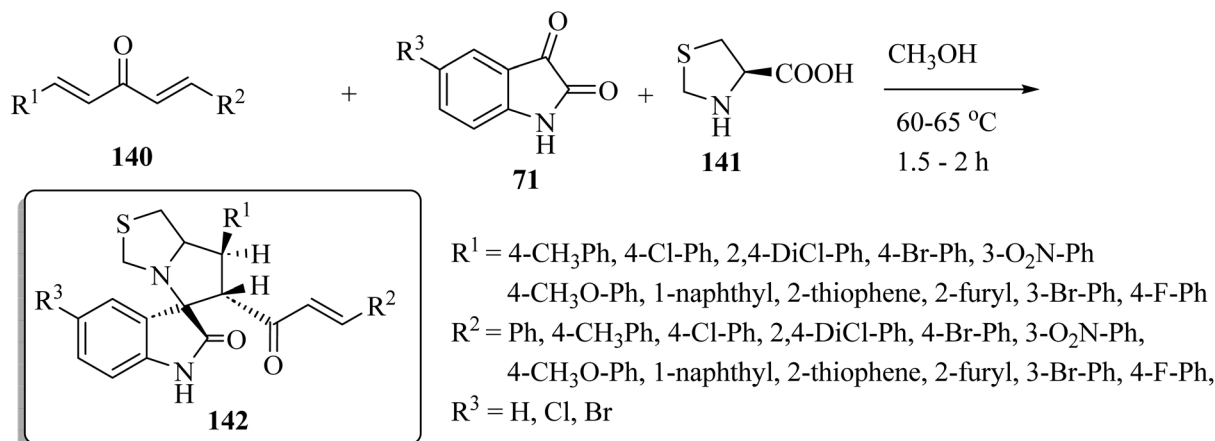
product was obtained.⁸² An excellent yield of **139** was obtained when taurine (28 mol%) was used as a catalyst using H_2O as a solvent (Scheme 35).⁸²

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

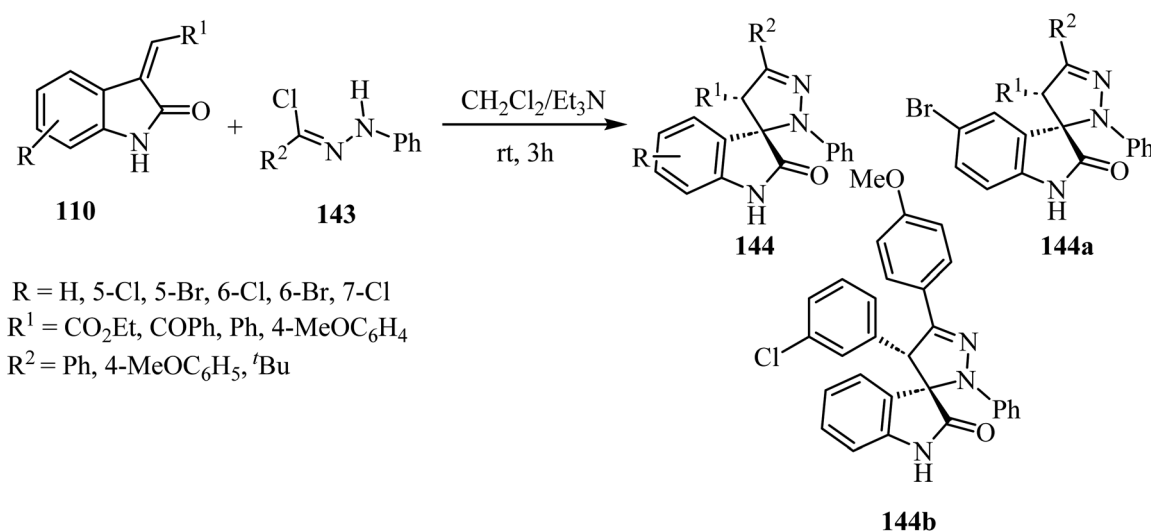
The synthesis of racemic spiro(2-oxindolo)pyrazolines **144** was accomplished by treating hydrazoneyl chlorides **143** with 3-alkenyl-2-oxindoles **110** in the presence of triethylamine (Et_3N) as the organic basic agent and CH_2Cl_2 as a solvent. The regioselective cycloaddition of the dipolar intermediate 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**: $\text{IC}_{50} = 13.1 \pm 1.0\text{ }\mu\text{M}$, **144b**: $\text{IC}_{50} = 10.9 \pm 0.8\text{ }\mu\text{M}$), 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

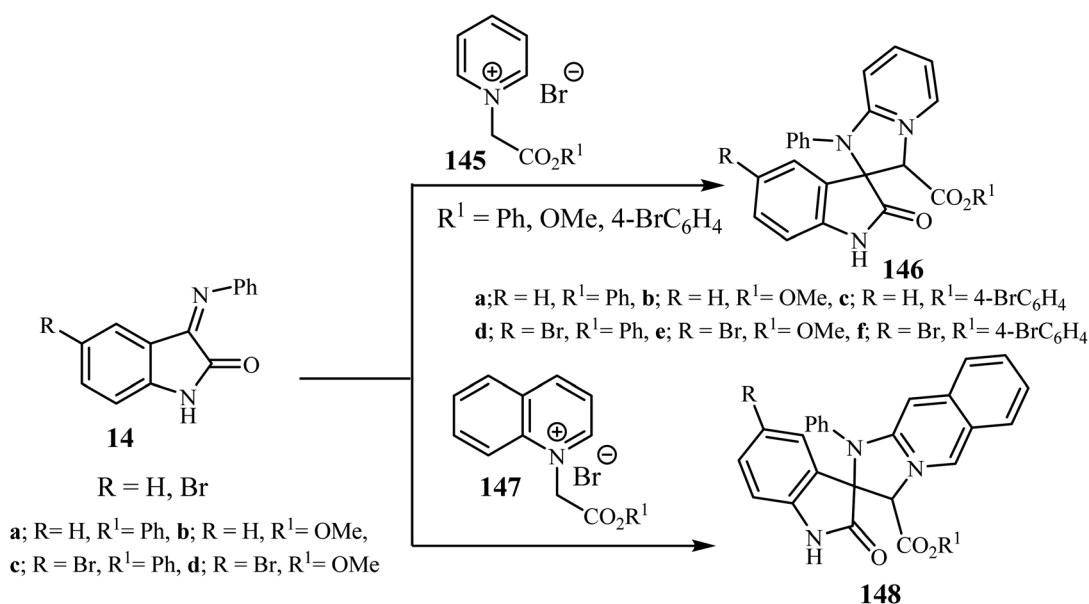
Sheibani and co-workers⁸⁷ reported that cycloaddition between isatin-3-imines **14** and pyridinium or isoquinolinium salts gave racemic spiro(2-oxindolo) imidazolines **146/148** in 90–95% yield. Mild conditions, operational simplicity and easily accessible starting materials were features of these



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** and hydrazonoyl chloride **143**.



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



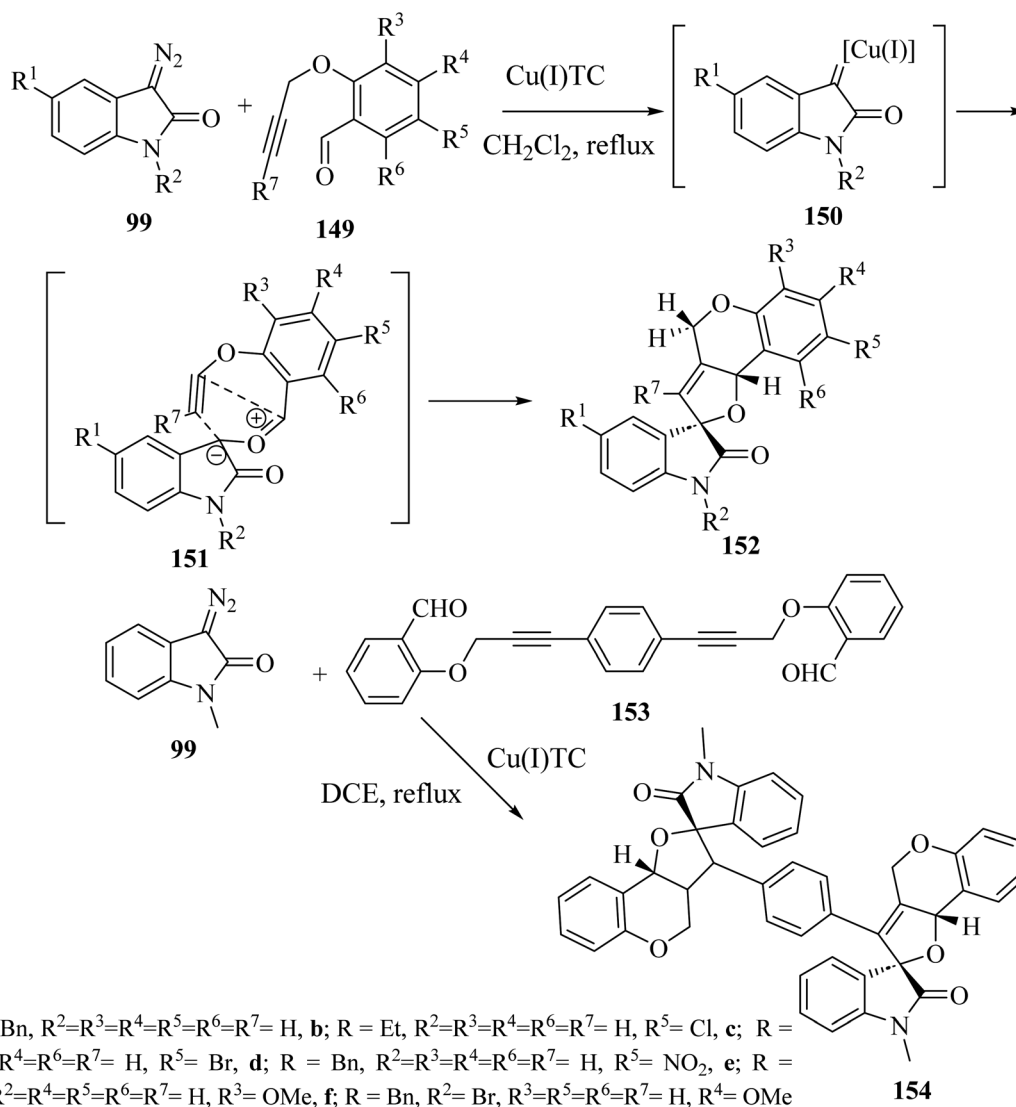
cycloadditions (Scheme 38).⁸⁷ The cycloaddition reactions involved the nucleophilic attack by the isoquinolinium-ylides on isatin-3-imines **14** which act as a dipolarophile.⁸⁷

Addition of 3-diazoisatins **99** to *O*-propargyl salicylaldehydes **149** in the presence of copper(I) thiophenecarboxylate $[(\text{Cu(I)TC})]$ 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

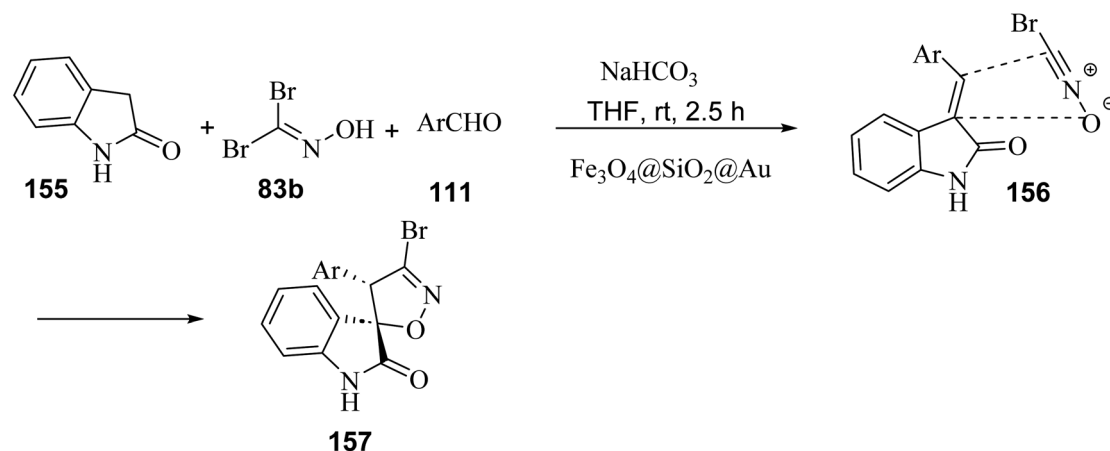
A regio- and diastereo-selective three-component reaction between aldehydes **111**, dibromoformaldoxime (**83b**) and 2-oxindole (**155**) has been pursued in the presence of ferrite-silica nanoparticles decorated with Au(0) nanoparticles

($\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{Au}$) 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 oxindole-derived α -aryl- β -amino acids has been described.⁹¹ Oxindole derivatives **159** were obtained stereoselectively by an organo-catalyzed asymmetric Mannich reaction between homophthalic anhydrides **158** and isatin-derived *N*-Boc imines **14** with

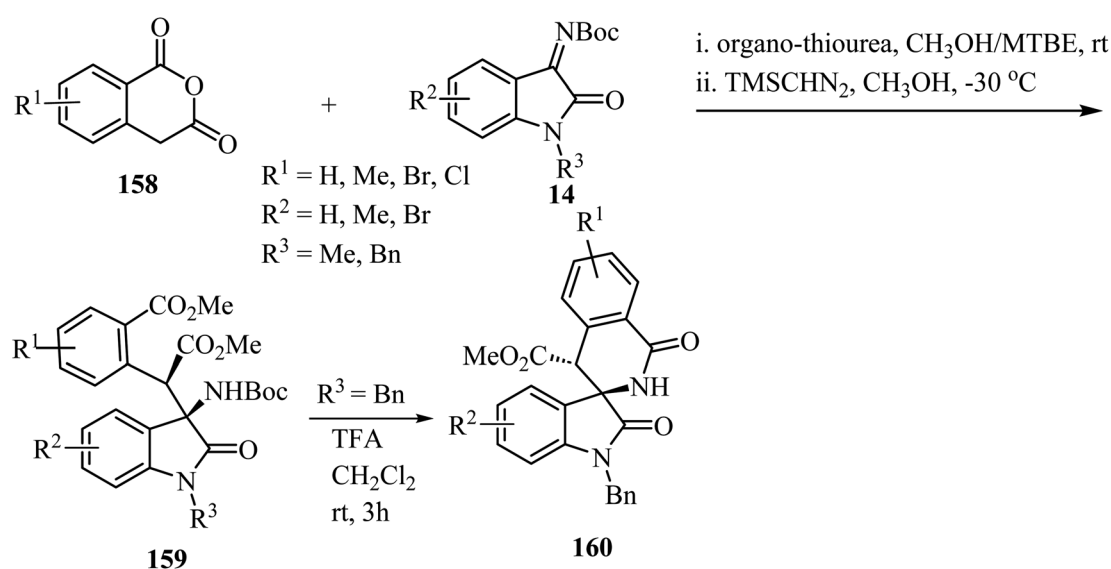


Scheme 39 Intramolecular cycloaddition of the indolic carbonyl ylide **151**.



$\text{Ar}_1 = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-EtCO}_2\text{C}_6\text{H}_4, \text{BrC}_6\text{H}_4, 2\text{-naphthyl}$

Scheme 40 $\text{Fe}_3\text{O}_4@\text{SiO}_2@\text{Au}$ -catalyzed three component reactions between 2-oxindole, aromatic aldehydes and dibromoaldoxime.



Scheme 41 TFA-mediated *N*-Boc deprotection/intramolecular *N*-acylation reaction of oxindole-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

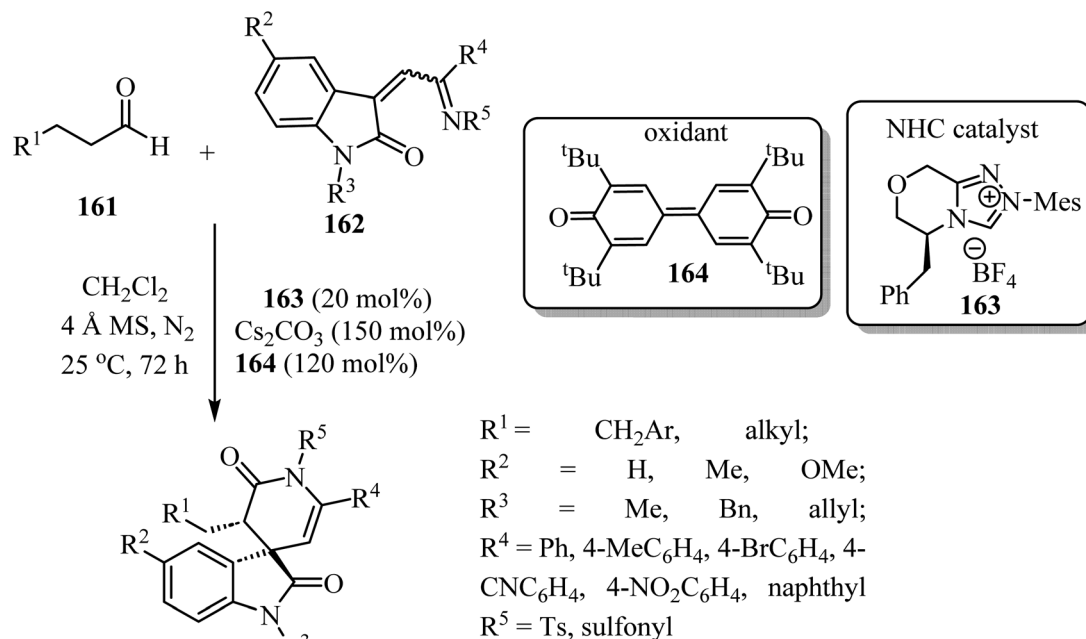
Spiro-oxindole- δ -lactams **165** were synthesized *via* an NHC-catalyzed oxidative [4 + 2] annulation of aliphatic aldehydes **161** with oxindole-derived α,β -unsaturated imines **162** using chiral pre-NHC catalyst **163** (Scheme 42).⁹² The target spirocyclic lactams **165** were obtained in good 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 $\text{H}_2/\text{Pd-C}$ 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-

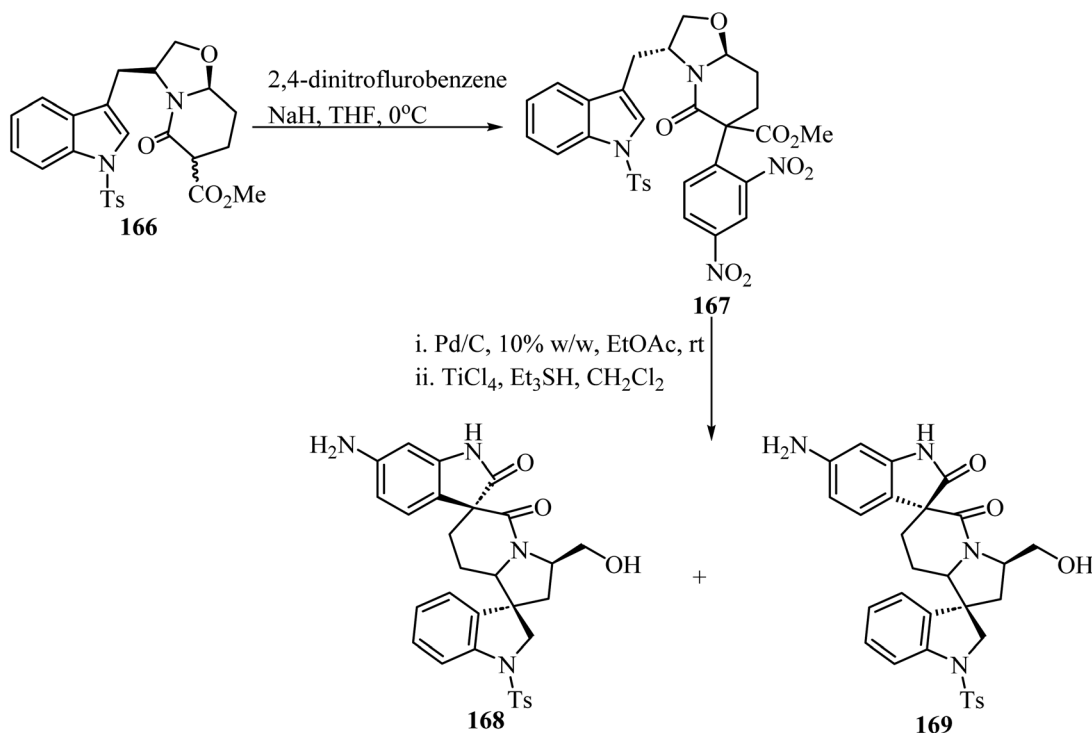




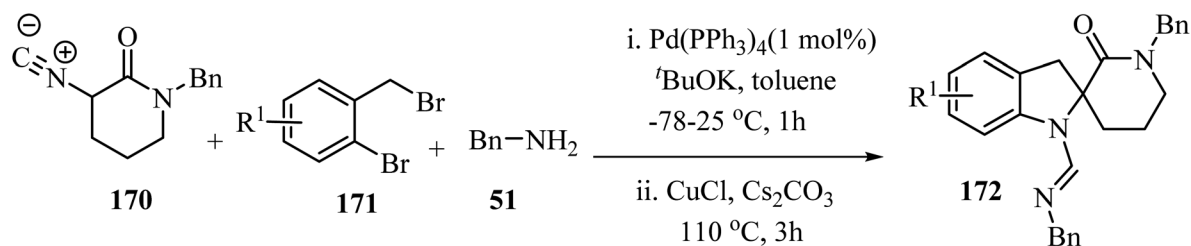
Scheme 42 NHC-catalyzed [2 + 4] spiroannulation of aliphatic aldehydes **161** with oxindole-derived α,β -unsaturated imines **162**.

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

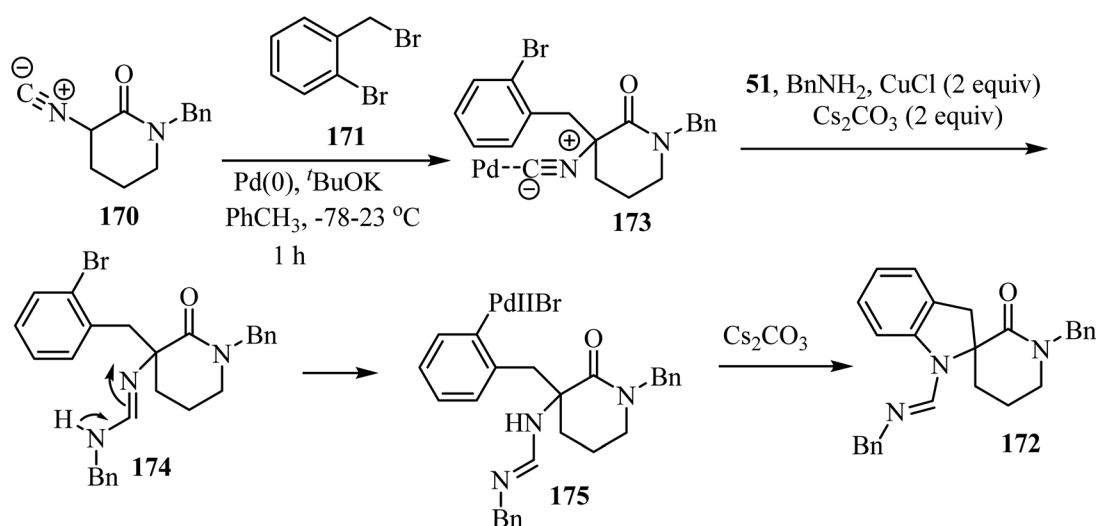
Recently, an efficient catalytic asymmetric three-component reaction of isoquinolines **76**, allene dicarboxylates **176** and methylene indolinones **110** was realized for the synthesis of spiro-indolino-pyrido[2,1-*a*]isoquinolines **178**.⁹⁵ In the presence of the chiral *N,N'*-dioxide/Mg(OTf)₂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



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



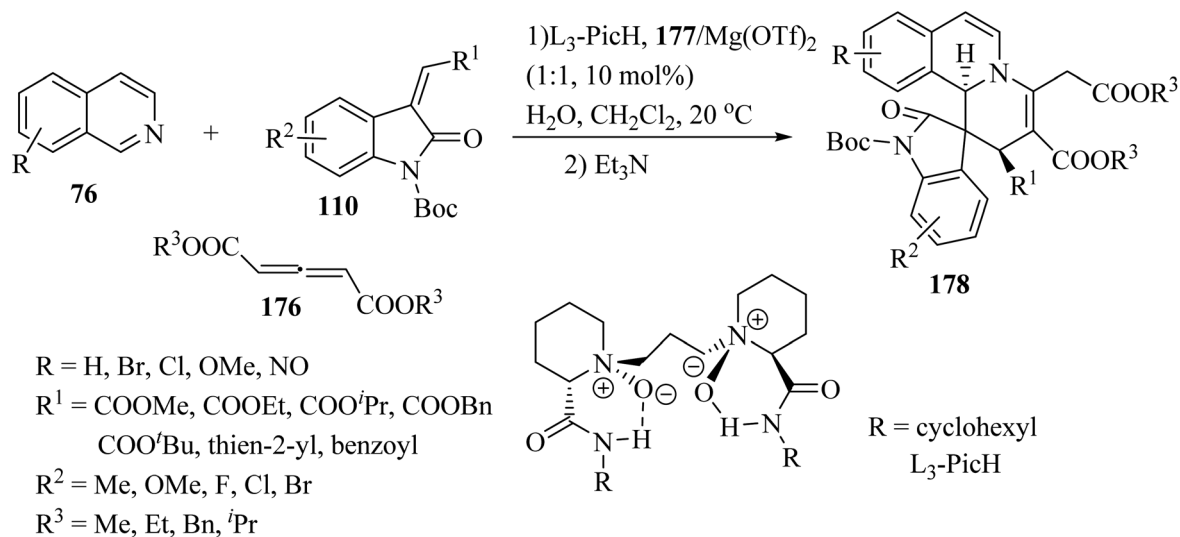
Scheme 44 Cooperative Pd/Cu-catalyzed tandem three-component reaction involving δ -lactams **170**, amines **51** and 2-bromobenzyl bromides **171**.



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

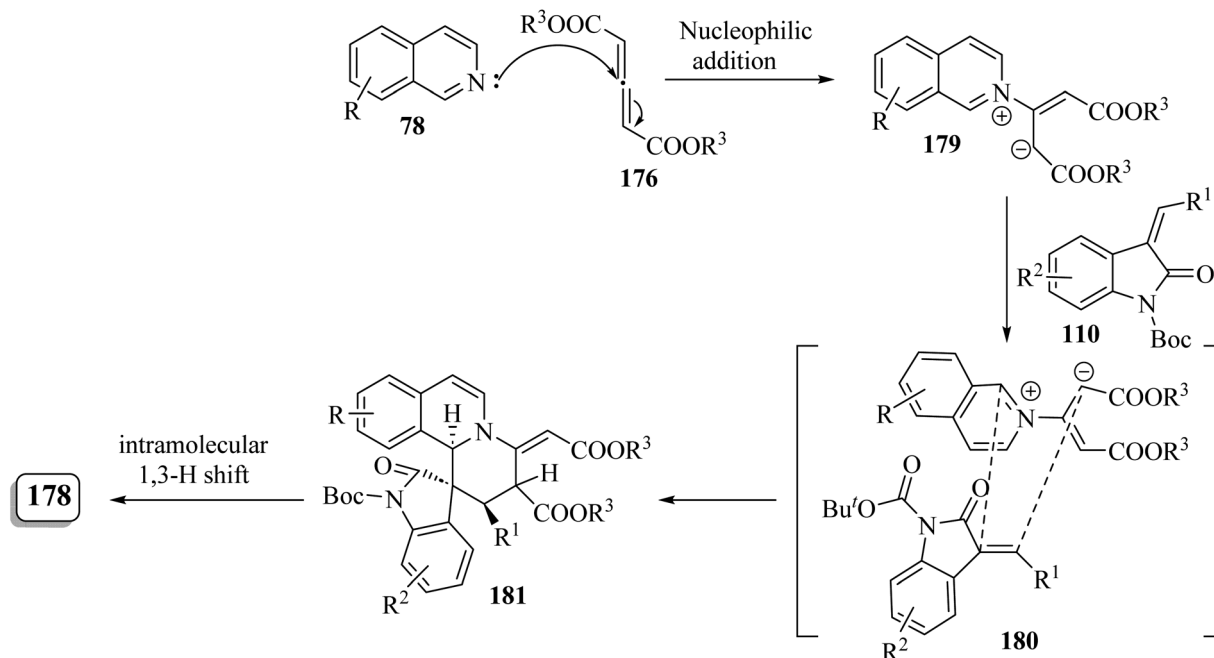
isomerization sequence. The tandem reaction enabled rapid access to the spiro-products with good to excellent stereoselectivities under mild reaction conditions (Scheme 46).

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**.





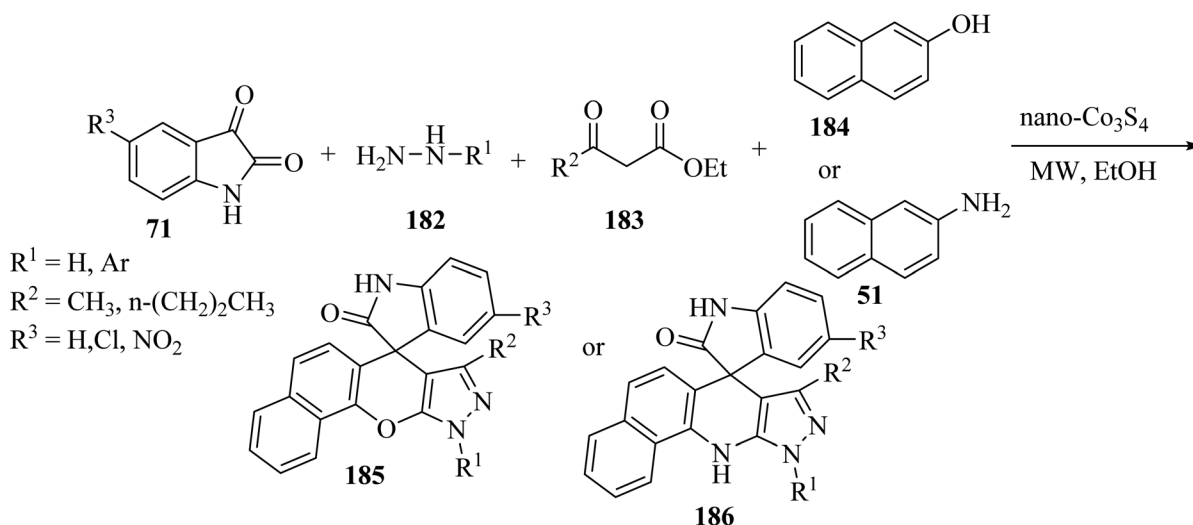
Scheme 47 Rational pathway for the formation of 178.

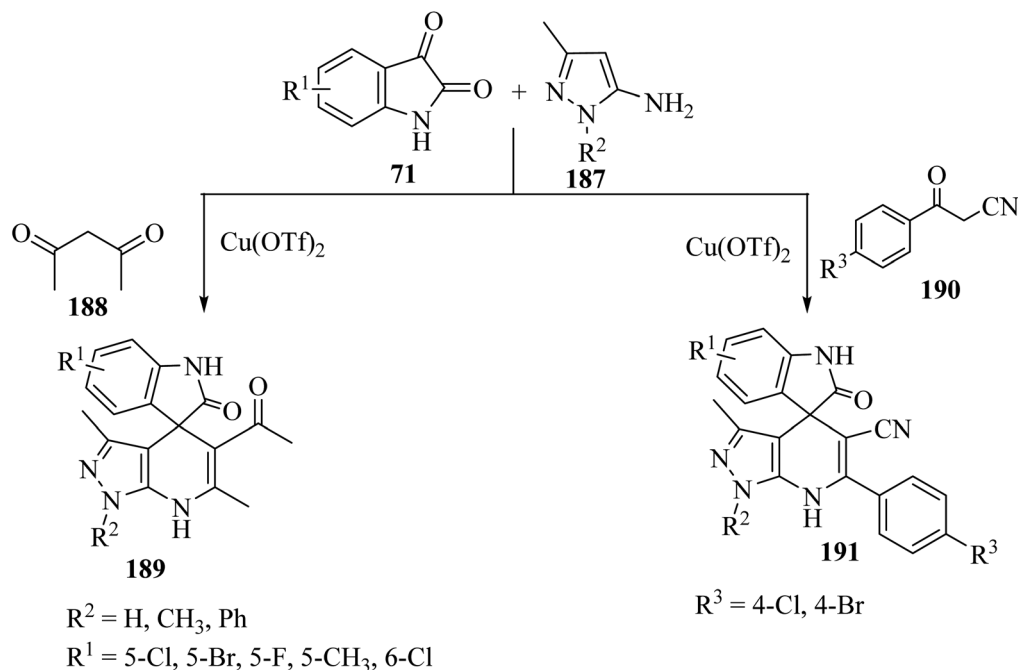
proceeded *via* the simultaneous Si/ β -*Re* face attack, affording the exocyclic alkene intermediate **180**. Finally, intramolecular [1,3]-hydrogen shift resulted in the isomerized product **178** (Scheme 47).⁹⁵

Khojasteh-Khosro and Shahbazi-Alavi⁹⁶ 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 -oxo-benzenepropanenitriles **190** catalyzed by copper triflate [$\text{Cu}(\text{OTf})_2$] in EtOH (Scheme 49).⁹⁷

Choudhury and co-workers⁹⁸ have described a medium-dependent, metal-free three-component condensation of isatin derivatives **71**, 4-hydroxycoumarin (**192**) and aminopyrazole

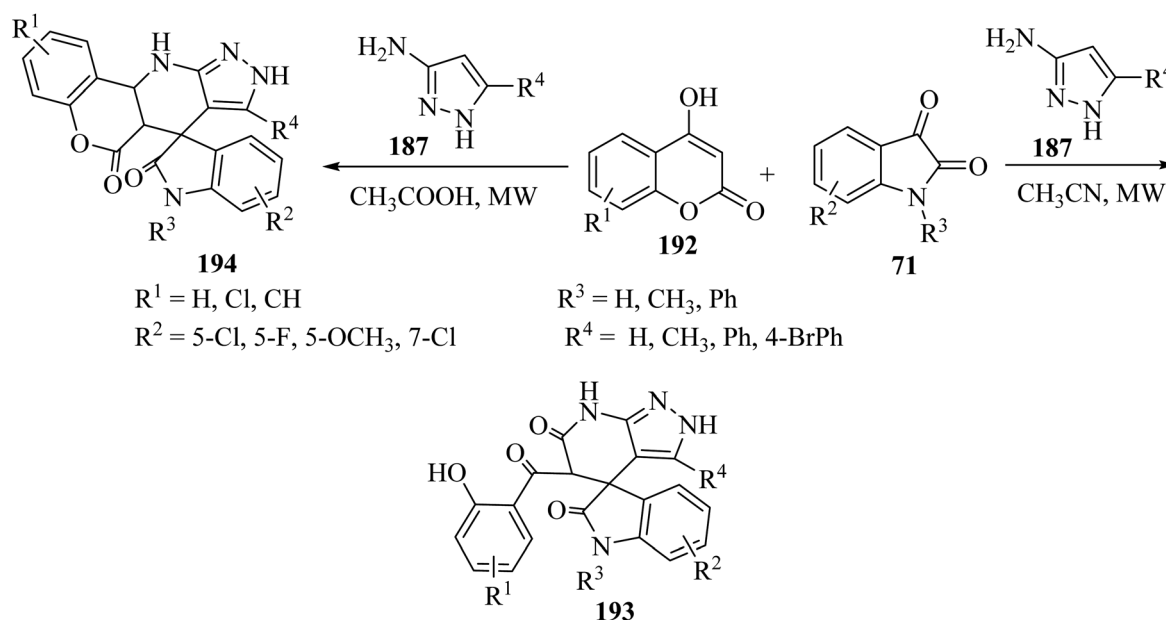
Scheme 48 Synthesis of spirooxindoles **185** and **186** under microwave (MW) irradiation.

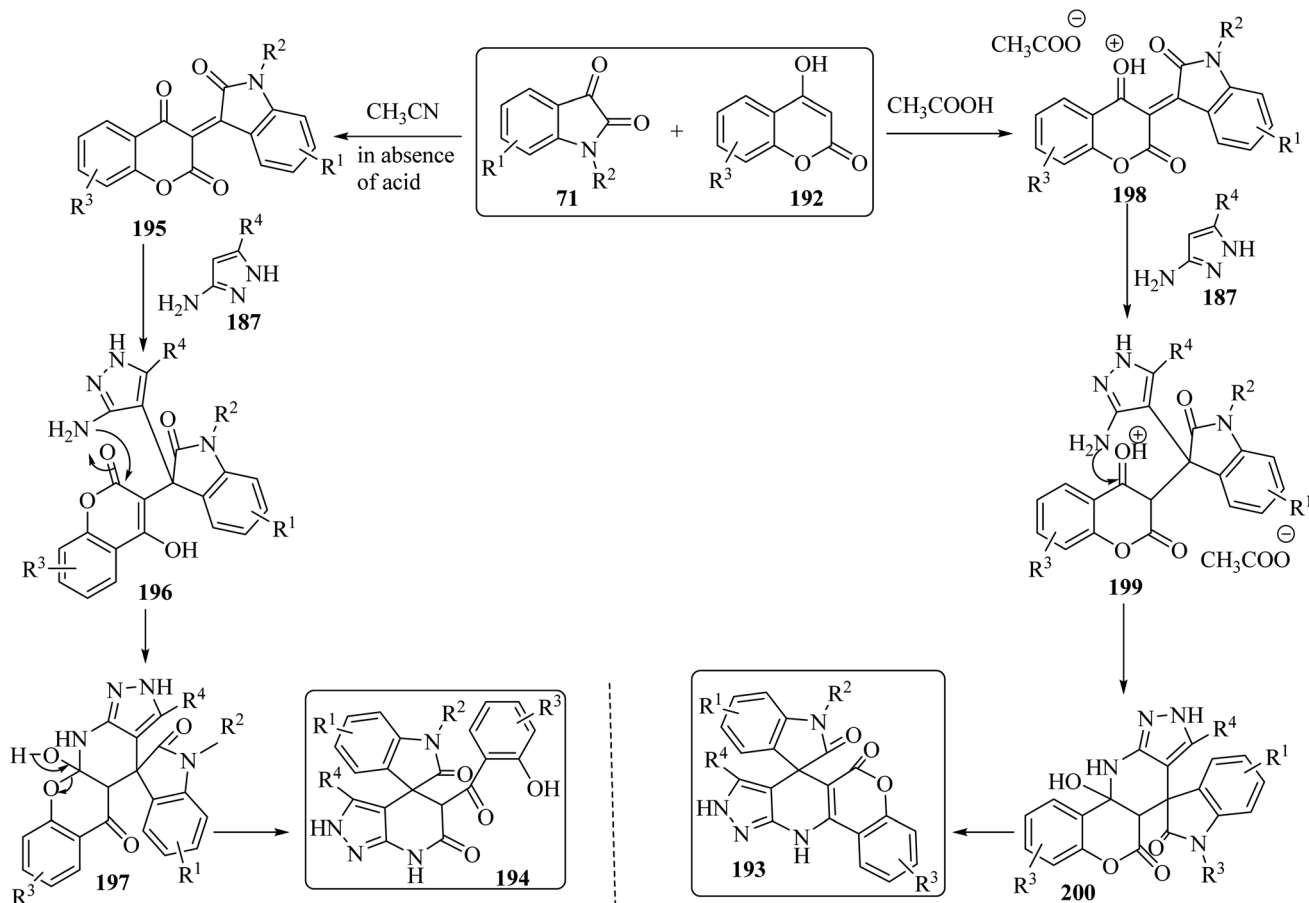
Scheme 49 Synthesis of spiro compounds **189** and **191**.

(**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 spirooxindoles **193** and **194** *via* the reaction of 4-hydroxy coumarin derivatives **192** and amino pyrazole **187**.



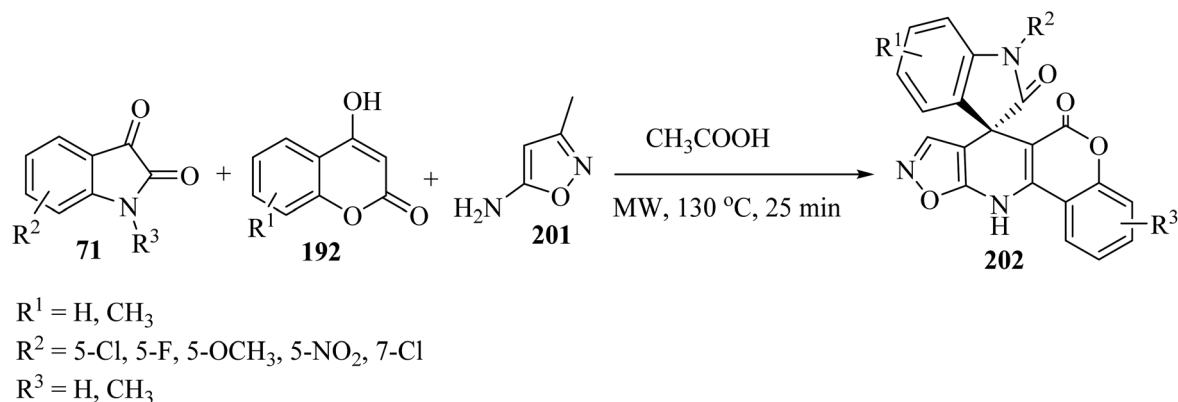
Scheme 51 A rational mechanism for the formation of **193** and **194**.

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

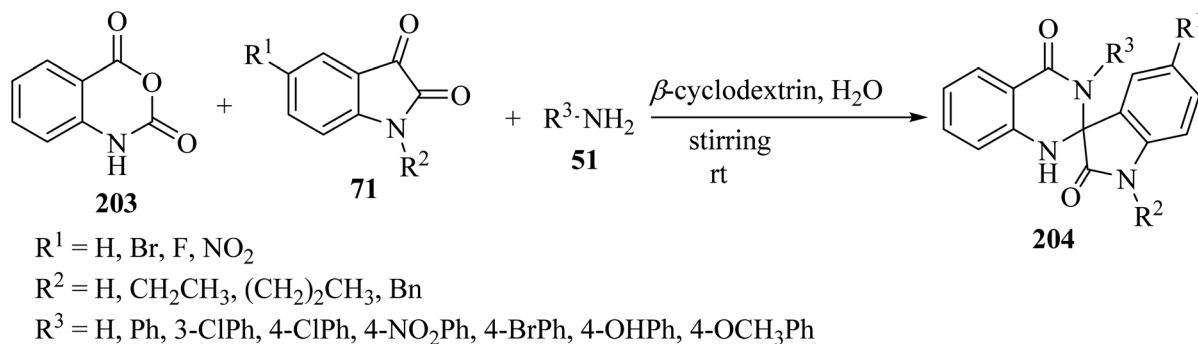
In order to expand the substrate scope, the same authors have prepared another spiro-oxindole fused with coumarin-dihydropyridine-isooxazole tetracycle **202** by applying 5-amino-3-methylisoxazole (**201**) (Scheme 52).⁹⁸

Tripathi⁹⁹ 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**),



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





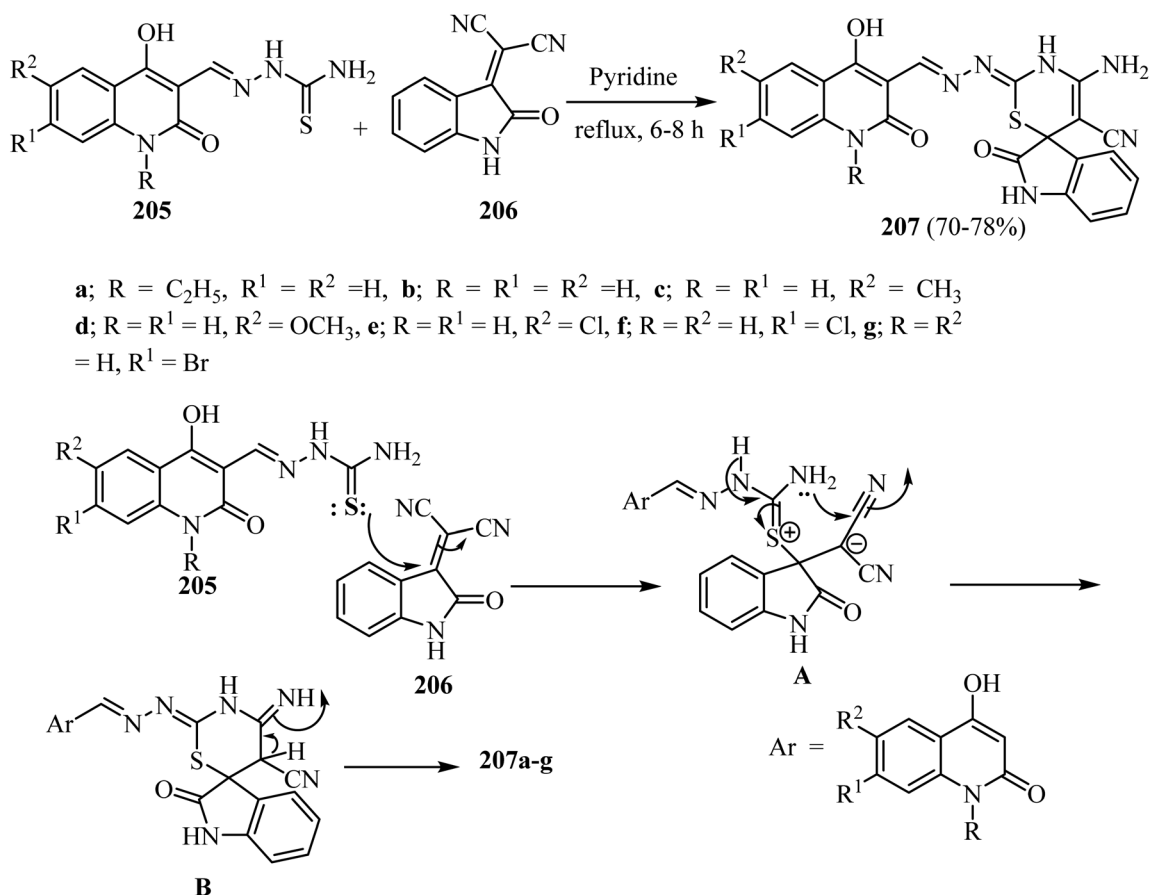
Scheme 53 Synthesis of various spiroindole quinazoline derivatives 204.

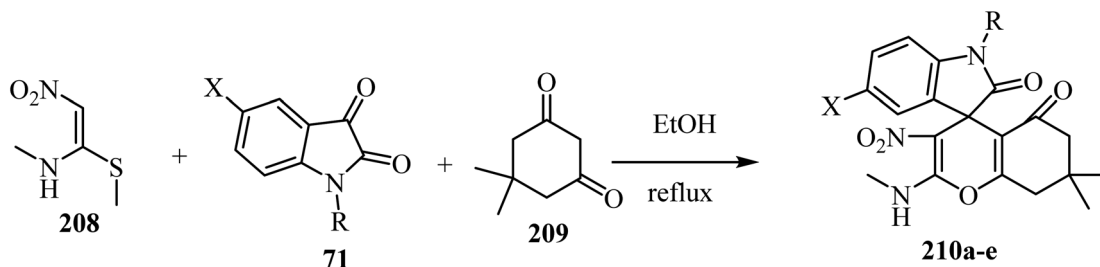
isatin derivatives **71**, and primary amines **51**, which was catalyzed by β -cyclodextrin in an aqueous medium (Scheme 53). Due to the use of environmentally friendly catalysts and green solvents, this is a green method to produce valuable spiroheterocycles.⁹⁹

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-oxindolin-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

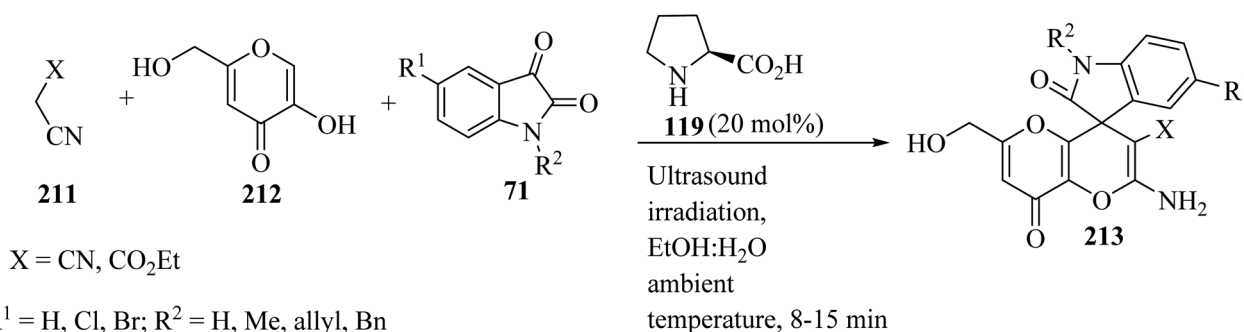
(*E*)-*N*-Methyl-1-(methylthio)-2-nitroethenamine (NMSM) (**208**) has drawn significant attention as an important synergistic building block due to the presence of push-pull skeleton for the synthesis of various O/N-heterocyclic ring systems *via* multicomponent reactions (MCRs).^{101,102} By using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

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 = NO₂, **e**; R = Me, X = H

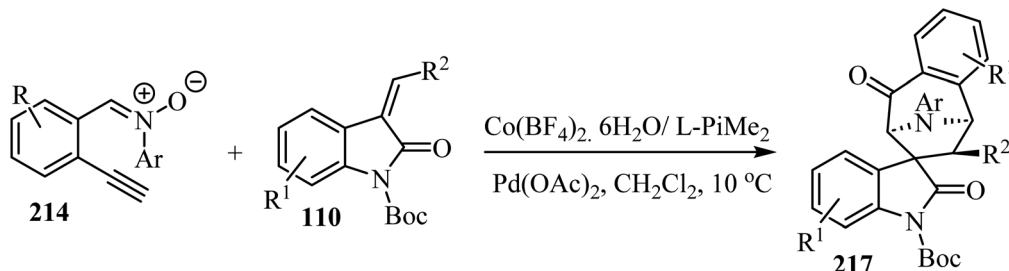
Scheme 55 Utility of NMSM for the one-pot synthesis of fused spiro 4*H*-pyrans **210**.



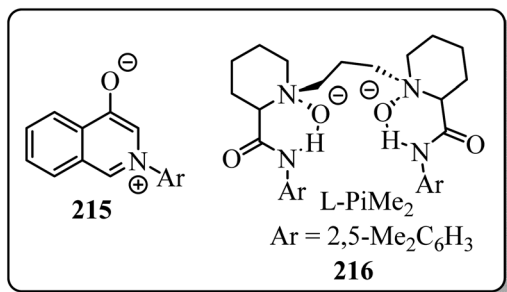
Scheme 56 Ultrasound-assisted organocatalytic domino synthesis of spiro[indoline-3,4'-pyrano[3,2-*b*]pyran **213**.

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-nitroethylenes (NMSM) **208** under catalyst-free conditions to furnish compounds **210** (Scheme 55).¹⁰² These compounds were initially screened for *in vitro* antibacterial



a: R = R¹ = H, R² = CO₂tBu; **b**: R = H, R¹ = 5-CH₃, R² = CO₂tBu; **c**: R = H, R¹ = 5-OCH₃, R² = CO₂tBu; **d**: R = H, R¹ = 5-Cl, R² = CO₂tBu; **e**: R = H, R¹ = 5-F, R² = CO₂tBu; **f**: R = H, R¹ = 6-Cl, R² = CO₂tBu; **g**: R = H, R¹ = 6-OCH₃, R² = CO₂tBu; **h**: R = R¹ = H, R² = CO₂Me



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

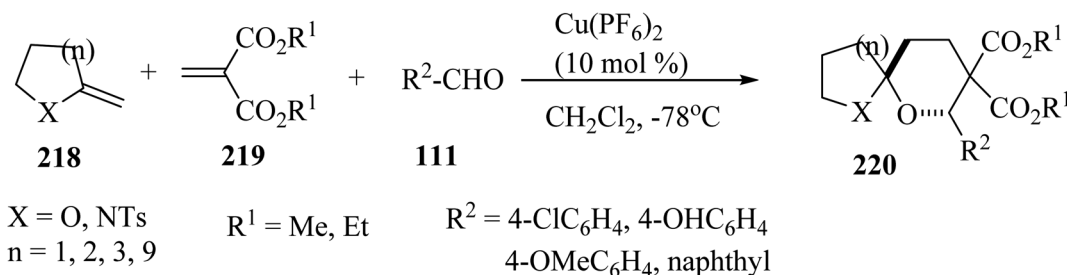
Spiroketal **220** were synthesized in an excellent yield by the reaction of exocyclic enol ether **218**, methylene malonate (**219**),

and aldehydes **111**. The reaction was carried out with 10 mol% of Cu(PF₆)₂ as a catalyst in dichloromethane (CH₂Cl₂) at -78 °C (Scheme 58).¹⁰⁵

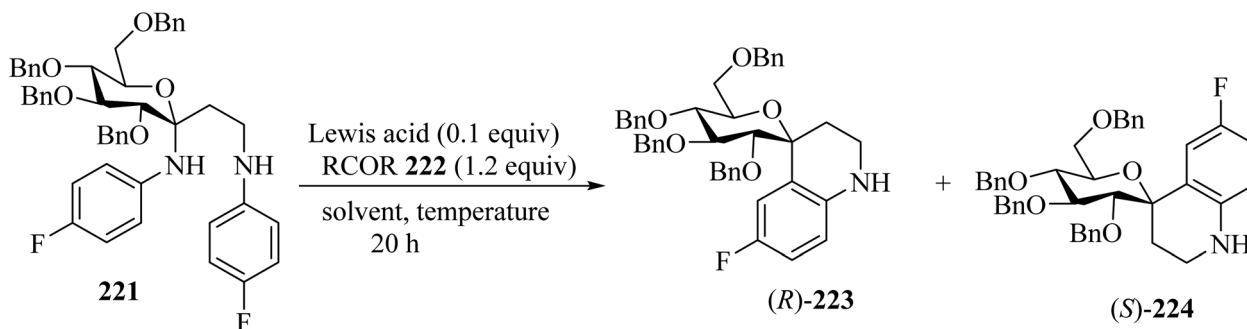
Mixing of *C,N*-glucoside **221** with benzophenones **222** in the presence of InCl₃ (0.1 equiv.) in dichloroethane (DCE) at 60 °C for 20 h resulted in the formation of spiro[pyran-4-quinoline] **223/224** in 59% yield as a mixture of diastereomers (ratio of (*R*)-**223**/*(S)*-**224** = 2.5/1). The 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 catalysts¹⁰⁸ 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

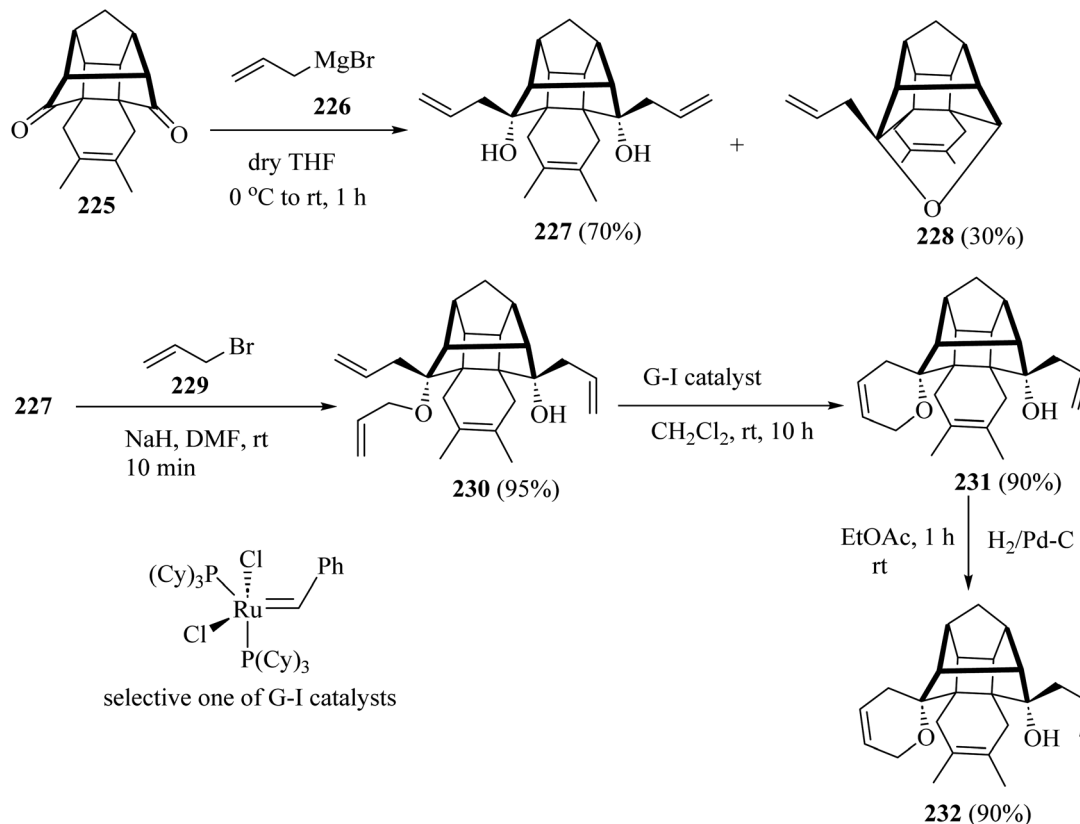


Scheme 58 Synthesis of spiroketals **220**.



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





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

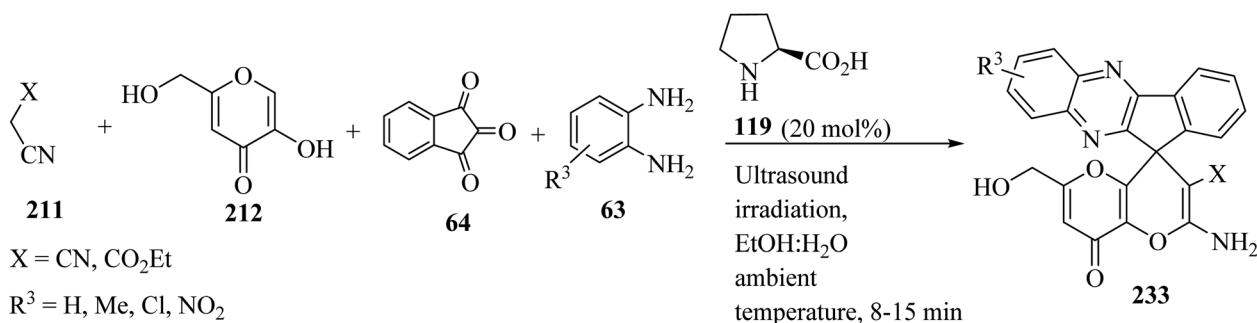
synthesized *via* ultrasound-assisted organocatalytic domino, four-component reactions of active methylene compounds **211**, kojic acid (**212**), ninhydrin (**64**), and 1,2-diamines **63** in the presence of L-proline (**119**) in aqueous ethanolic solution at ambient temperature (Scheme 61).¹⁰³

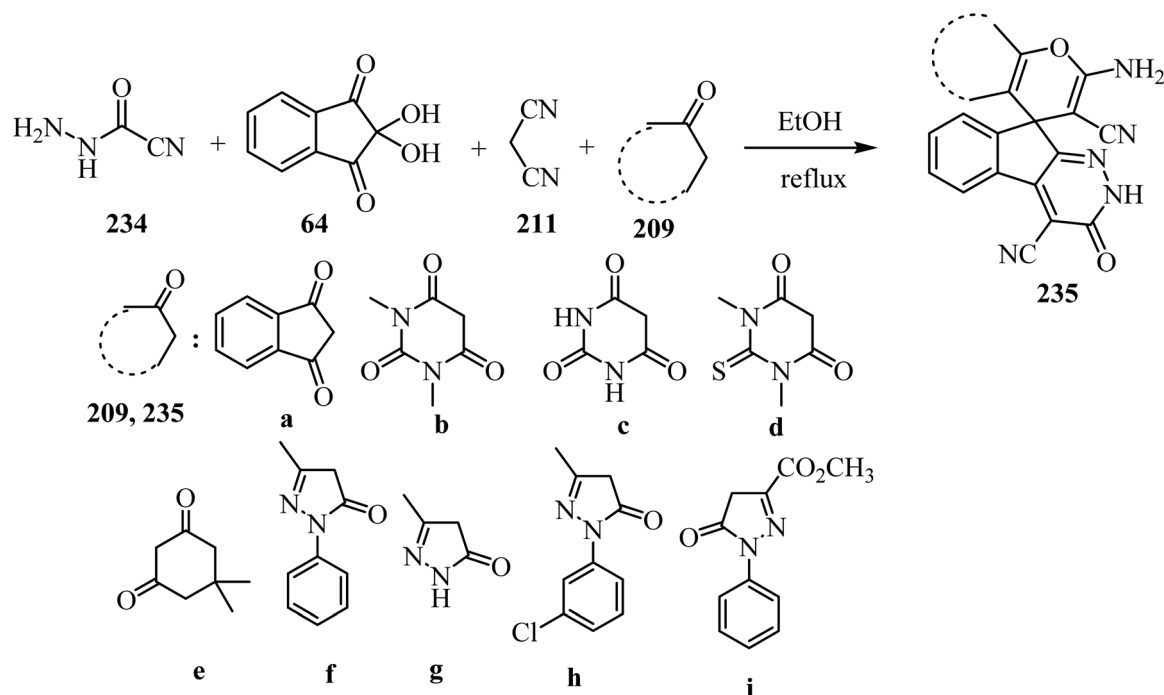
As shown in Scheme 62, spiro[indeno[2,1-*c*]pyridazine-9,4'-pyran]-3',4'-dicarbonitrile derivatives **235** were synthesized by refluxing a mixture of cyanoacetohydrazide (**234**), ninhydrin (**64**), malononitrile (**211**) and various cyclic CH-acids **209** in EtOH under catalyst-free conditions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

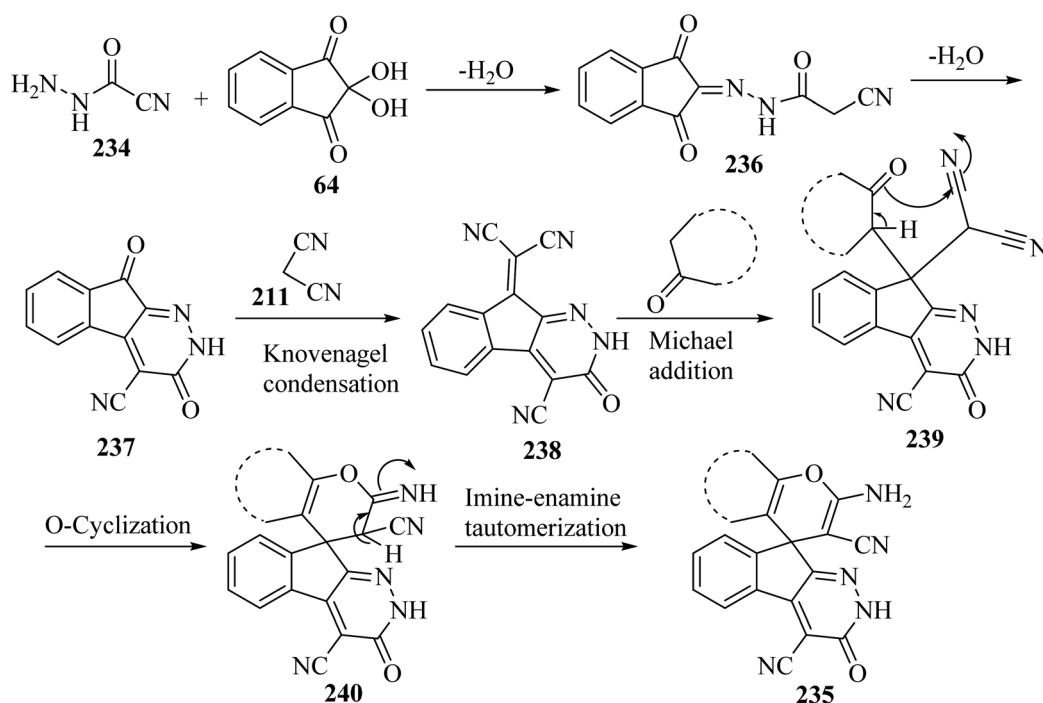
Scheme 61 Ultrasound-assisted organocatalytic domino synthesis of 2'-amino-6'-(hydroxymethyl)-8'-oxo-8'H-spiro[indeno[1,2-*b*]quinoxaline-11,4'-pyrano[3,2-*b*]pyran]-3'-carbonitrile/carboxylate derivatives **233**.



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

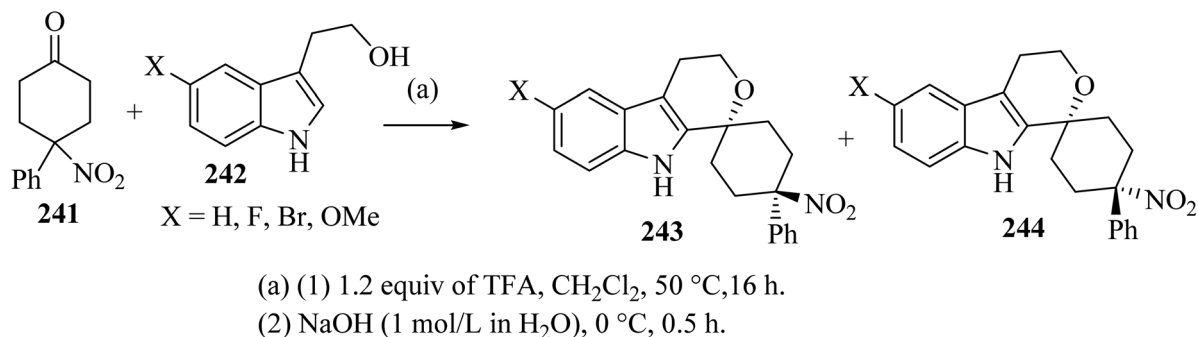
in TFA-CH₂Cl₂ proceeded straightforwardly (Scheme 64).¹¹⁰ In general, the *trans* diastereoisomers **243** were precipitated from the reaction mixture and were collected by filtration. The supernatants contained the *cis*-diastereoisomers **244** together with residual amounts of the *trans*-isomers **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

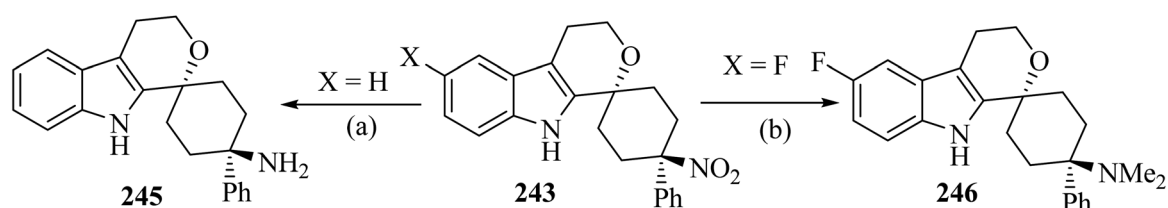


Scheme 63 Proposed mechanism for the formation of products 235.





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 pharmaceuticals. 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.

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