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Recent applications of isatin in the synthesis of organic compounds

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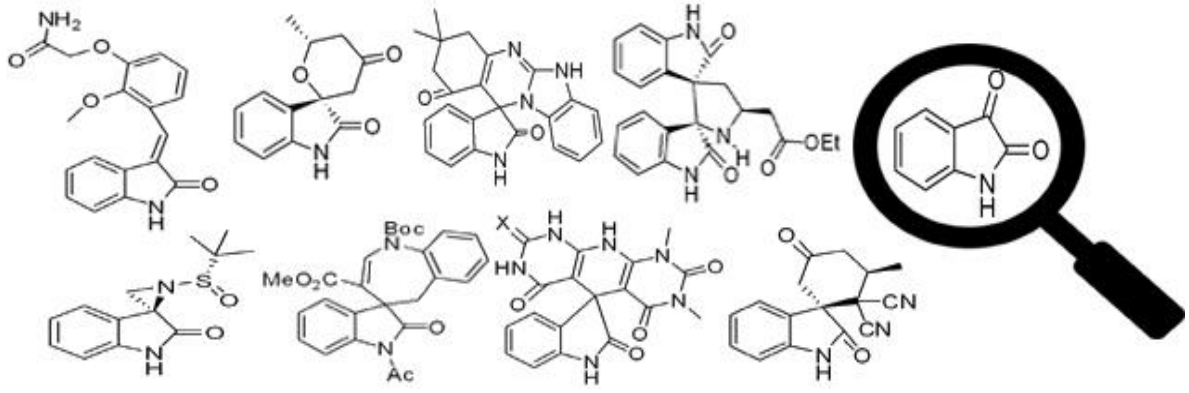
Abstract

Isatin has been used in design and synthesis of diverse types of heterocyclic and carbocyclic compounds and considered as a valuable building block in organic synthesis. There is a diversity of multicomponent reactions of this useful reagent. This article aims to review the advances in the use of isatin as starting material in the synthesis of various organic compounds and drugs up to June 2016.



Keywords: Isatin, organic compounds, heterocyclic compounds, carbocyclic compounds

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1. Introduction

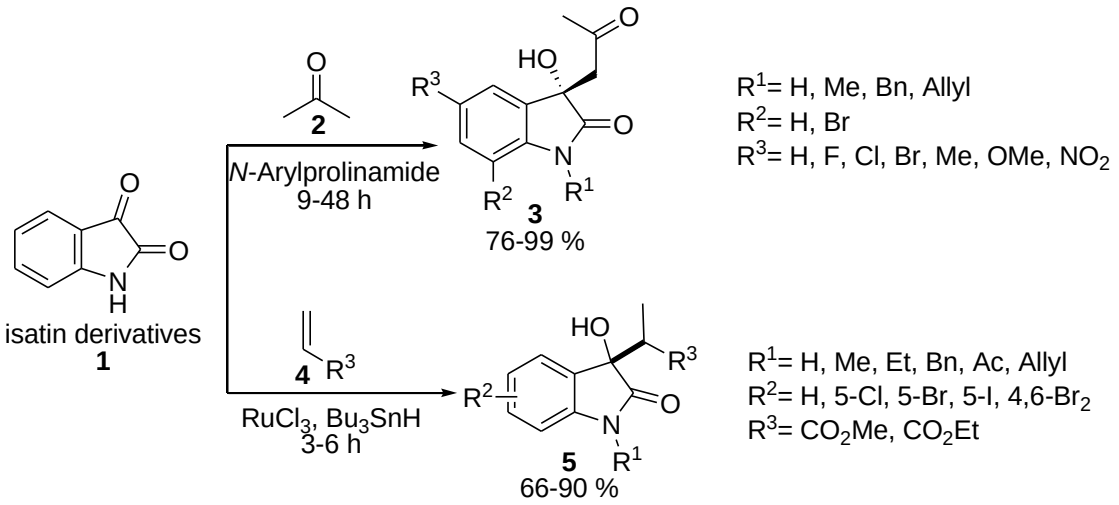
Isatin was first obtained by Erdmann[1] and Laurent[2] in 1840 as a product of the oxidation of indigo dye by nitric acid and chromic acid. Isatin is one of the most important heterocyclic compounds. For example, Schiff bases of isatin are used for their pharmaceutical properties.[3] Oxindole as an isatin derivative represents an important class of heterocyclic compounds endowed of interesting pharmacological[4,5] and biological activities such as antimicrobial,[6] antitumor,[7,8] antitubercular,[9,10] antimalaria,[11] anti-HIV[12] and antibacterial activities.[13] On the other hand, the chiral 3,3-disubstituted oxindole framework is a privileged motif found in various natural products and pharmaceutically active compounds.[14] As a class of important 3,3-disubstituted oxindoles, 3-substituted 3-hydroxyindolin-2-ones have attracted considerable attention because of their diverse biological activities.[15,16]

During recent years several review articles were published on isatins. Singh and Desta reviewed isatin as a privileged molecule in design and synthesis of spiro-fused cyclic frameworks.[17] Synthesis of spiro[18] and multispiro[19] heterocyclic compounds from isatin were studied by Borad et al. The enantioselective reactions of isatin were also the subject of several review articles.[20-22] Herein, in continuation of our studies towards isatin,[23-25] and since there is a wide range of reactions that include isatin in the synthesis of organic compounds, this review presents the recent applications of isatin in the synthesis of different types of organic compounds up to June 2016.

2. Reactions at the C-3 Position of Isatin

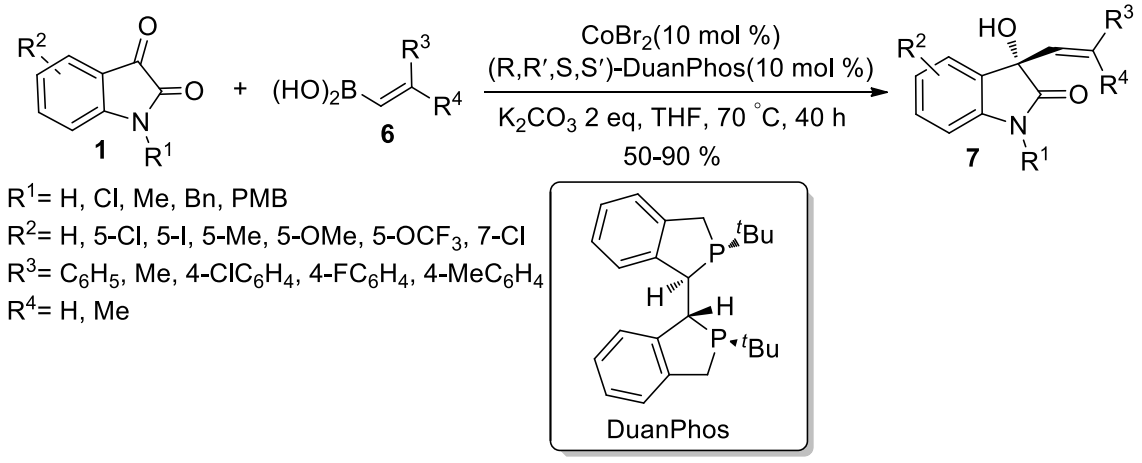
The direct asymmetric aldol reaction between isatin derivatives **1** and acetone **2** at -35 °C in EtOH using *N*-

arylprolinamides has been developed and the corresponding aldol products **3** were obtained (Scheme 1).[26] The same authors used trans-4-hydroxy-L-prolinamide as a catalyst in this reaction.[27] In a similar reaction, α-cross-coupling aldol addition of activated olefins **4** with isatins **1** has been described in the presence of ruthenium(III) chloride and tributyltin hydride (TBTH) at room temperature to afford 3-substituted-3-hydroxy-2-oxindoles **5** (Scheme 1).[28]



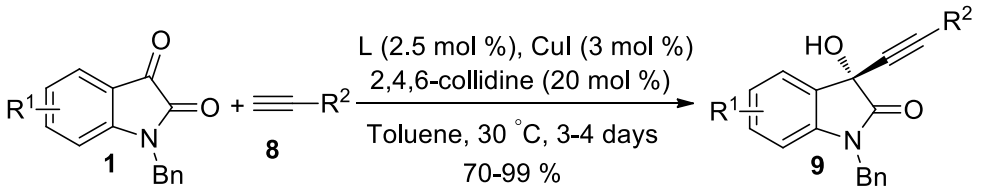
Scheme 1

The vinylation of isatins **1** by vinyl boronic acids **6** catalyzed by $CoBr_2$ in the presence of DuanPhos was reported for the synthesis of the tertiary allylic alcohols **7** (Scheme 2).[29]

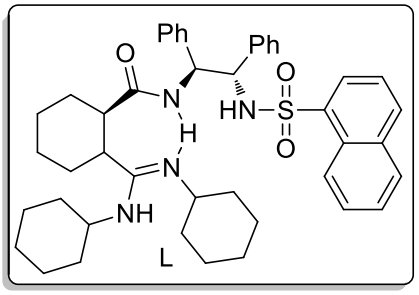


Scheme 2

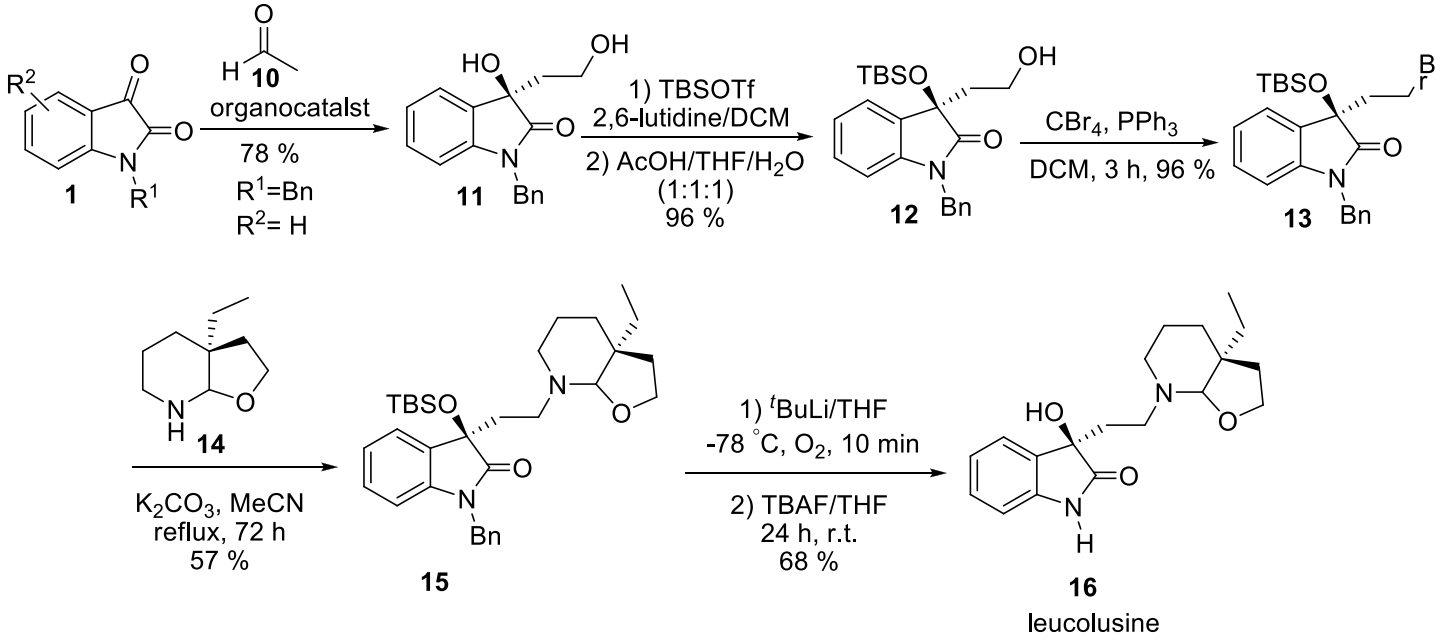
The alkynylation reaction of isatins **1** and aryl-substituted alkynes **8** in the presence of bifunctional guanidine/CuI as catalyst was accomplished for the synthesis of 3-substituted 3-hydroxyoxindole scaffolds **9** (Scheme 3).[30] In another study, zink dust was also used as catalyst in this reaction.[31]

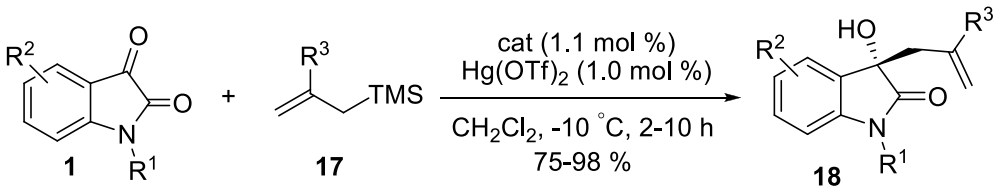


R^1= H, 4-Cl, 5-F, 5-Br, 5-I, 5-MeOO, 5-CF_3O, 7-F, 7-Br, 7-Cl, 7-I, 7-CF_3, 7-CF_3O
R^2= 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, $CH_2C_6H_4$, CH_2OCOEt, CH_2OCOPh, CH_2O^tBu, CH_2NHBoc, ^{i}Pr, cyclopropyl, $^nC_5H_{11}$, $^nC_{10}H_{21}$, cyclopentyl, cyclohexyl, propenyl, octynyl, 2-methylisoindolinyl-1,3-dione

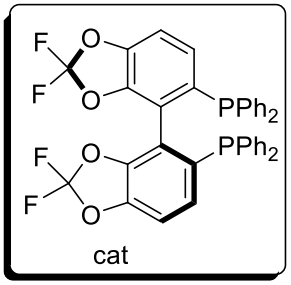


Scheme 3





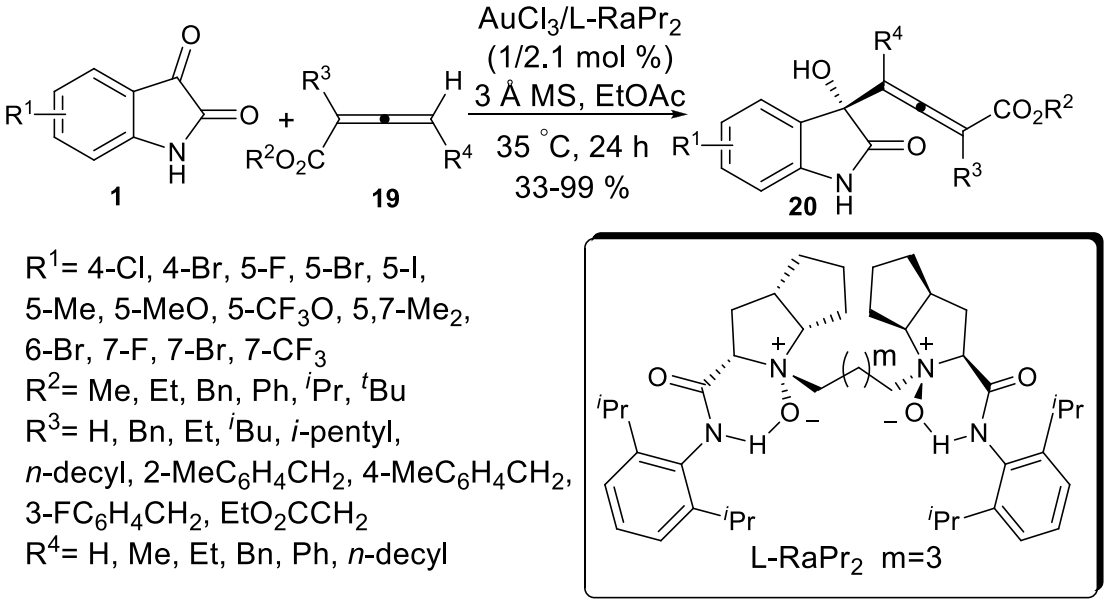
R^1= H
R^2= H, 5-Me, 5-MeO, 5-F, 5-Cl, 5,7-Me_2, 4,6-Br_2, 6-Br, 7-Me, 7-Cl, 6,7-Me_2, 6-Cl-7-Me
R^3= H, Me, CH_2OAc



Scheme 4

The diastereoselective total synthesis of leucolusine **16** was described by the coupling of enantioenriched (*R*)-1-benzyl-3-(2-bromoethyl)-3-((tert-butyldimethylsilyl)oxy)indolin-2-one **13** with **14**, which gave **15** in 57% yield (Scheme 4).[32] Precursor **13** was prepared from **12** that obtained from 3-alkyl-3-hydroxyindolin-2-one **11** by the known organocatalytic cross-aldol reaction between acetaldehyde **10** and *N*-benzylisatin **1**. Global deprotection of **15** using ^{t}BuLi/O_2 in THF at -78 ^{o}C followed by treatment with TBAF led to the formation of natural leucolusine **16** with 68% isolated yield. In another study, the 3-allyl-3-hydroxyoxindoles **18** were obtaind from allylation reaction of isatin derivatives **1** and allyltrimethylsilane **17** using the (*S*)-difluorophos derived chiral $Hg(OTf)_2$ complex as a catalyst (Scheme 4).[33]

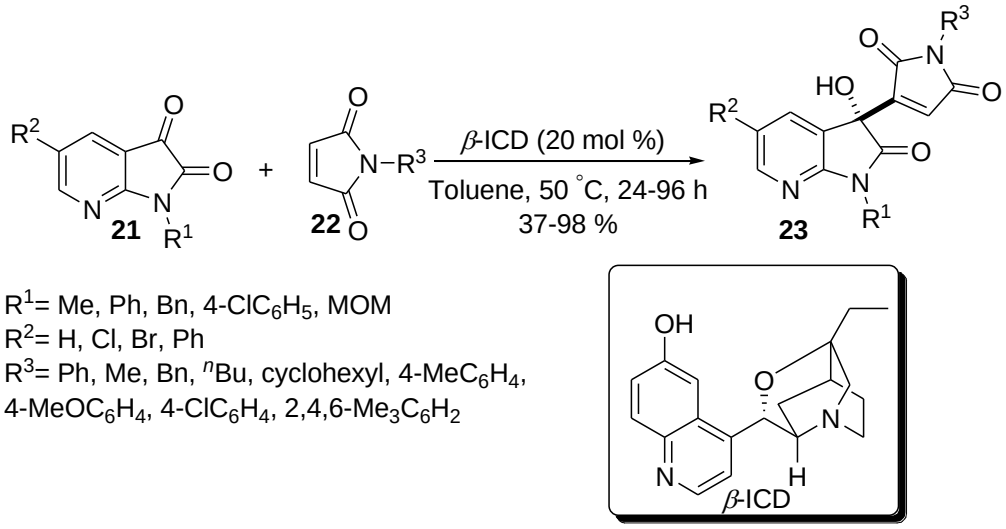
The diastereo- and enantio-selective aldol addition of allenic esters **19** to isatins **1** in the presence of $AuCl_3$ and chiral *N*,*N*'-dioxide has been reported for the synthesis of the carbinol allenoates **20** (Scheme 5).[34] The decrease in yield and enantioselectivity was mainly due to the steric hindrance of vicinal 4-substituted bulky halogen atoms (4-Cl, 4-Br). 5,7-Dimethyl-substituted isatin provided the best enantioselectivity.



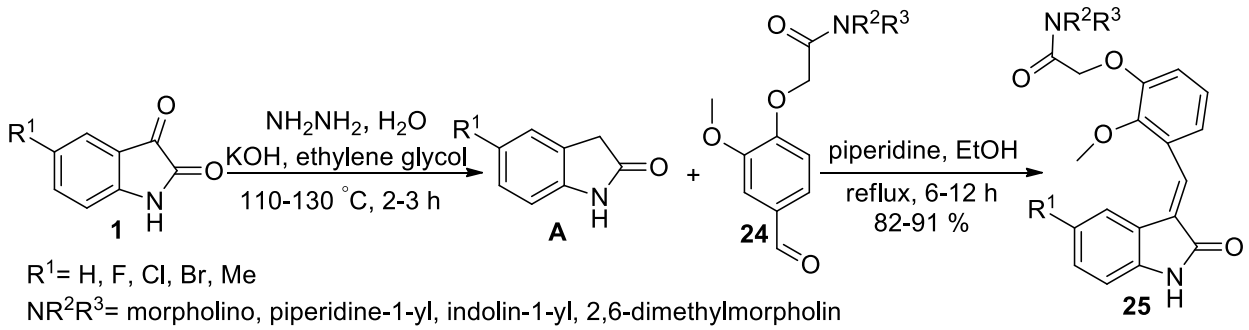
Scheme 5

A series of 3-hydroxy-7-aza-2-oxindoles **23** have been synthesized in good yields and moderate to high enantioselectivity via the enantioselective Morita–Baylis–Hillman (MBH) reaction of 7-azaisatins **21** with maleimides **22** in the presence of bifunctional tertiary amine, β-isocupreidine (β-ICD) as the catalyst (Scheme 6).[35]

Shankaraiah's group designed the synthesis of new (*Z*)-3-(3´-methoxy-4´-(2-amino-2-oxoethoxy)benzylidene)indolin-2-one derivatives **25** from the Knoevenagel condensation reaction of isatin derivatives **1** and 3-methoxy-4-(2-amino-2-oxoethoxy)-benzaldehydes **24** (Scheme 7).[36] The products were evaluated for their cytotoxic activity against selected human cancer cell lines of prostate (PC-3 and DU-145), breast (BT-549 and MDA-MB-231) and non-tumorigenic prostate epithelial cells (RWPE-1).

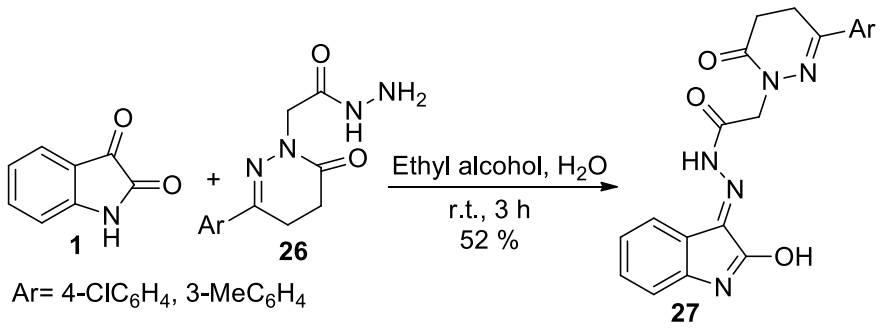


Scheme 6



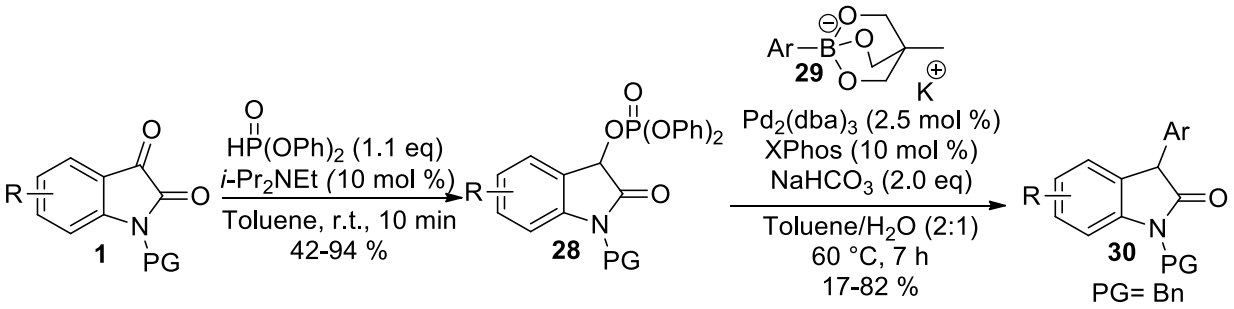
Scheme 7

Shaker and Marzouk investigated the condensation of isatin **1** with acetohydrazide **26** to yield the oxoindolinylidene **27** (Scheme 8).[37] The newly prepared compound was tested *in vitro* against a panel of four human tumor cell lines, namely hepatocellular carcinoma (liver) HePG-2, colon cancer HCT-116, human prostate cancer PC3, and mammary gland breast MCF-7. It was also tested as an antioxidant.



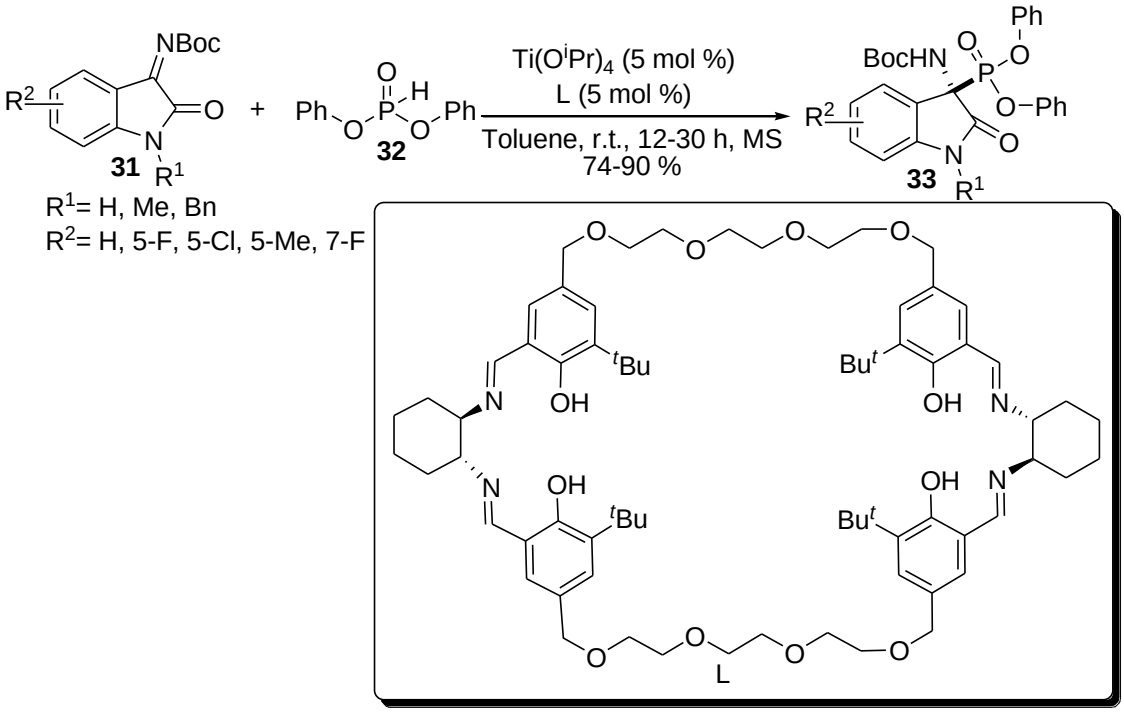
Scheme 8

Terada's group developed a methodology based on the two-step sequence strategy for the synthesis of 3-arylisatin derivatives **30** from the isatin derivatives **1** and aryl boron salts **29**. The methodology involves the formation of an oxindole having a phosphate moiety **28** at the C-3 position via the [1,2]-phospha-Brook rearrangement under Brønsted base catalysis and the subsequent palladium-catalyzed cross-coupling reaction with aryl boron **29** reagents (Scheme 9).[38]



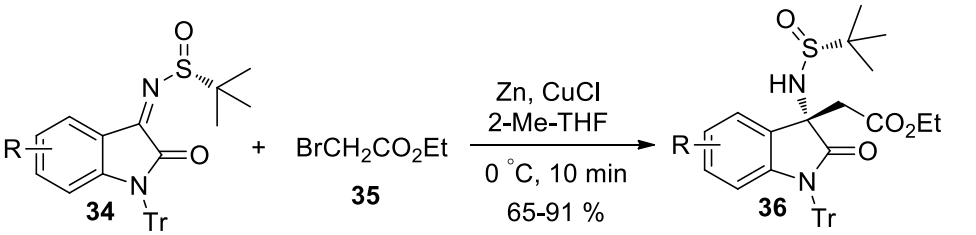
Scheme 9

Bajaj and co-workers reported the use of macrocyclic Ti(IV)-salen complexes as catalysts for enantioselective hydrophosphonylation (EHP) reaction of isatin derived ketimines **31** with diphenyl phosphate **32** as nucleophile. The corresponding phosphonylated products **33** were obtained in high enantioselectivity (ee up to 99%) (Scheme 10).[39]



Scheme 10

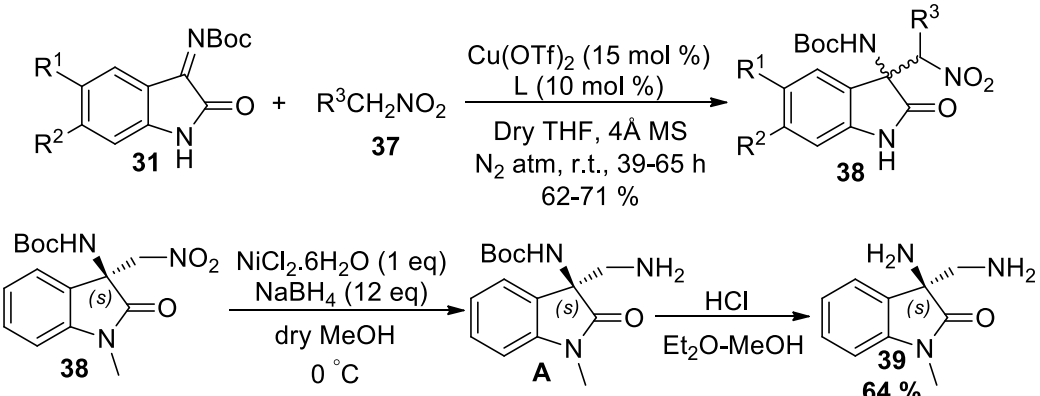
In another study, Su and Xu developed the synthesis of optically pure 2-oxoindolinyl-β^{3,3}-amino esters **36** in good yields via the diastereoselective asymmetric Reformatsky-type reaction of isatin-derived chiral *N*-sulfinyl ketimines **34** with ethyl bromoacetate **35** (Scheme 11).[40]



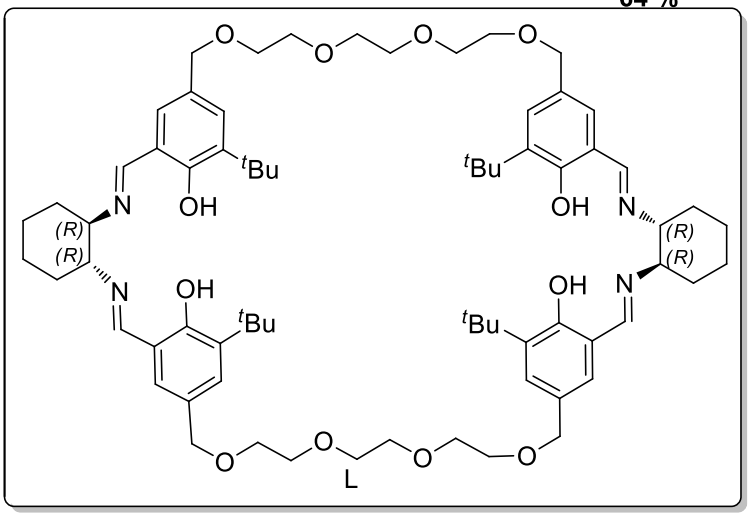
R= H, 5-F, 5-Cl, 5-Br, 5-I, 5-Me, 5-MeO, 5-^{i}Pr, 6-Cl, 6-Br, 7-F, 4,6-F_2, 5-F-6-MeO

Scheme 11

Kureshy's group synthesized the β-nitro amines **38** from the asymmetric aza-Henry reaction of various isatin derived *N*-Boc ketimines **31** with nitromethanes **37** in the presence of the chiral Cu(*II*) dimeric macrocyclic salen complex as catalyst (ee, up to 99%). This protocol was also used for the synthesis of enantiomerically pure (*S*)-β-diamines **39** via asymmetric aza-Henry reaction of *N*-Boc ketimine **31** in two steps in good yield and high enantioselectivity (Scheme 12).[41]

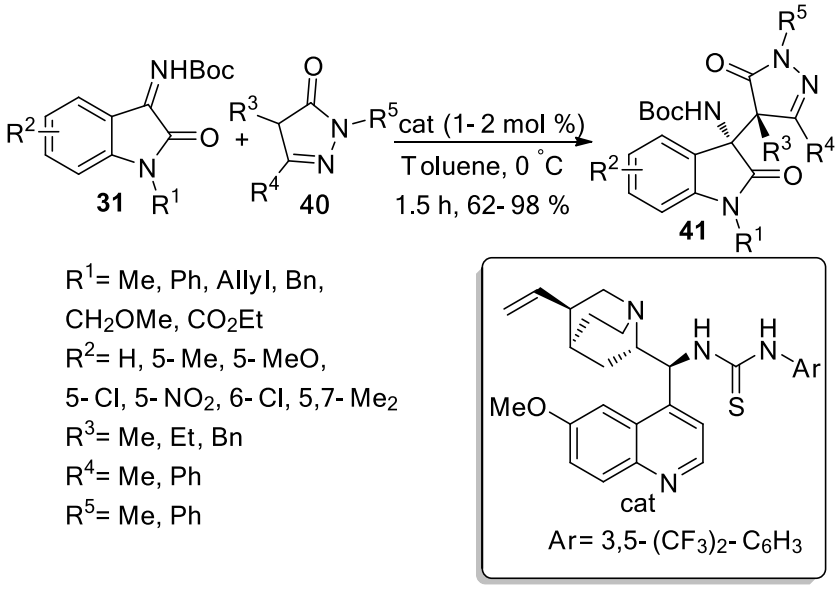


R^1= H, Cl
R^2= H, Br
R^3= Me, ^{n}Bu, Me_2

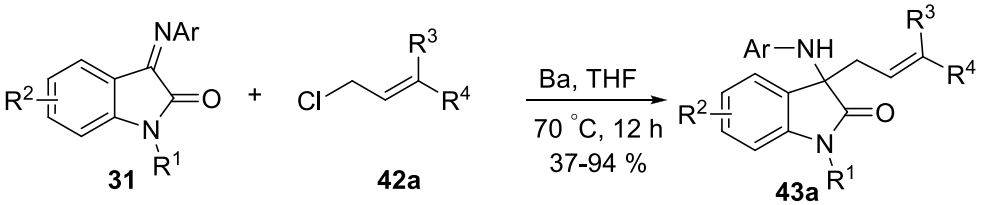


Scheme 12

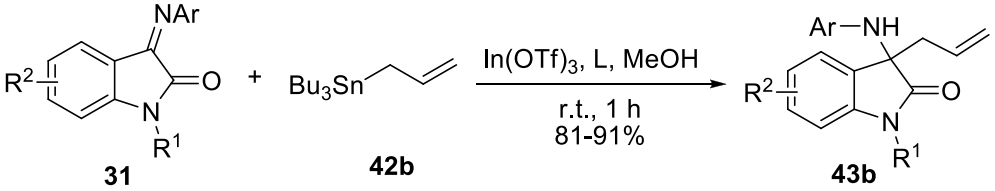
Pedro's group reported the enantioselective addition of 4-substituted pyrazolones **40** to isatin-derived ketimines **31**. In this study, the authors used a bifunctional organocatalyst (a quinine-derived thiourea) to provide a variety of chiral heterocyclic compounds containing both aminooxindole and pyrazolone moieties bearing vicinal quaternary stereocenters **41** (Scheme 13).[42,43]



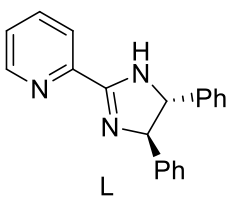
Scheme 13



R1= Bn, Ph_3C, 4-$MeOC_6H_4CH_2$, Me
R2= H, 6-Br, 7-F
R3= H, Me, *n*-C_6H_{13}, $Me_2C{=}CH(CH_2)_2$
R4= H, Me, *n*-C_6H_{13}, $Me_2C{=}CH(CH_2)_2$, Ph
Ar= C_6H_5, 4-MeC_6H_4, 4-*i*-PrC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4,4-ClC_6H_4, 4-BrC_6H_4, 4-IC_6H_4, 4-$F_3CC_6H_4$, 3,5-$Me_2C_6H_3$, 2,4-$F_2C_6H_3$



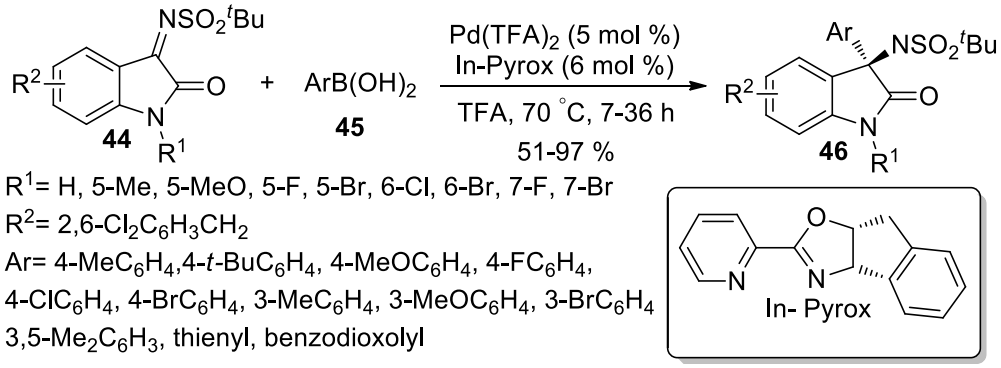
R1= H, Me, Ph, Bn
R2= H, 5-Me, 5-MeO, 5-Cl, 6-Cl, 7-Cl
Ar= C_6H_5, 2-MeC_6H_4, 3-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$,4-ClC_6H_4, 4-BrC_6H_4



Scheme 14

Various α-allylated 3-amino-2-oxindoles **43a** were achieved by the Barbier-type allylation of isatin imines **31** with allylic comppounds **42a** using metallic barium as the promoter (Scheme 14).[44] In a similar study, Chen and Cai described the $In(OTf)_3$-catalyzed allylation of ketimines derived from isatins **31** in the presence of an imidazolylpyridine ligand, L (Scheme 14).[45]

The 2-oxindoles bearing chiral *α*-tertiary amines at the 3-position **46** were prepared in good yields and with high enantioselectivities via a Pd(II)/Pyrox-catalyzed addition of arylboronic acids **45** to 3-ketimine isatins **44** (Scheme 15).[46] The absolute configuration of one of the products (R^2= H) was determined to be *R* and the absolute configuration of the C=N bond of the 3-ketimine isatin was determined to be *E* by X-ray crystallographic analysis.

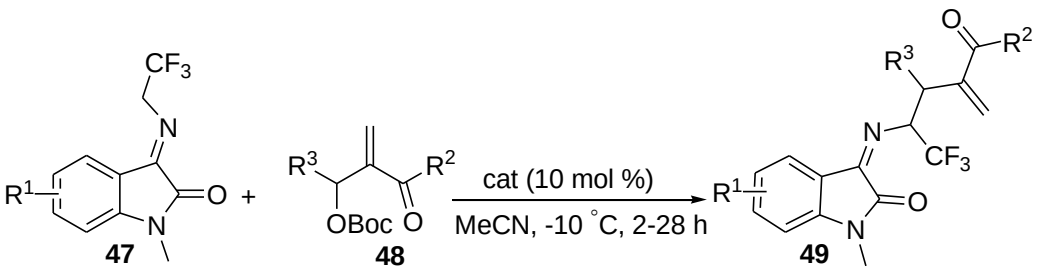


Scheme 15

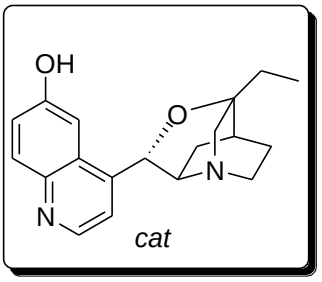
A simple and efficient way for the synthesis of a series of chiral α-trifluoromethylamines **49** with excellent yields and stereoselectivities was reported by Li and co-workers. The reaction was performed between *N*-2,2,2-trifluoroethylisatin ketimines **47** and MBH type carbonates **48** using β-isocupreidine (β-ICD) as catalyst. A possible mechanism of this reaction was proposed, as shown in scheme 16, β-ICD attacks the MBH carbonate **48** via an S_N2' process (intermediate **B**). It behaves as a Lewis base chiral catalyst. This is followed by another S_N2'-type process, with the isatinketimine **47** acting as an active nucleophile (intermediate **A**) (Scheme 16).[47]

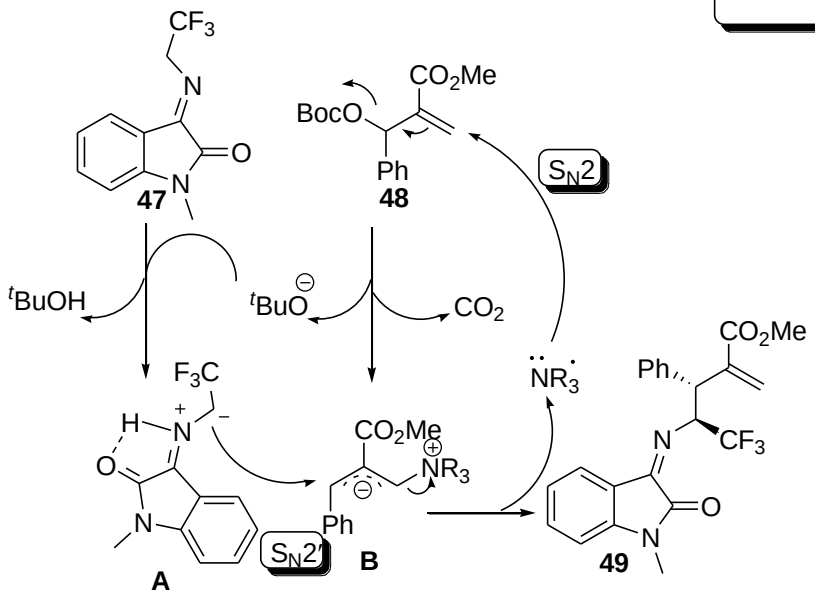
Elghamry and Al-Faiyz developed a new method for the synthesis of quinoline-4-carboxylic acids **51** using isatin **1** and enaminones **50** as a substitute for 1,3-dicarbonyl compounds in the Pfitzinger reaction (Scheme 17).[48]

Microwave assisted synthesis of 4-phenyl-1,3-thiazole derivatives **54** from the reaction of isatin **1**, 2-bromoethanones **52** and thiosemicarbazide **53** has been accomplished (Scheme 18).[49] The synthesized compounds were tested for their antimicrobial activities.

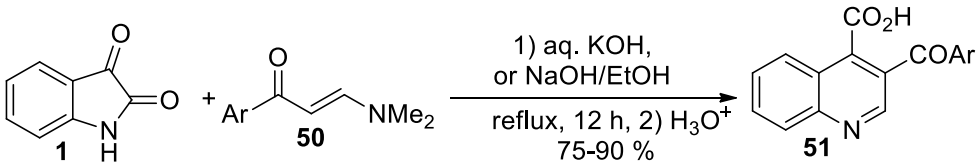


R^1= H, 4-Cl, 4-Br, 5-Me, 5-Br
R^2= Me, Et, OMe, OEt, O^{t}Bu
R^3= C_6H_5, 2-ClC_6H_4, 2-MeC_6H_4, 2-$MeOC_6H_4$, 3-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, thienyl, α-naphthyl, β–naphthyl



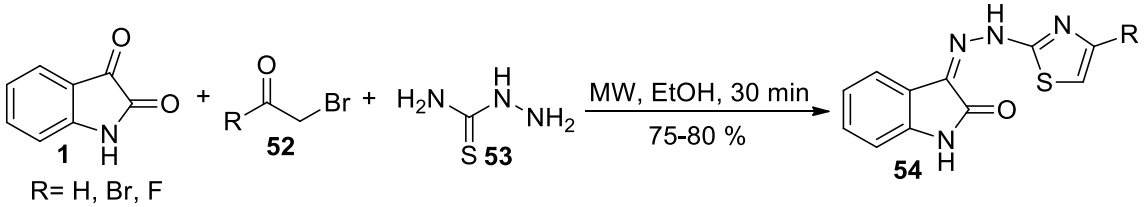


Scheme 16



Ar= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

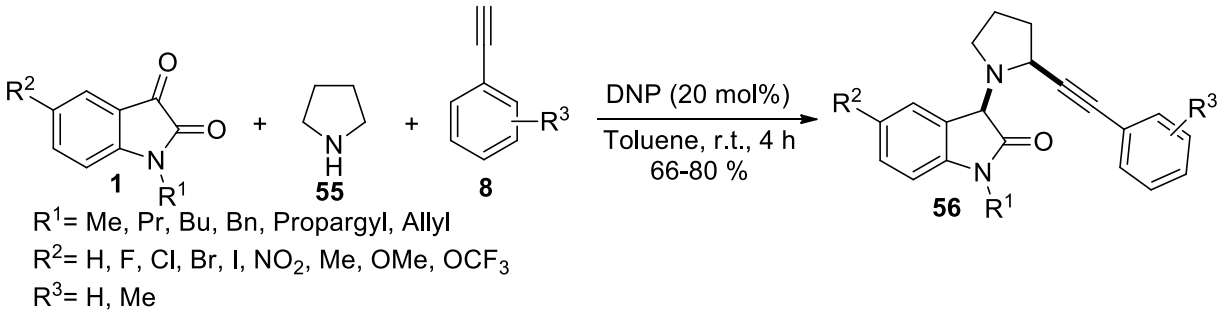
Scheme 17



R= H, Br, F

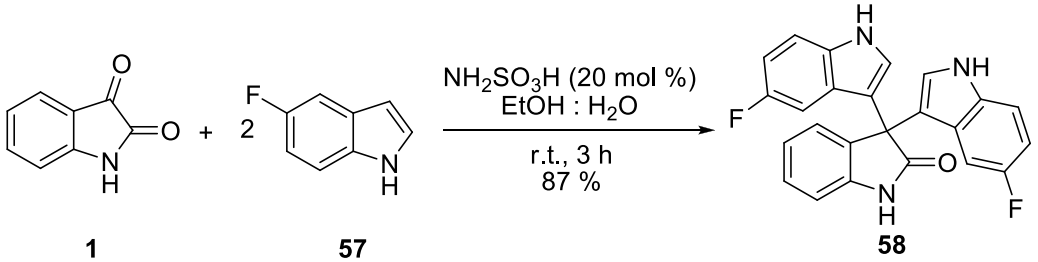
Scheme 18

2,4-Dinitrophenol (DNP) facilitated the three component reaction of isatins **1**, cyclic-amines **55** and alkynes **8** to prepare the mono-functionalized *α*-alkynyl-3-amino-2-oxindole derivatives **56** (Scheme 19).[50]



Scheme 19

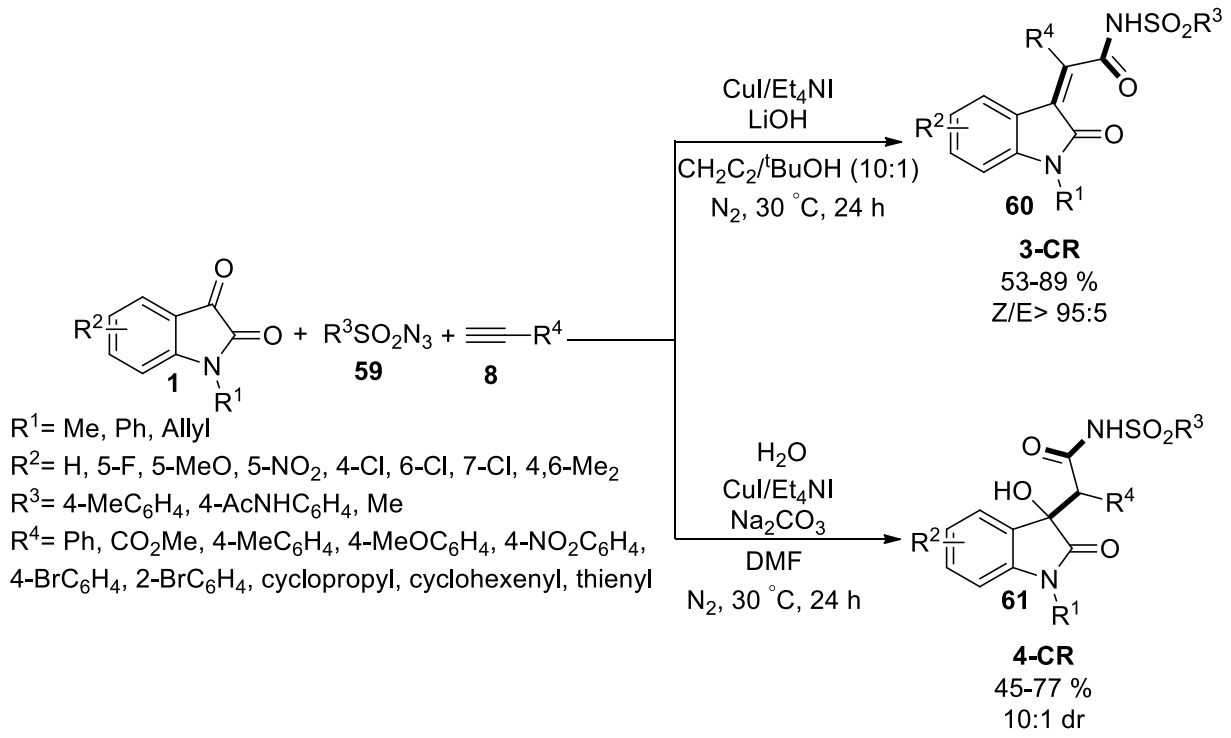
The new indole derivative 5,5”-difluoro-1*H*,1”*H*-[3,3’:3’,3”-terindol]-2’(1’*H*)-one **58** has been synthesized from the reaction of isatin **1** and 2 eq. 5-fluoroindole **57** in the presence of sulfamic acid as an efficient organocatalyst (Scheme 20).[51] Crystal structure of the product was determined by X-ray structure analysis. In other studies, the reactions of various isatin derivatives **1** and indoles **57** were also investigated in the presence of nano SiO_2[52] and Fe_3O_4@SiO_2@SO_3H[53] as catalysts.



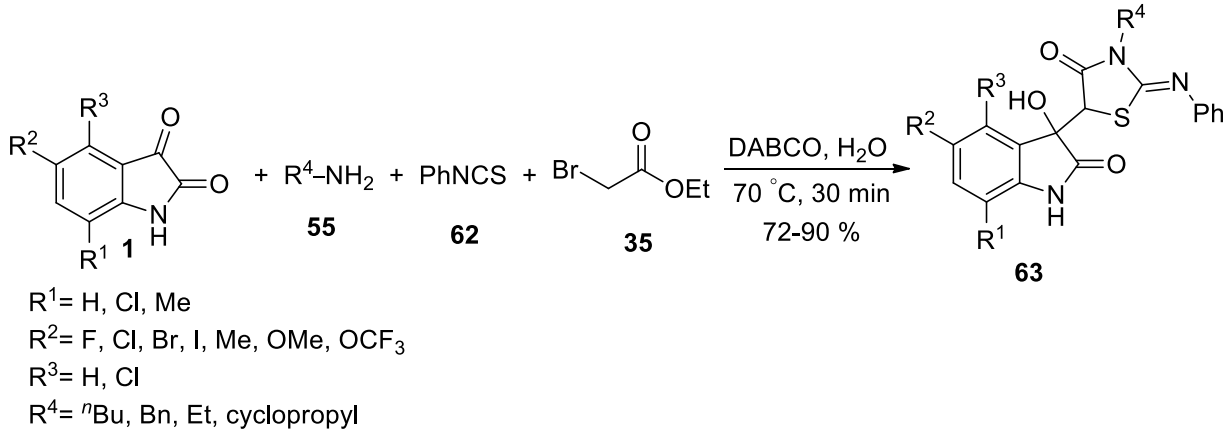
Scheme 20

A tunable copper-catalyzed azide-alkyne cycloaddition (CuAAC)-initiated multicomponent reaction strategy for the construction of 3-functionalized indolin-2-ones have been reported. In this regard, the reaction of isatins **1**, tosyl azides **59**, and terminal alkynes **8** the presence of CuI and Et_4NI was developed. This tandem process can be manipulated to proceed in three-component and four-component fashion respectively, yielding a range of (*Z*)-3-alkenyloxindole **60** or 3-substituted 3-hydroxyoxindole **61** compounds (Scheme 21).[54]

Meshram and co-workers reported a one-pot four component protocol for the synthesis of a novel class of functionalized (*Z*)-5-(3-hydroxy-2-oxoindolin-3-yl)-2-iminothiazolidin-4-ones **63** by the reaction of substituted isatins **1**, amines **55**, phenylisothiocyanate **62** and ethyl bromoacetate **35** in the presence of DABCO as catalyst in aqueous medium (Scheme 22).[55] The 5-halo isatins reacted under standard condition and resulted in moderate yields of products while other 5-substituted isatins reacted smoothly to furnish the desired products in high yields. As like monosubstituted isatins, disubstituted isatins reacted in the same way and afforded comparatively less yield of desired products under standard reaction conditions.



Scheme 21



Scheme 22

3. Synthesis of Isatin-based Spiro-fused Heterocyclic Frameworks

The heterocyclic spirooxindole ring system is a widely distributed structural framework in a number of pharmaceuticals and natural products,[56] including cytostatic alkaloids such as spirotryprostatins A, B, and strychnophylline.[57] The unique structural array and the highly pronounced pharmacological activity displayed by the class of spirooxindole compounds have made them attractive synthetic targets (Figure 1).[58-60]

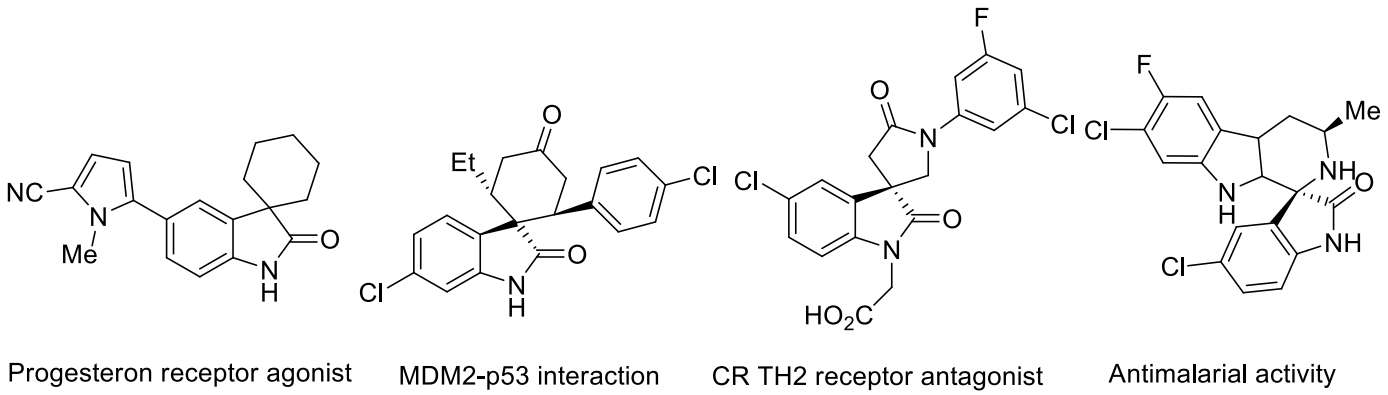
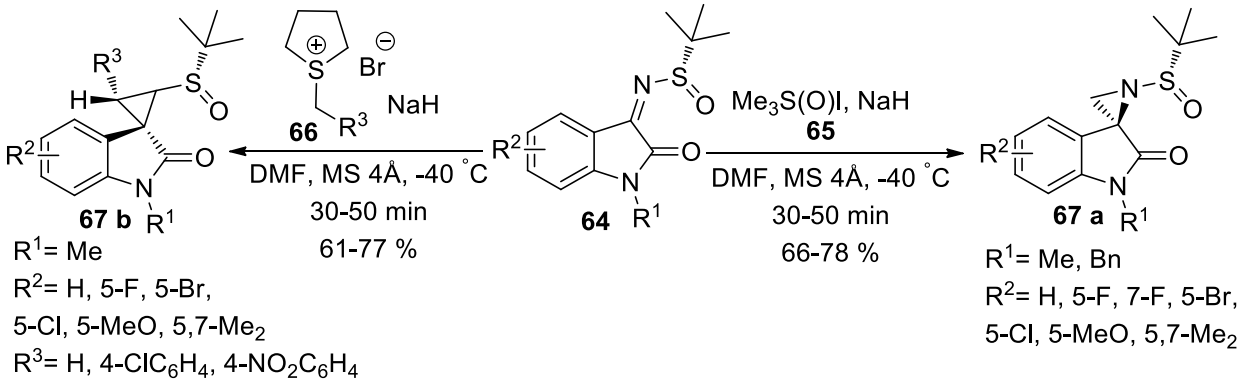


Figure 1

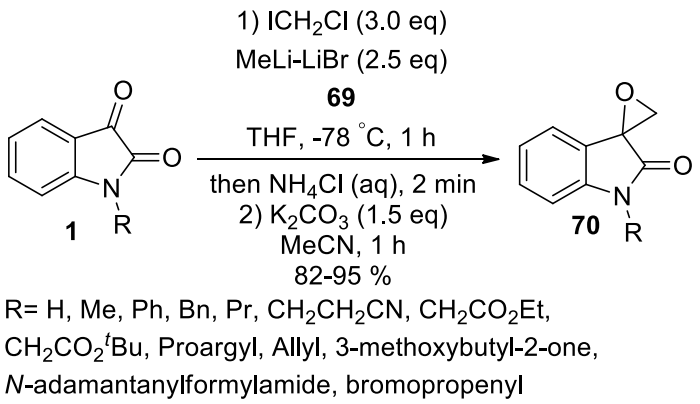
3.1. Synthesis involving two-component reactions of isatins

3.1.1. Three-membered heterocycles. Hajra *et al*. carried out the asymmetric synthesis of spiroaziridine oxindoles **67a**, **67b** via the aza Corey-Chaykovsky reaction of isatin-derived tert-butanesulfinyl ketimines **64** with *in situ* generated sulfur ylide from trimethylsulfonium iodide **65** (or the reaction of benzyl sulfur ylides generated from *S*-benzyl tetrahydrothiophenium bromide **66** with chiral tertbutanesulfinyl ketimines **64**) and NaH (Scheme 23).[61]



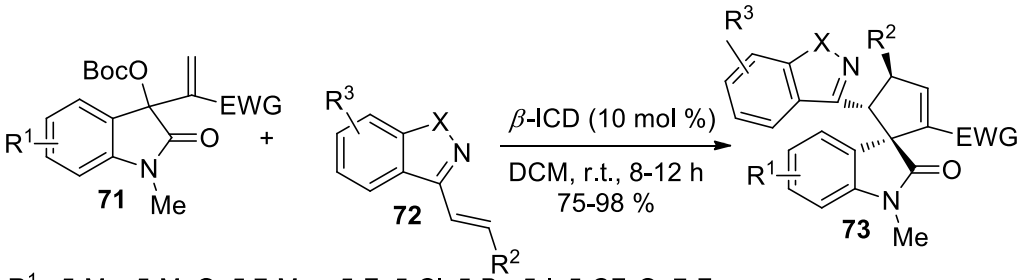
Scheme 23

An efficient chemoselective access to rare spiro-epoxyoxindoles **70** has been developed through the addition of the carbenoidic chloromethyllithium **69** to various *N*-functionalized isatins **1** followed by the ring closure (Scheme 24).[62]



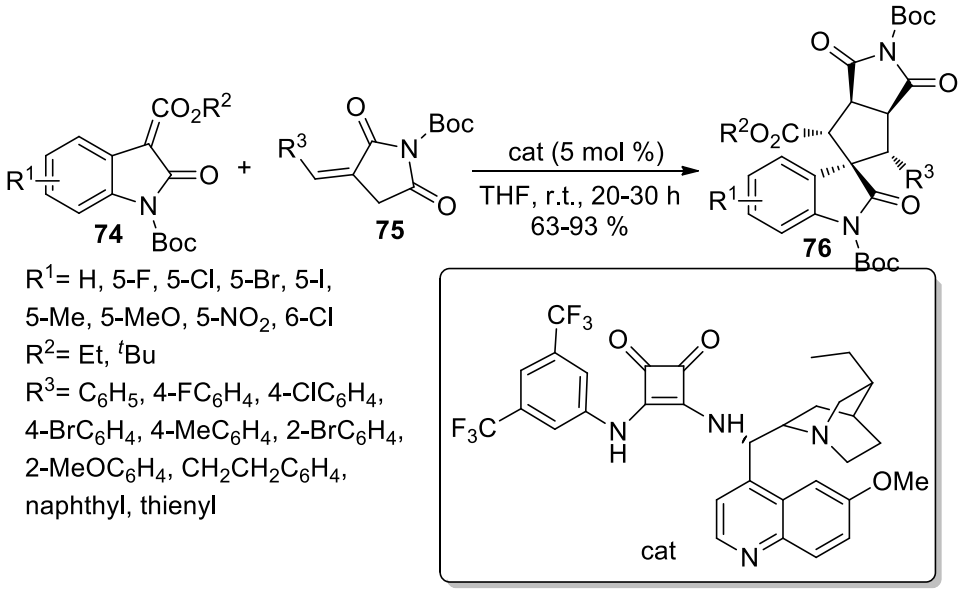
Scheme 24

3.1.2. Five-membered heterocycles. Wang *et al*. developed an α-regioselective asymmetric [3 + 2] annulation reaction of isatins **71** and 1-azadienes **72** for the synthesis of bulky 1,2-benzoisothiazole 1,1-dioxide motifs **73** (Scheme 25).[63]



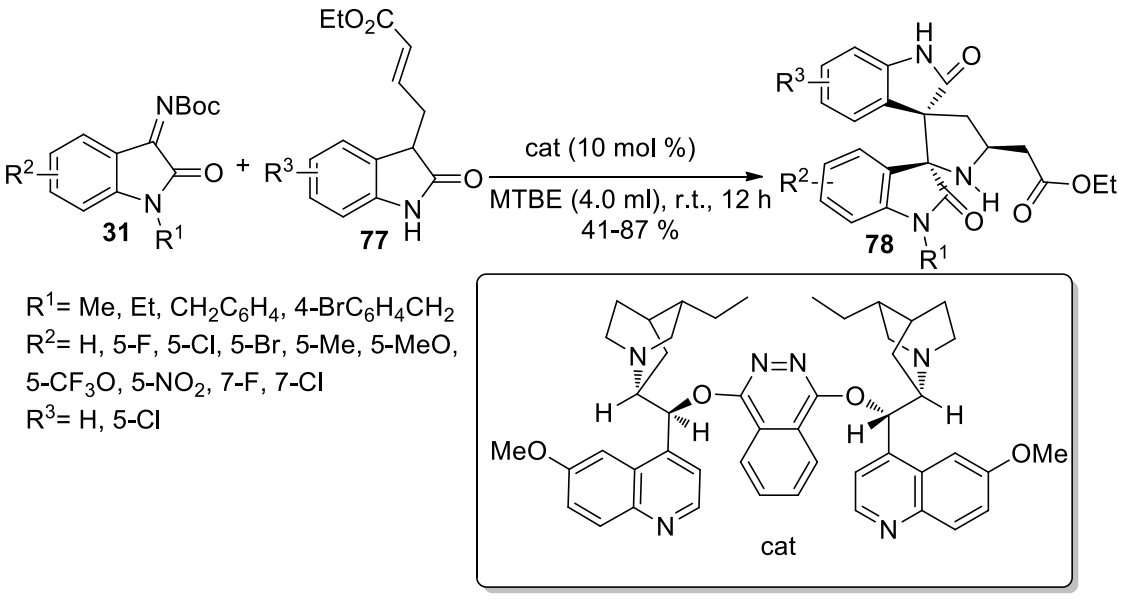
Scheme 25

Zhao and Du developed an efficient cascade Michael/Michael reaction catalyzed by a bifunctional tertiary amine–squaramide catalyst for the asymmetric synthesis of five-membered spirooxindoles containing five contiguous stereocenters **76** from the reaction of isatin derived enoates **74** and α-alkylidene succinimides **75**. The products were obtained with excellent diastereoselectivities and enantioselectivities (Scheme 26).[64]



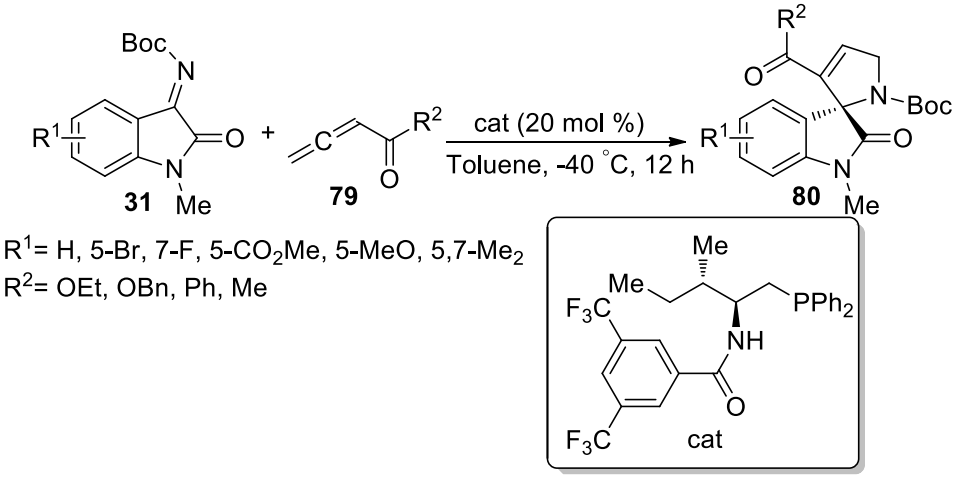
Scheme 26

The functionalized 3,3'-pyrrolidinyldispirooxindole derivatives **78** with three stereogenic centers, including two contiguous spiro-stereocenters were achieved from the stereoselective organocatalytic Mannich/Boc-deprotection/aza-Michael sequence reaction of isatin imines **31** and the 3-substituted oxindoles **77** employing the commercially available $(DHQD)_2PHAL$ as the catalyst (Scheme 27).[65]



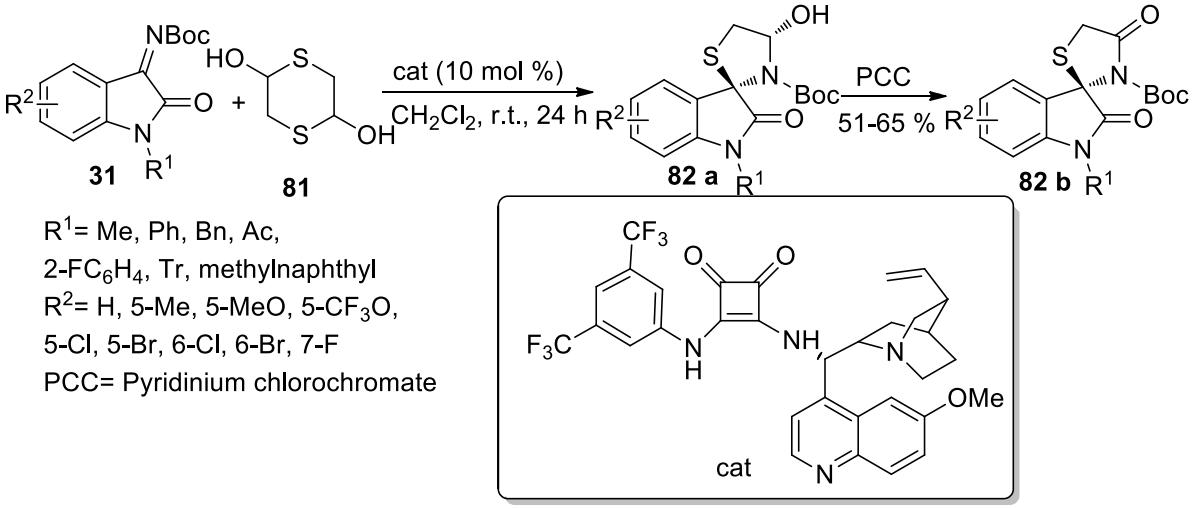
Scheme 27

The synthesis of 3,2'-dihydropyrrolyl spirooxindoles **80** with excellent enantioselectivities (up to >99%) was accomplished by asymmetric [3 + 2] annulation of isatin imines **31** with zwitterions generated from allenyl esters as well as allenyl ketones **79** catalyzed by L-isoleucine derived bifunctional *N*-acylaminophosphine (Scheme 28).[66]



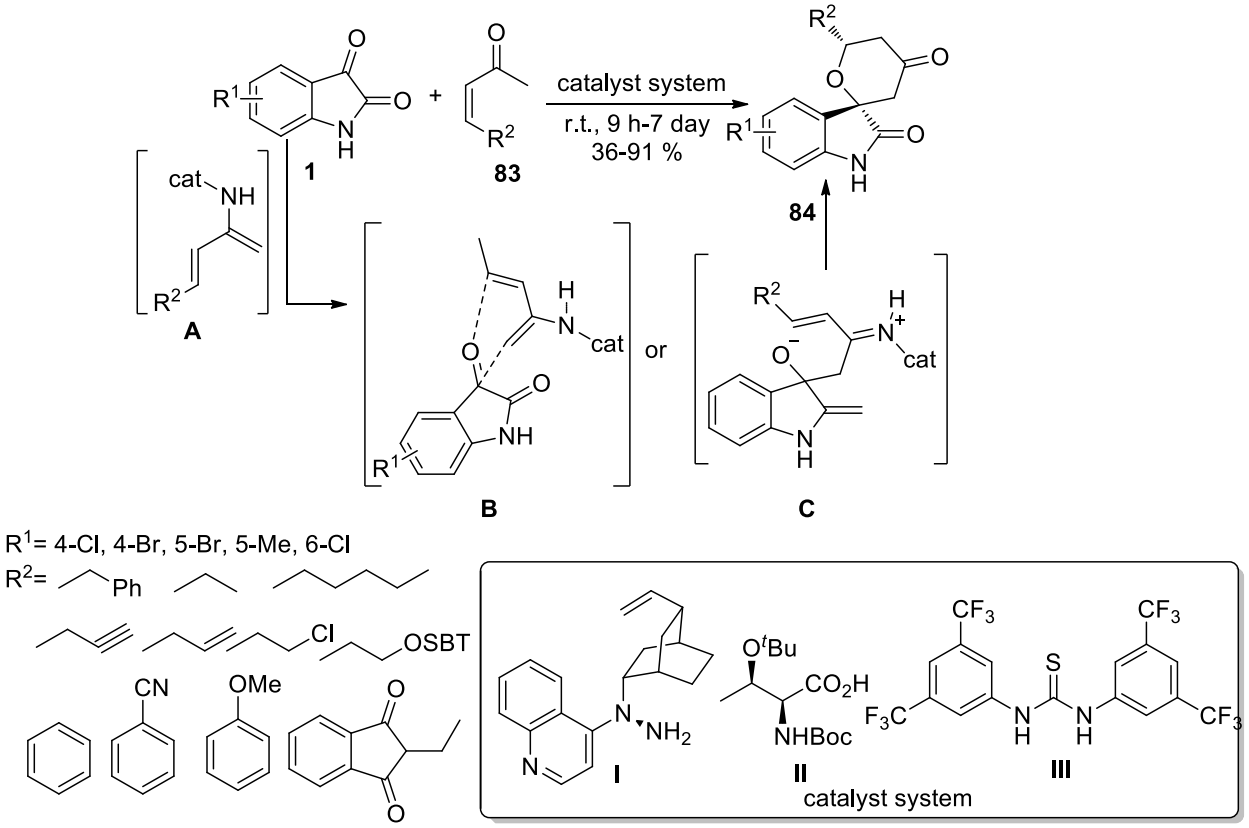
Scheme 28

The enantioenriched spirooxindole based 4-thiazolidinones **82** were accessed through the catalytic asymmetric [3 + 2] annulation of isatin ketimines **31** with the 1,4-dithiane-2,5-diol **81** using a bifunctional catalyst followed by simple oxidation with high enantioselectivity (up to 98% ee) (Scheme 29).[67]



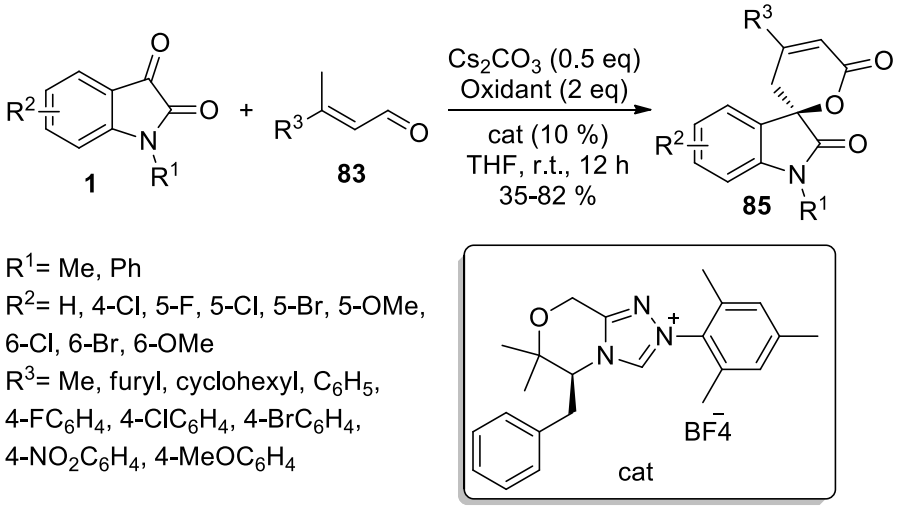
Scheme 29

3.1.3. Six-membered heterocycles. The hetero-Diels–Alder (hDA) reaction of isatins **1** with enones **83** that was catalyzed by an amine-based catalyst system composed of three molecules (an amine, an acid and a thiourea) was accomplished for synthesis of the functionalized spirooxindole tetrahydropyran derivatives **84** according to intermediates **A-C** (Scheme 30).[68,69]



Scheme 30

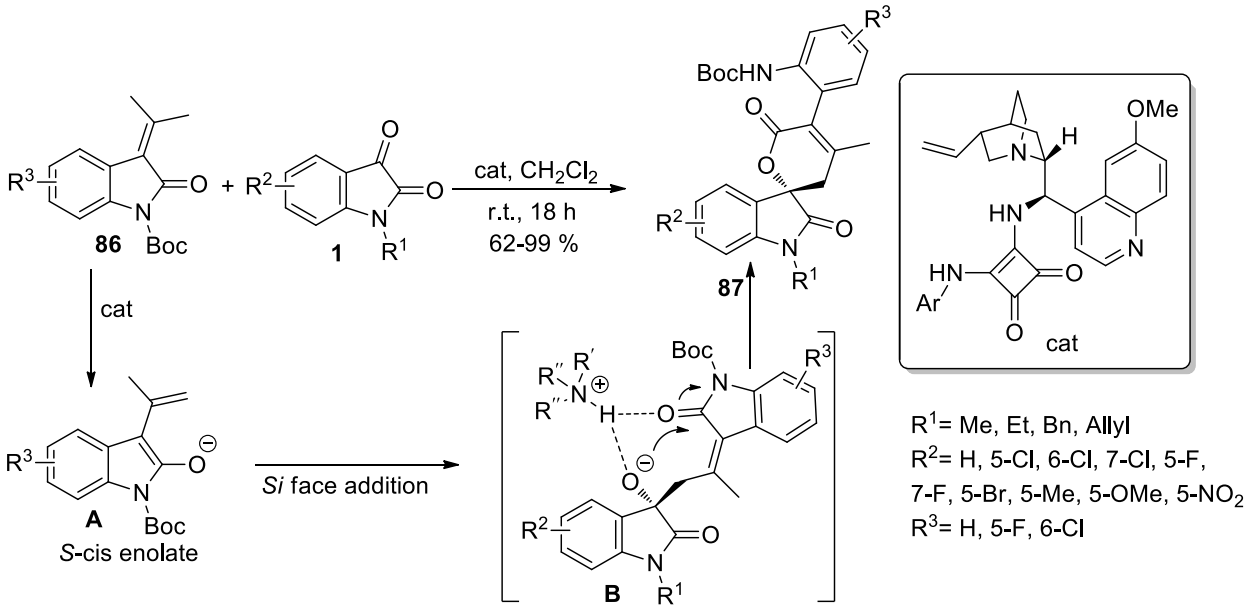
The enantioselective [4 + 2] assemble of spirolactones **85** through a chiral *N*-heterocyclic carbene (NHC)-catalyzed remote *γ*-carbon addition of enals **83** with isatins **1** was reported by Zhou and co-workers (Scheme 31).[70] Yao and co-workers studied this reaction using the same catalyst and base.[71]



Scheme 31

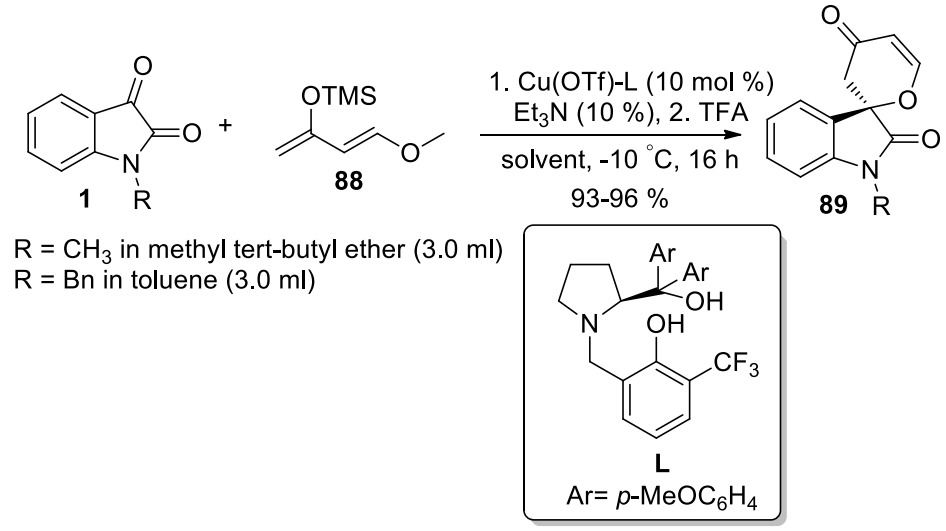
The vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles **86** to isatins **1** has been achieved by using bifunctional organocatalysts in CH_2Cl_2 at room temperature. According to the proposed

mechanism, first oxindole **87** was deprotonated by catalyst and generated *s-cis* enolate **A**, which then was added through the *Si* face to isatin **1** to give alkoxide intermediate **B**. After cyclization and protonation of the intermediate **B**, the desired product **87** was delivered and catalyst was regenerated (Scheme 32).[72]



Scheme 32

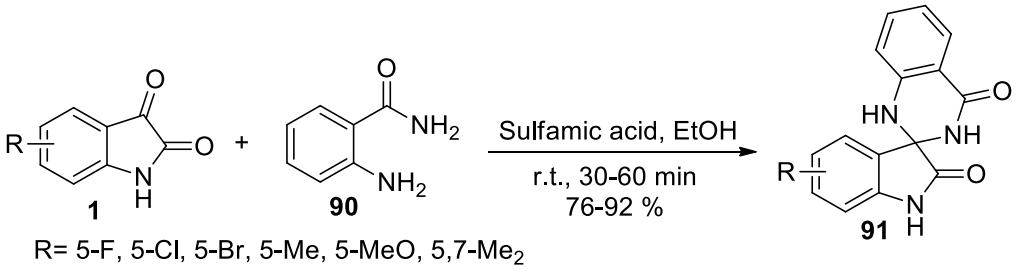
The biologically active dihydropyrones **89** with a high level of enantioselectivities were synthesized from the hetero-Diels–Alder reaction of isatins **1** and glyoxal **88** in the presence of chiral copper catalyst (Scheme 33).[73]



Scheme 33

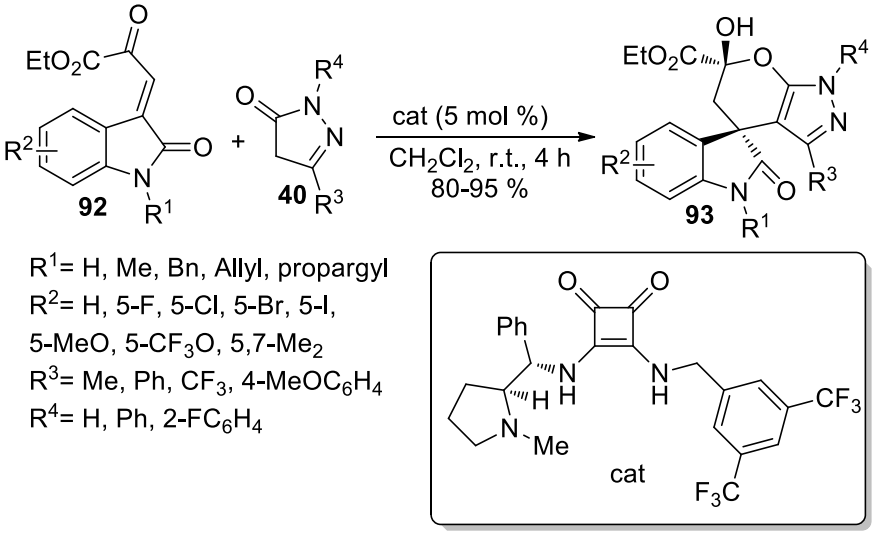
The synthesis of 1-*H*-spiro[isoindoline-1,2'-quinazoline]-3,4'(3'*H*)-diones **91** has been expediently accomplished by a reaction of isatins **1** and anthranilamide **90** in the presence of sulfamic acid as an efficient

catalyst (Scheme 34).[74] The products were found to be fluorescent with absorption in UV region (302, 362 nm) and emission in visible region (413-436 nm) with Stokes shift of 44-72 nm.



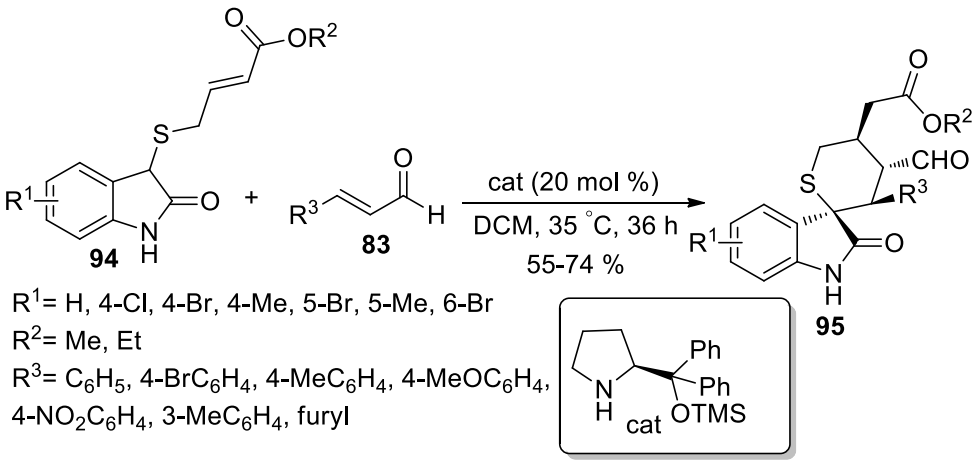
Scheme 34

Kumarswamyreddy and Kesavan used the bifunctional squaramide organocatalyst derived from L-proline in the reaction between isatylidine β,γ-unsaturated *α*-ketoesters **92** and pyrazolones **40** for the synthesis of dihydrospiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives **93** (Scheme 35).[75]



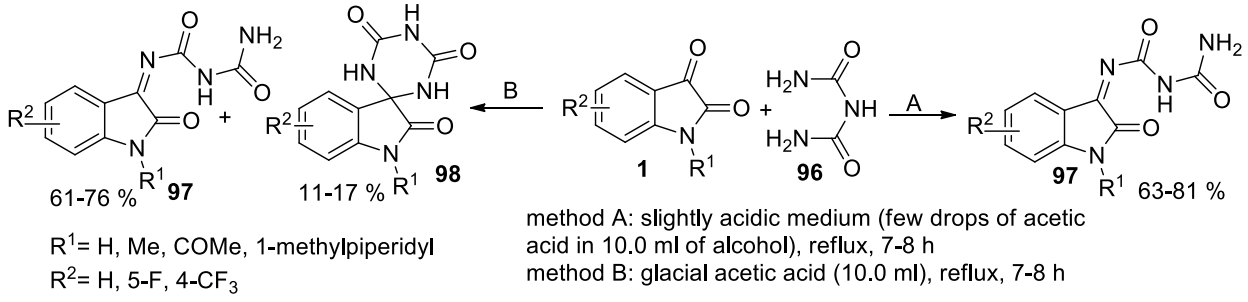
Scheme 35

An enantioselective Michael−Michael cascade reaction for the synthesis of chiral spirotetrahydro-thiopyrans **95** was studied by Wang *et al*. In this reaction, highly functionalized scaffolds were assembled via the reaction of chiral spiro-tetrahydrothiopyranoxindoles **94** with *trans*-enones **83** using the organocatalyst in excellent diastereo- and enantio-selectivities (>30:1 dr, ≥99% ee) with the creation of four consecutive stereogenic centers. The novel spiro-oxindole scaffolds were validated as a new class of p53-MDM2 protein-protein interaction inhibitors with good antitumor activity (Scheme 36).[76]



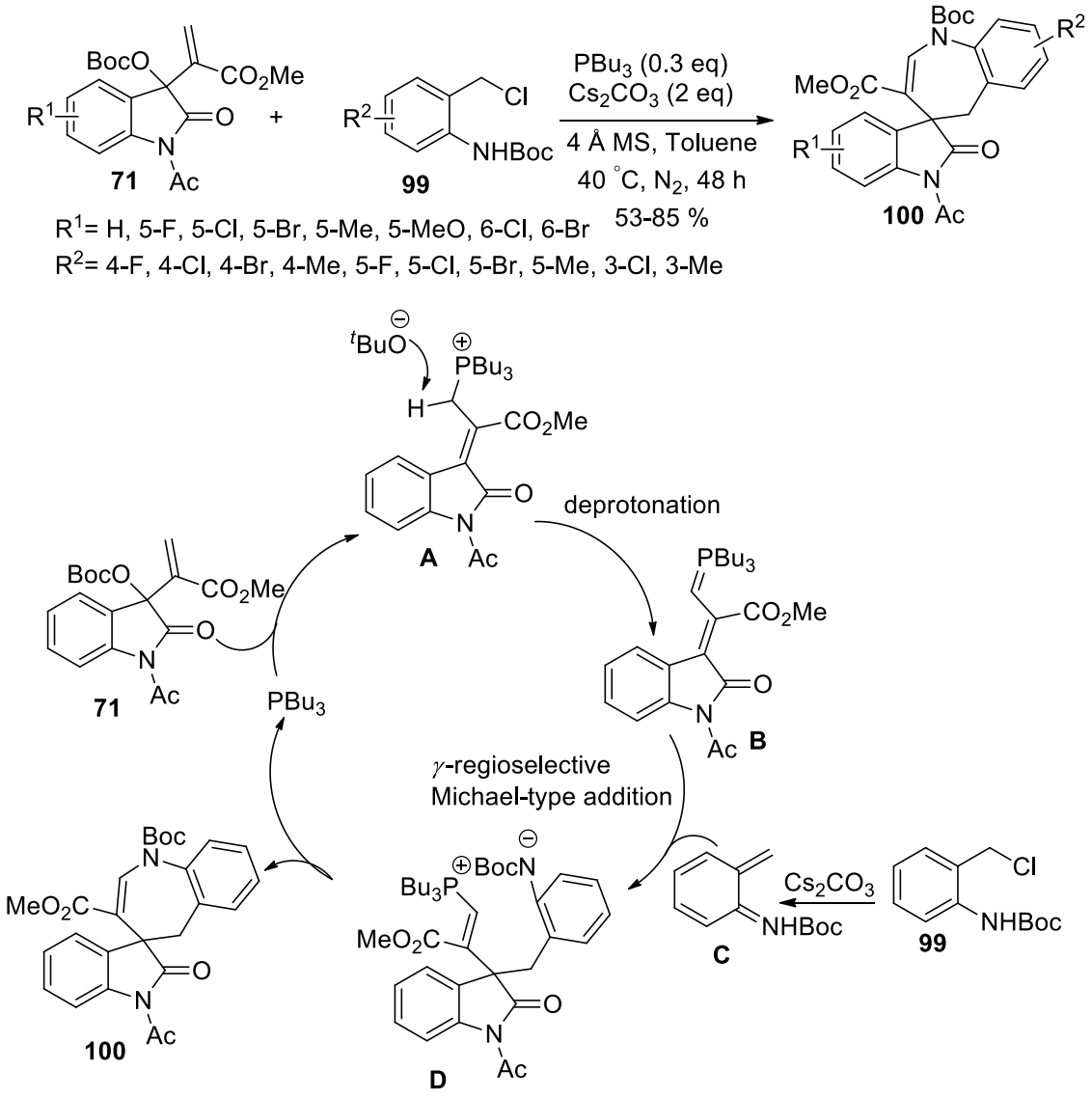
Scheme 36

Kumar *et al*. reported the synthesis of 1,3-dihydro-3-ureidoformimido-2*H*-indol-2-ones **97** and spiro[3*H*-indole-3,2'(1'*H*)-(1,3,5)triazine]-2,4',6'(1*H*,3'*H*,5'*H*)-triones **98** from the reaction of isatins **1** and biuret **96** (Scheme 37).[77] The reactions were carried out in two different methods; method A under slightly acidic conditions and method B in the presence of glacial acetic acid as reaction medium. It was observed that under both conditions compound **97** was obtained as the main product, however method B also resulted in the formation of compound **98** as a minor product.



Scheme 37

3.1.4. Seven- membered heterocycles. The quaternary aza-spirocycloheptane oxindole scaffolds **100** have been synthesized via the [4 + 3] cycloaddition reaction of MBH carbonates derived from isatin **71** and *N*-(*o*-chloromethyl)aryl amides **99** catalyzed by Lewis base and Brønsted base (Scheme 38). According to the proposed mechanism, the nucleophilic reaction of Bu_3P with MBH carbonate affords intermediate **A** with the concurrent release of CO_2. The *in situ* generated *tert*-butoxide anion then deprotonates intermediate **A** to yield the allylic phosphonium ylids **B**. Intermediate **D** is obtained by a *γ*-regioselective Michael type addition between allylic phosphonium ylide **B** and aza-*o*-quinone methide **C** generated *in situ* through the Cs_2CO_3-mediated elimination of **99**. Finally, intermediate **D** undergoes an intramolecular cyclization process to afford the desired product **100** with the regeneration of Bu_3P (Scheme 38).[78]



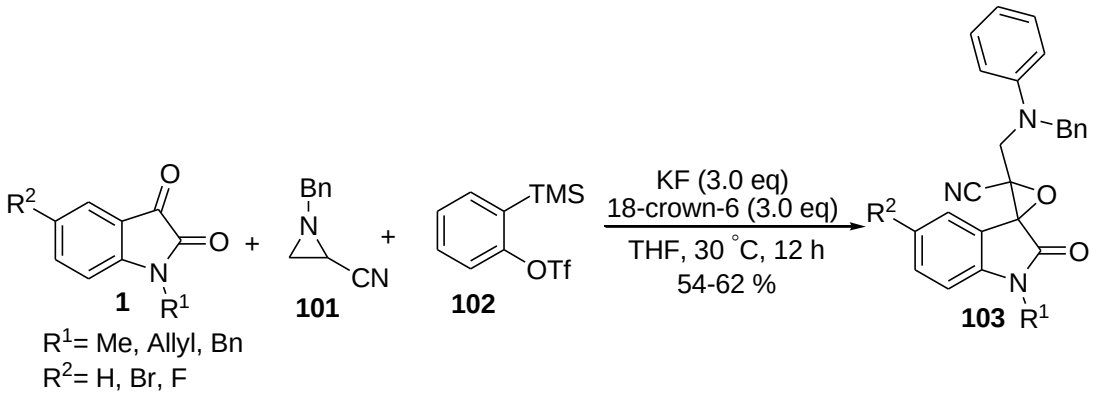
Scheme 38

4. Synthesis Involving Multicomponent Reactions

Reactions involving more than two components are usually referred to as multicomponent reactions (MCRs). Multicomponent reactions have emerged as powerful synthetic strategies because of their efficiency, atom economy, high selectivity and convenient construction of multiple new bonds.[79-81] These characteristics give rapid access to combinatorial libraries of complex organic molecules for efficient lead structure identification and optimization in drug discovery.[82-84] This section reviews three-, four and five-component reactions of isatins that have been employed in the synthesis of three- to seven membered spiro-heterocycles bearing one or more heteroatoms.

4.1. Three-membered heterocycles

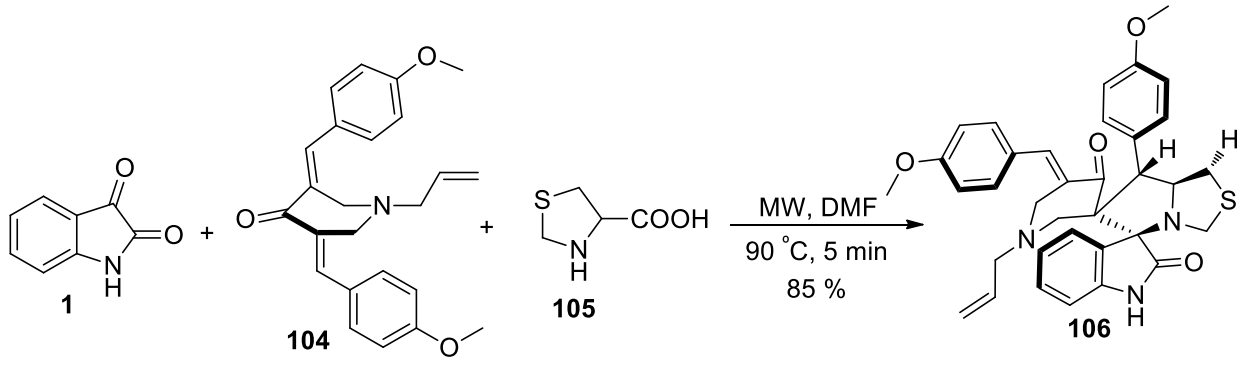
The three-component reaction of isatins **1**, *N*-substituted aziridine **101** and 2-(trimethylsilyl)aryl triflate **102** was carried out for the synthesis of trisubstituted *N*-aryl *α*-amino epoxides **103** (Scheme 39).[85]



Scheme 39

4.2. Five-membered heterocycles

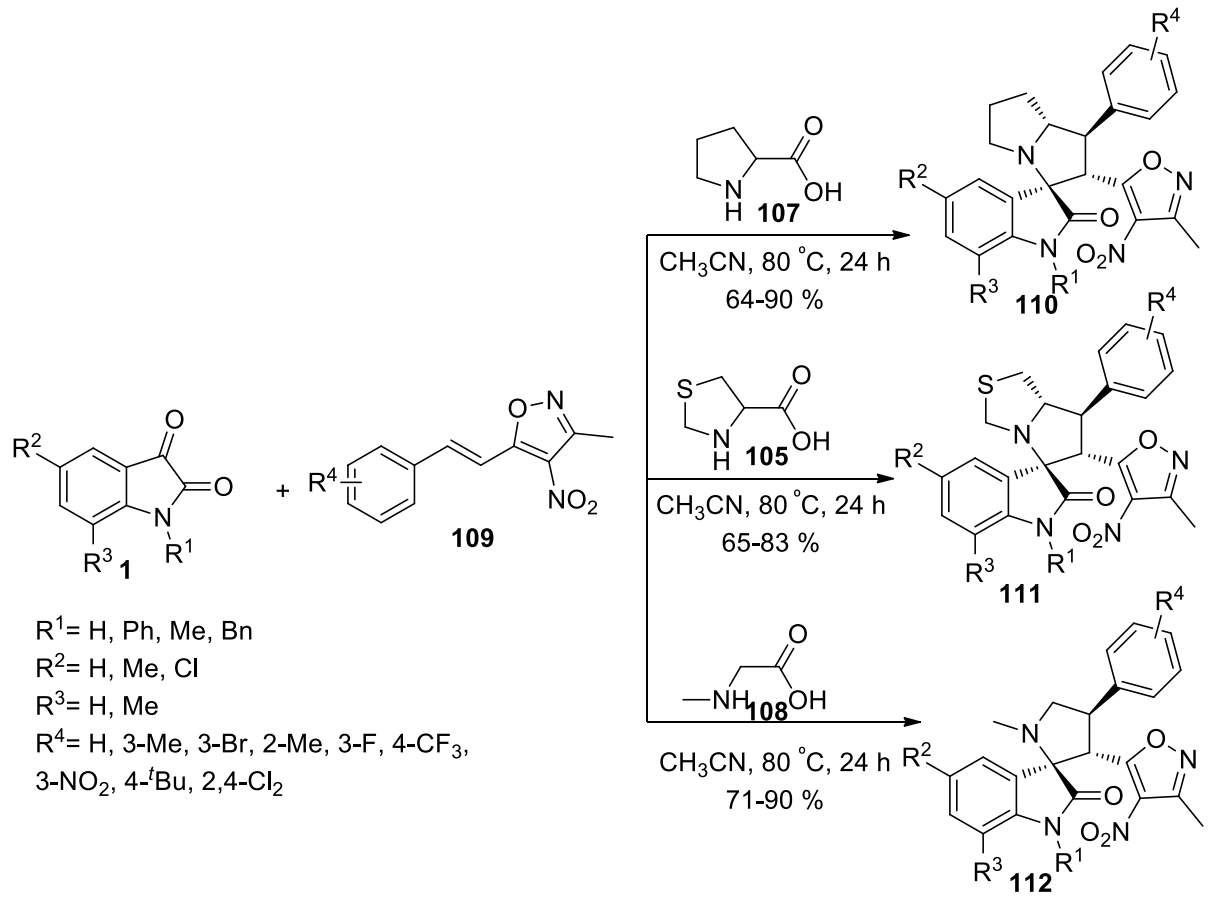
Kumar and co-workers reported the microwave-assisted three-component 1,3-dipolar cycloaddition reaction of isatin **1**, 1-allyl-3,5-bis(4-methoxyphenylmethylidene)piperidin-4-one **104** and thioproline **105** for the regioselective synthesis of dispiro oxindole-pyrrolothiazole-piperidones **106** (Scheme 40).[86]



Scheme 40

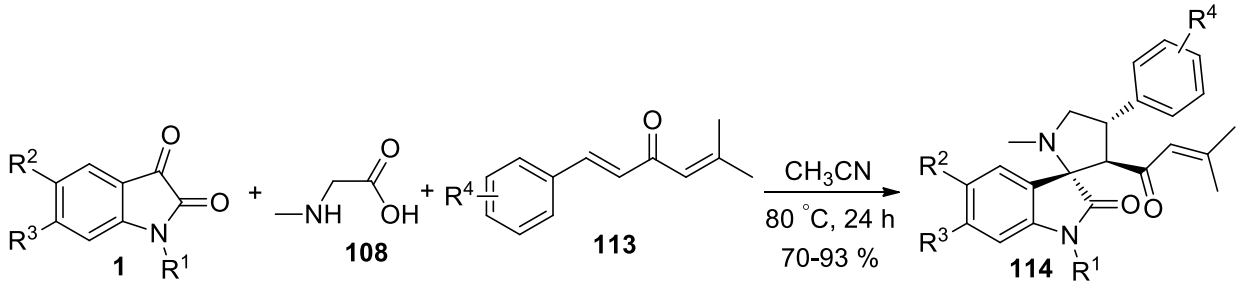
Liu *et al.* developed a method for the synthesis of isoxazole-fused spiropyrrolidine oxindoles **110**-**112** via a 1,3-dipolar cycloaddition reaction of azomethine ylides (thermally generated *in situ* from isatin **1** derivatives and proline **107**/ thioproline **105**/ sarcosine **108**) with 3-methyl-4-nitro-5-alkenyl-isoxazoles **109** (Scheme 41).[87] The products showed considerable cytotoxicities against human prostate cancer cells PC-3, human lung cancer cells A549 and human leukemia cells K562.

The multicomponent 1,3-dipolar cycloaddition reaction of azomethine ylides (generated *in situ* from isatin derivatives **1** and sarcosine **108**) with dienones **113** was carried out and novel turmerone motif fused spiropyrrolidine oxindoles **114** were obtained in high yields and good diastereoselectivity (up to >20:1) (Scheme 42).[88] The biological activity test results demonstrated that most of the compounds showed considerable cytotoxicities to cell lines of K562 and A549, showed comparably potent or even more potent than the positive control of cisplatin (up to 5.1 times).



R^1= H, Ph, Me, Bn
R^2= H, Me, Cl
R^3= H, Me
R^4= H, 3-Me, 3-Br, 2-Me, 3-F, 4-CF_3, 3-NO_2, 4-^{t}Bu, 2,4-Cl_2

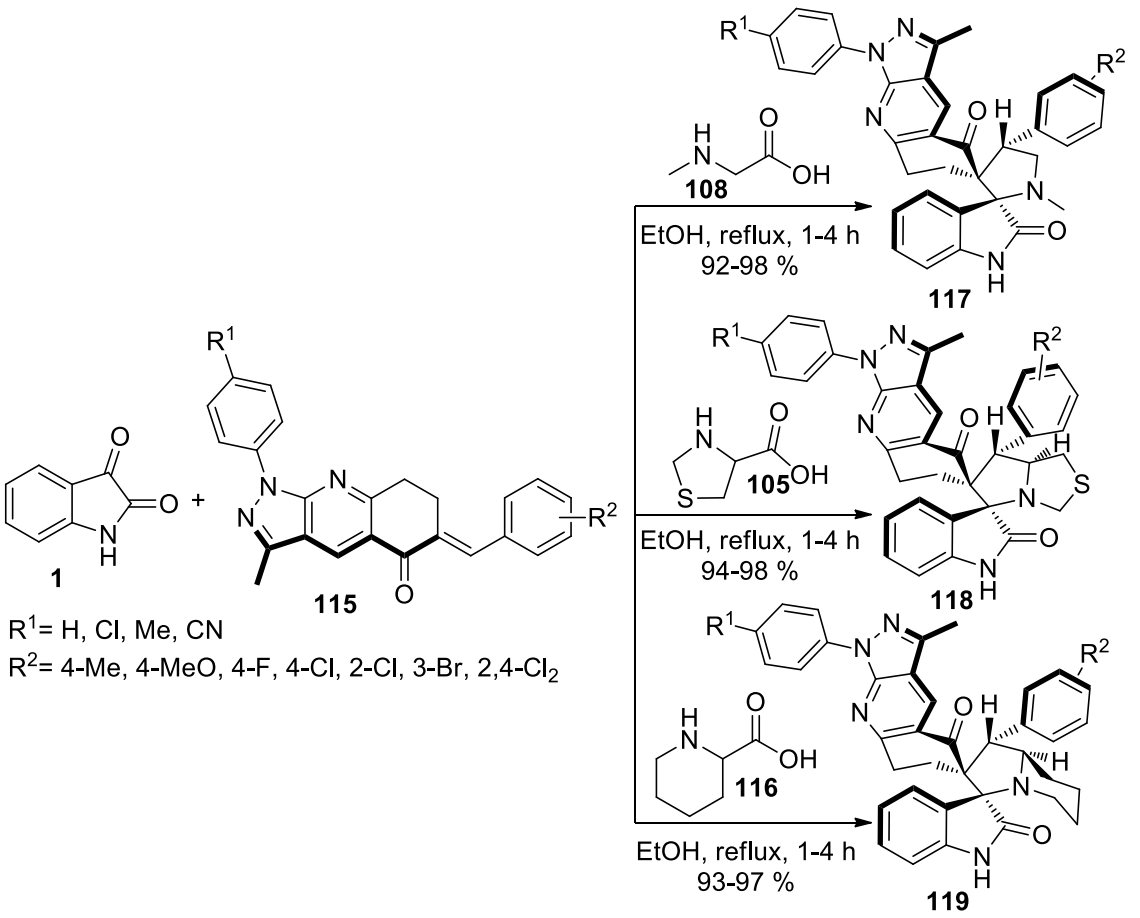
Scheme 41



R^1= H, Me, Bn, Ph
R^2= H, Me, Br
R^3= H, Me, Cl
R^4= C_6H_5, 4-MeC_6H_4, 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 3,4,5-$(MeO)_3C_6H_2$, Cisplatin

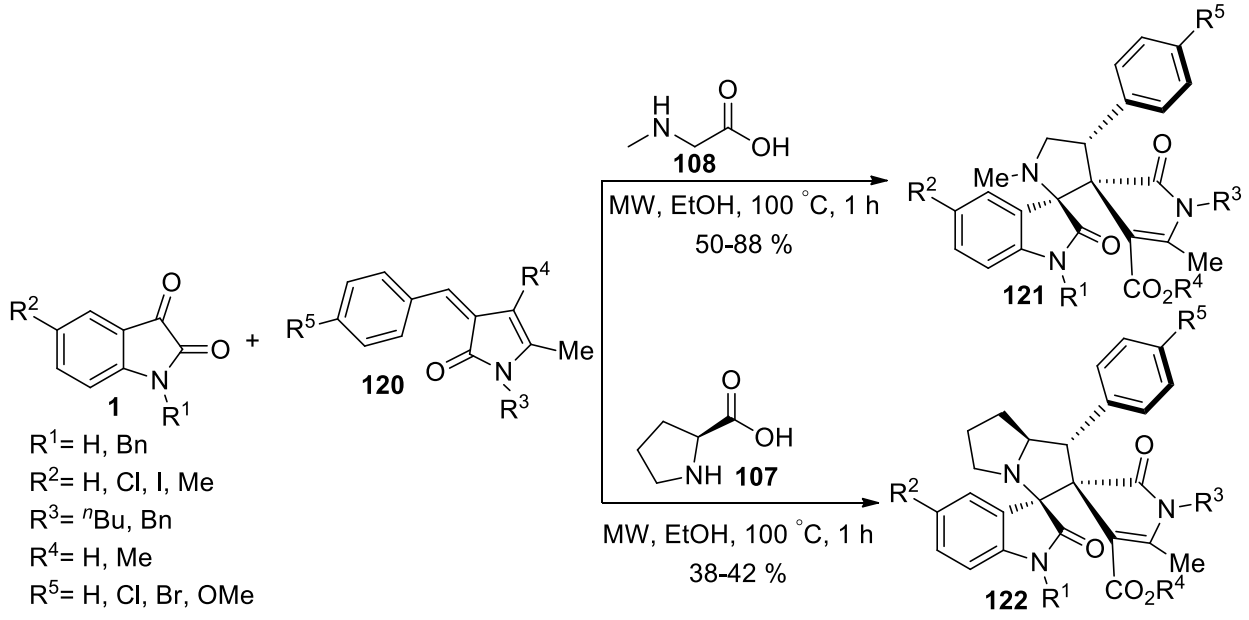
Scheme 42

Novel spiro-tethered pyrazolo[3,4-*b*]quinoline hybrids **117-119** from the reaction of isatin **1**, α-amino acids **(108, 105, 116)** and 6-arylidene-pyrazolo[3,4-*b*]quinolin-5-ones **115**, have been synthesized (Scheme 43).[89]



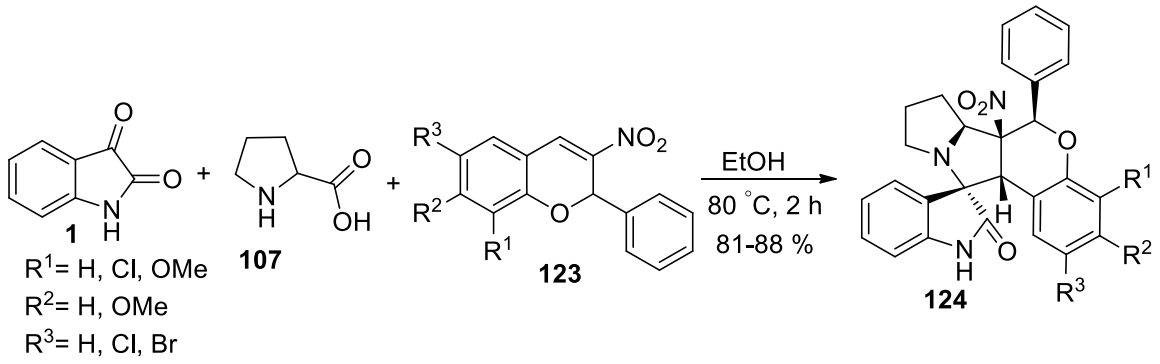
Scheme 43

A series of novel functionalized dispirooxindoles **121, 122** have been synthesized through 1,3-dipolar cycloaddition of an azomethine ylide formed from isatins **1** and various amino acids such as sarcosine **108** and proline **107** with 4-arylmethylene-2-pyrrolin-5-one **120** under microwave irradiation conditions (Scheme 44).[90]



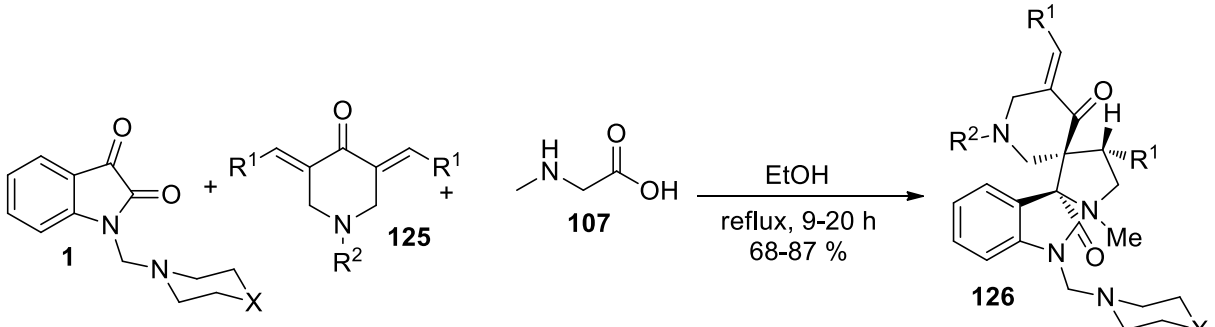
Scheme 44

The spirooxindole-pyrrolidine/piperidine fused nitrochromanes **124** were synthesized via cycloaddition reaction of isatin **1**, proline **107** and nitrochromene **123** (Scheme 45).[91] The regio- and stereo-chemical results were ascertained by X-ray crystallographic study.



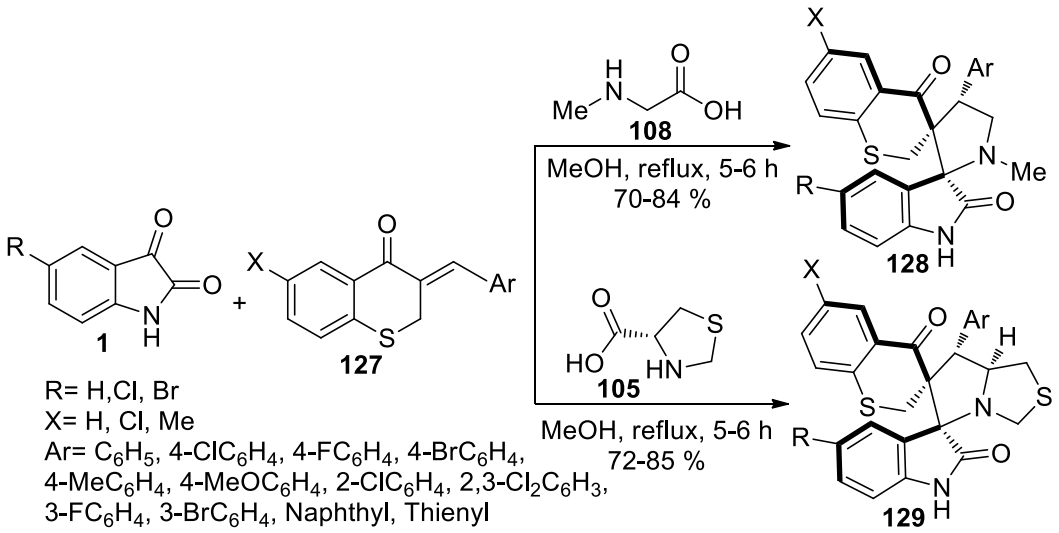
Scheme 45

The indole-based compounds **126** were obtained through the multi-component reaction of azomethine ylides (generated through condensation of isatins **1** with sarcosine **108**) with 1-alkyl-3,5-bis(arylidene)-4-piperidones **125** (Scheme 46).[92] X-ray studies of products provided good support for the regio- and stereoselectivity of the reaction. Many of the synthesized spiro-indoles exhibit antitumor properties against HeLa (cervical cancer) cell line.



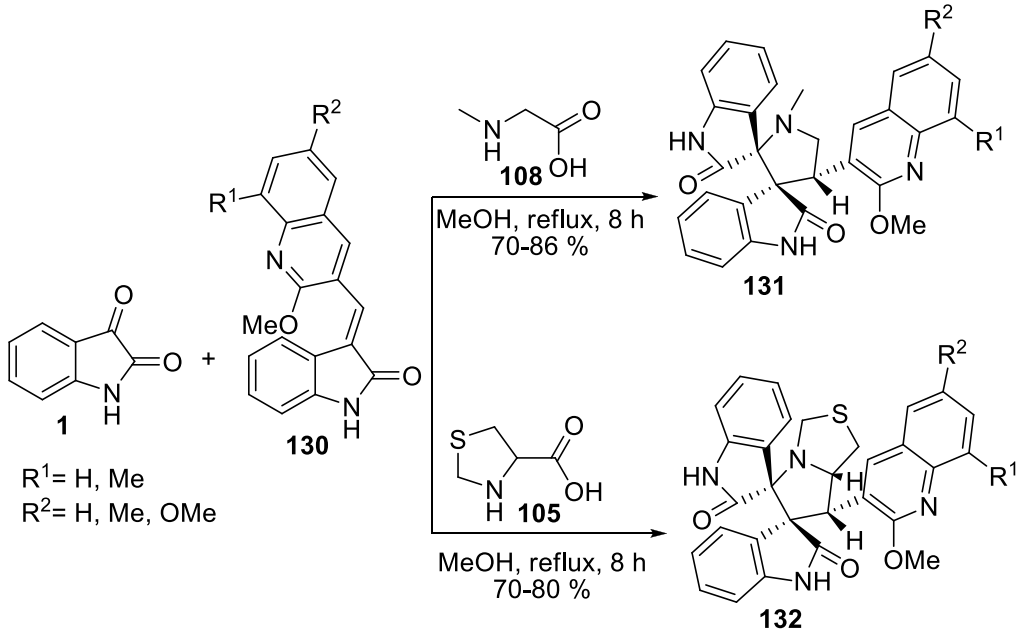
Scheme 46

The regio- and stereoselective fashion three-component 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from the condensation of isatins **1** and secondary amino acids (sarcosine **108**/*L*-thioproline **105**) with 3-arylidenethiochroman-4-ones **127** resulted in the formation of a series of novel dispiro compounds containing oxindole pyrrolidine/oxindolopyrrolothiazole-thiochroman-4-one hybrid frameworks **128, 129** (Scheme 47).[93]



Scheme 47

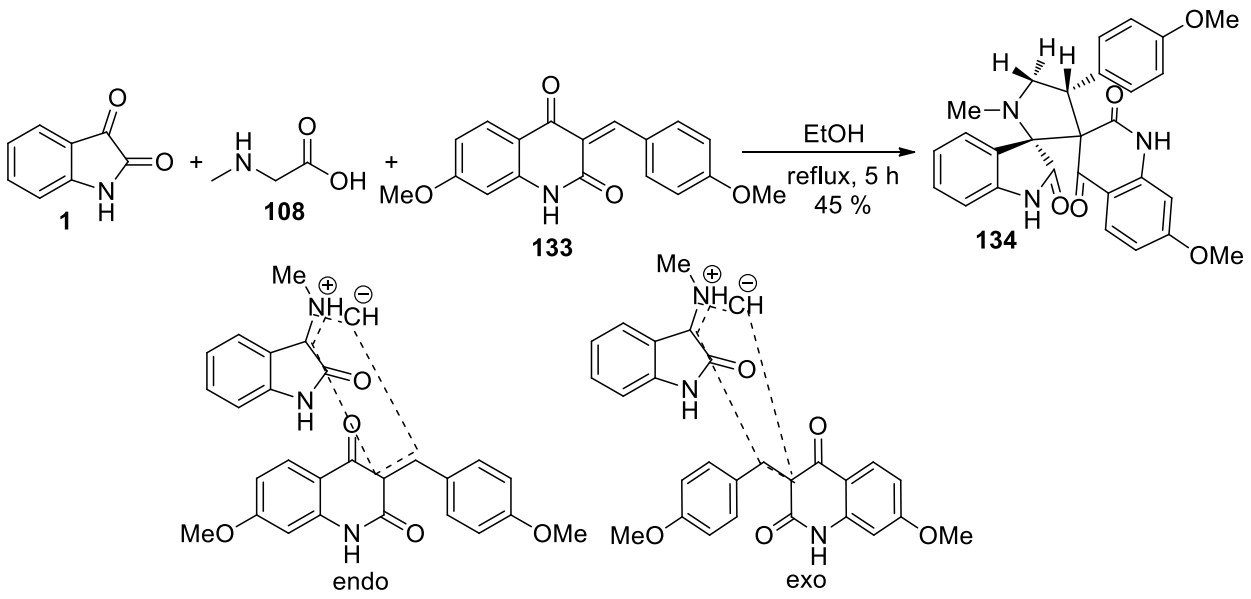
Mohan's group described the synthesis of new and highly functionalized regio- and stereoselective bisoxindole-containing dispiropyrrolidinyl/thiapyrrolizidinyl hybrid molecules **131, 132** obtained through 1,3-dipolar cycloaddition reactions of azomethines (generated *in situ* from isatin **1** and sarcosine **108** or thioproline **105**) with (*E*)-3-((2-methoxyquinolin-3-yl)-methylene)indolin-2-one dipolarophiles **130** (Scheme 48).[94] All synthesized compounds were evaluated for their *in vitro* antioxidant activities.



Scheme 48

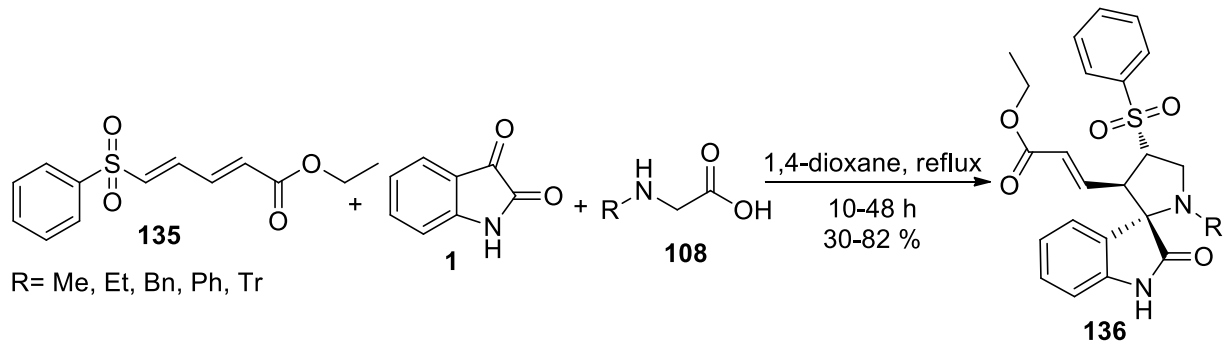
Hamama *et al.* described the azomethine cycloaddition reactions to the synthesis of dispiro[indoline-3,2'-pyrrolidine-3',3'-quinoline] **134** using isatin **1**, sarcosine **108**, and α,β-unsaturated ketone **133** (Scheme 49). From the calculations using frontier orbital theory, the authors found that the *endo* cycloaddition intermediate has a binding energy with 42.9 Kcal/mol more negative value than the *exo* cycloaddition intermediate.

Because the benzene ring of arylidene and the benzene ring of azomethine ylid are parallel to each other, the *endo* cycloaddition intermediate is more stable than the exo cycloaddition intermediate, and the dispiro *endo*-cycloaddition is formed while the dispiro *exo*-cycloaddition product is not formed by exocycloaddition (Scheme 49).[95]



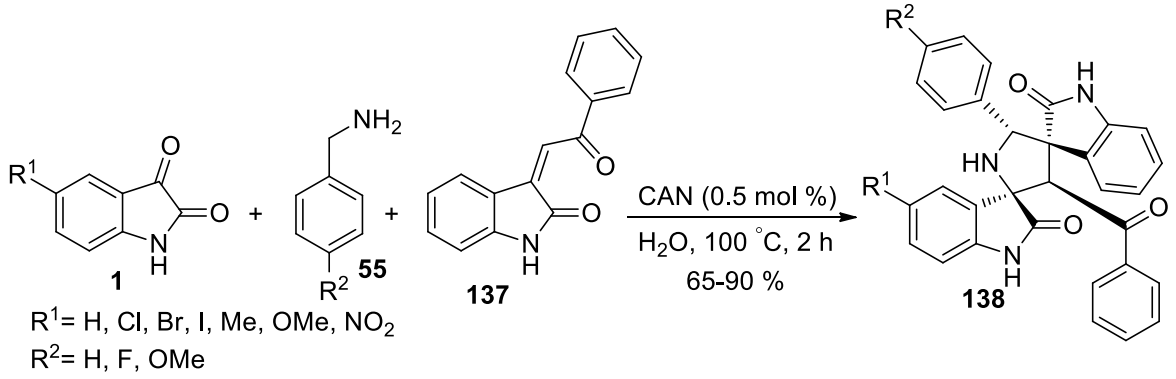
Scheme 49

The reaction of (2*E*,4*E*)-ethyl 5-(phenylsulfonyl)penta-2,4-dienoate **135** as a dipolarophile with *in situ* generated azomethine ylides from isatin **1** and sarcosine **108** derivatives in refluxing 1,4-dioxane furnished the cycloadducts **136** in good yields (Scheme 50).[96]



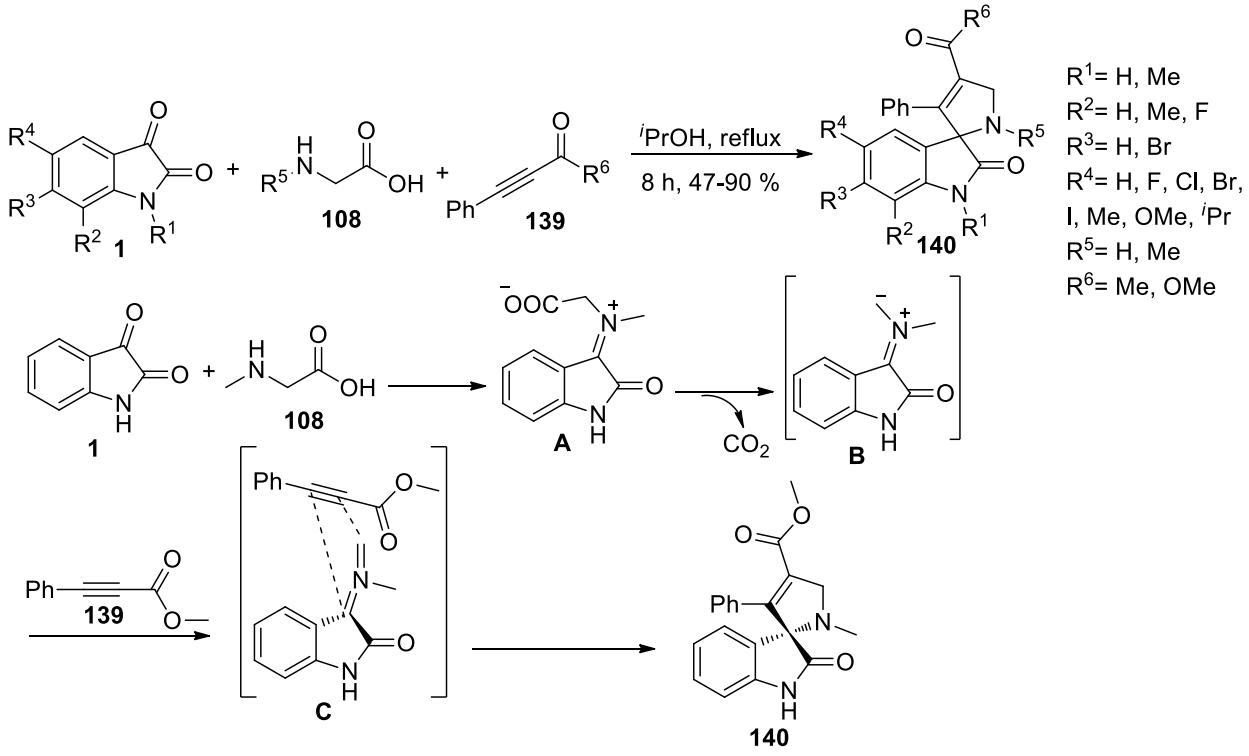
Scheme 50

Through the reaction of isatin derivatives **1**, benzyl amines **55** and (*Z*)-3-(2-oxo-2-phenylethylidene)indolin-2-one **137** using ceric ammonium nitrate (CAN), the functionalized spirooxindole-pyrrolidines **138** were synthesized (Scheme 51).[97] All the synthesized products showed good antimicrobial activity.



Scheme 51

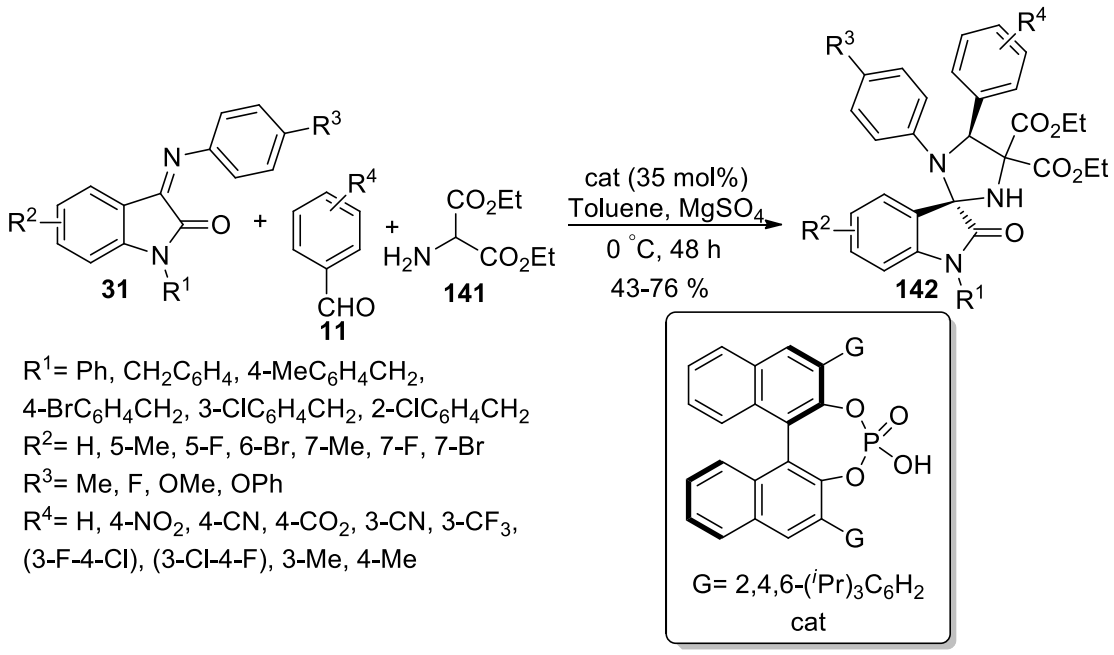
Spiro[indoline-3,2'-pyrrole] derivatives were obtained from the reaction of isatins **1**, α-amino acids **108** and phenylpropiolic acid esters **139** in refluxing isopropanol in high regioselectivity and yields. A plausible mechanism for this multicomponent reaction was proposed (Scheme 52).[98] First, the condensation of isatin **1** with sarcosine **108** afforded the corresponding azomethine ylide **A**. Subsequently, the protic solvent of isopropanol would promote the decarboxylation of azomethine ylide **A** to form the 1,3-dipole **B**. Then, the 1,3-dipolar cycloaddition of intermediate **B** with methyl 3-phenylpropiolate **139** results in the final product spiro[indoline-3,2'-pyrrole] **140.**



Scheme 52

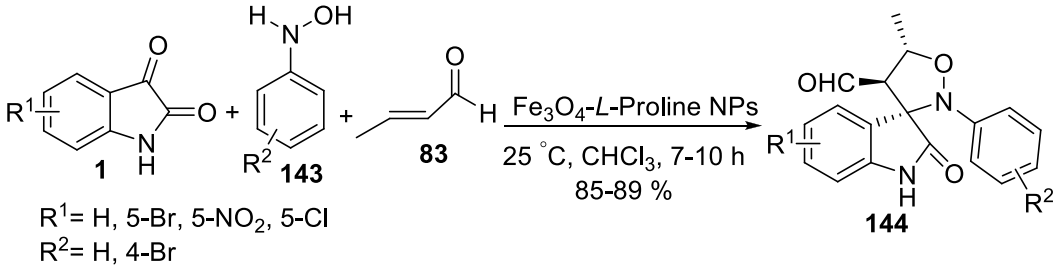
Shi and co-workers developed an asymmetric chemoselective 1,3-dipolar cycloaddition of azomethine ylide with imines via the three component reaction of isatin-derived imines **31**, aldehydes **11** and amino-ester

141 in the presence of chiral phosphoric acid. In this reaction, spiro[imidazolidine-2,3'-oxindole] frameworks **142** were obtained with high diastereo and enantioselectivities (97 : 3 er, all >95:5 dr) (Scheme 53).[99]



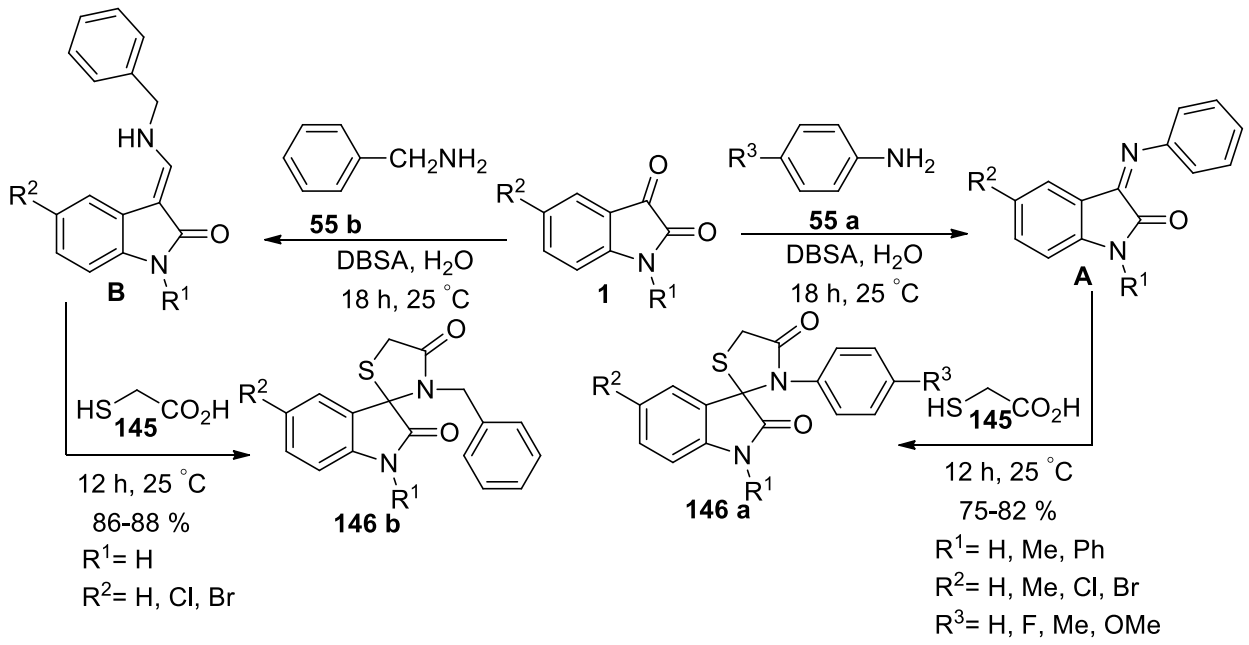
Scheme 53

Safaei-Ghomi and Zahedi reported application of Fe_3O_4-L-proline NPs as a chiral catalyst to achieve high diastereoselectivities in the asymmetric 1,3-dipolar cycloaddition reaction of isatins **1**, *N*-arylhydroxylamines **143** and enones **83** for the synthesis of spiroisoxazolidines **144** (Scheme 54).[100]



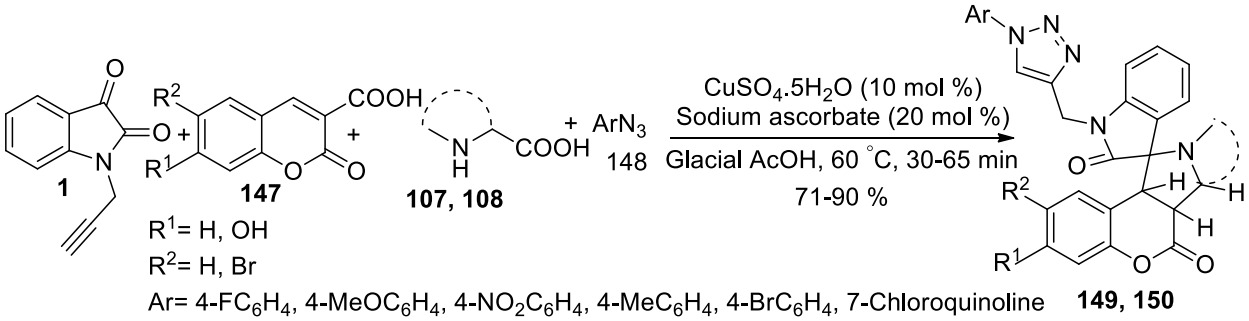
Scheme 54

DBSA (*p*-dodecylbenzenesulfonic acid) as an efficient Brønsted acid surfactant combined catalyst facilitated the reaction of isatin derivatives **1** with primary amines **55** and thioglycolic acid **145** for the synthesis of a series of pharmacologically important spiro[indoline-3,2'-thiazolidinones] **146, 147**. First, a reaction of isatin **1** and amines **55** was carried out to generate the corresponding Schiff base intermediate **A** and **B** which after the addition of thioglycolic acid in the same flask afforded the desired product (Scheme 55).[101]



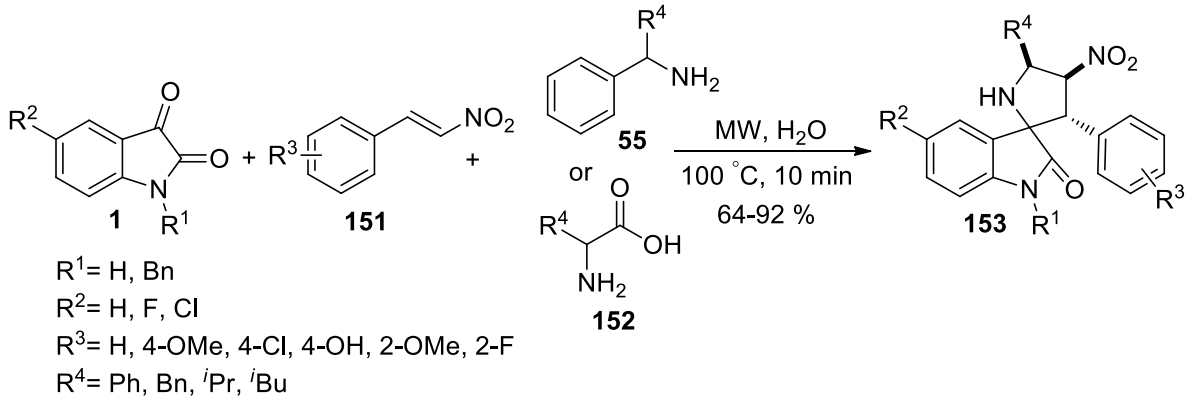
Scheme 55

Rajeswari *et al*. employed a one-pot four-component [3 + 2] cycloaddition process using *N*-propargylated isatin **1**, coumarin-3-carboxylic acid **147**, *L*-proline **107**/sarcosine **108** and aryl azides **148** with Cu as a catalyst to prepare the selective spirooxindole pyrrolizine linked 1,2,3-triazole conjugates **149**, **150** (Scheme 56).[102]



Scheme 56

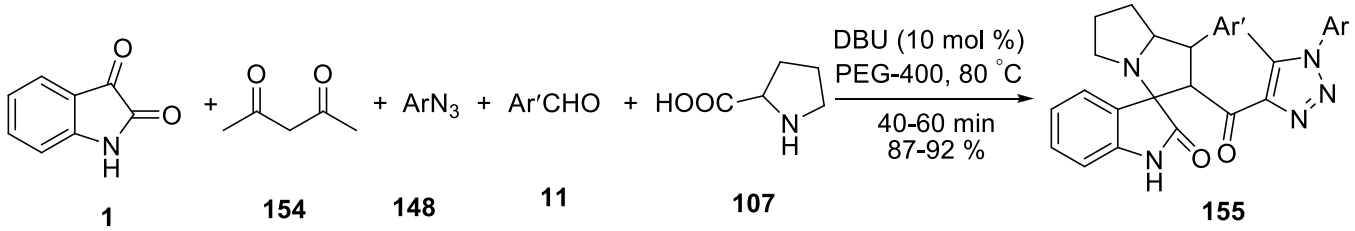
Meshram's group have demonstrated an efficient and regioselective synthesis of spirooxindoles **153** from the reaction of isatins **1**, β-nitrostyrenes **151** and benzylamine **55**/α-amino acids **152** under microwave irradiation (Scheme 57).[103] All products were screened for antimicrobial activity and the majority of compounds showed significant activities.



R^1= H, Bn
R^2= H, F, Cl
R^3= H, 4-OMe, 4-Cl, 4-OH, 2-OMe, 2-F
R^4= Ph, Bn, ^{i}Pr, ^{i}Bu

Scheme 57

Khurana's group reported the synthesis of novel heterocyclic triazolyl spirocyclic oxindoles **155** via the one-pot five component reaction of isatin **1**, 1,3-dicarbonyl **154**, aryl azides **148**, aromatic aldehydes **11**, and L-proline **107** using DBU as a catalyst in PEG-400 (Scheme 58).[104]

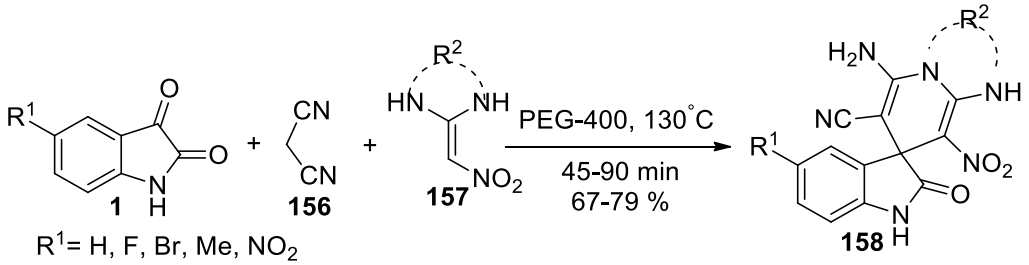


Ar=Ar′= 4-$NO_2C_6H_4$, 4-MeC_6H_4, 4-BrC_6H_4

Scheme 58

4.3. Six-membered heterocycles

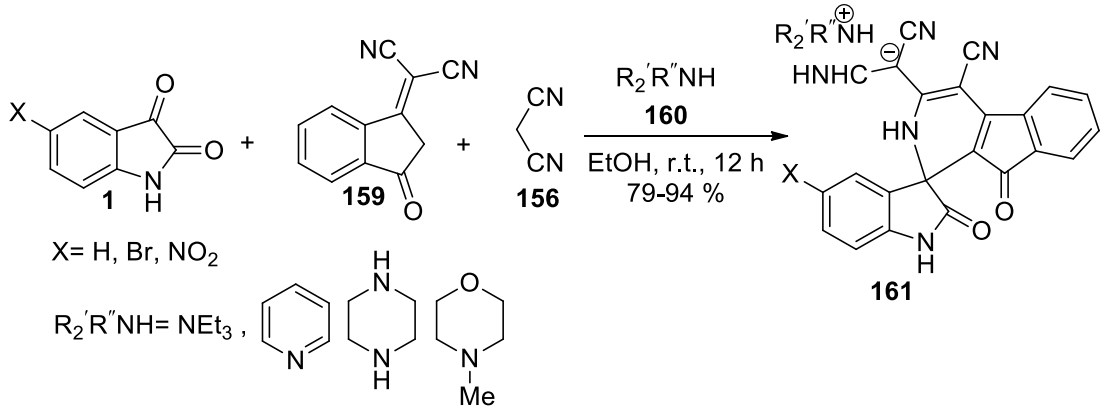
The spiro-dihydropyridine derivatives **158** were synthesized via a one-pot multicomponent condensation of isatin derivatives **1** and malononitrile **156** with ketene aminals **157** under catalyst-free conditions in PEG-400 as a highly efficient and green biodegradable polymeric medium (Scheme 59).[105] All compounds showed moderate to high level activity against acetyl and butyrylcholinesterase.



R^1= H, F, Br, Me, NO_2
R^2 = –CH_2CH_2–, –$CH_2CH_2CH_2$–, –$CH_2(CH_3)_2CCH_2$–, 2CH_2Ph

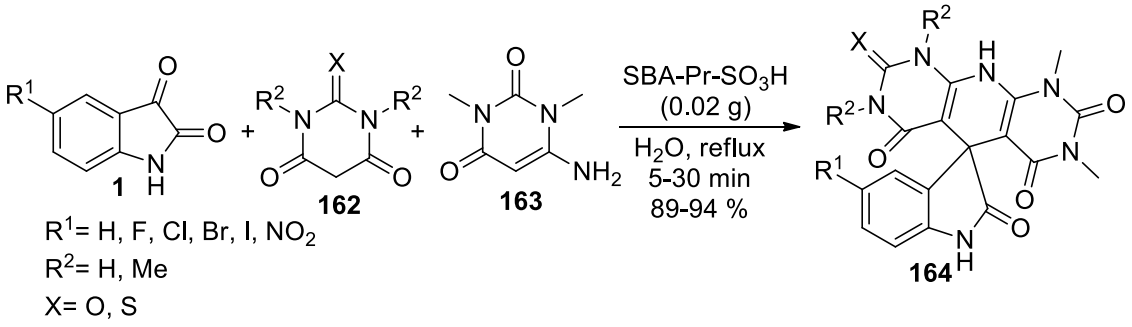
Scheme 59

Spirooxindoles incorporating a "medicinally privileged" indenopyridine moiety **161** have been synthesized regioselectively via multicomponent reaction of isatins **1**, 1,1-dicyanomethylene-3-indanone **159** and malononitrile **156** in the presence of amines **160** (Scheme 60).[106] The product is a spirooxindole-fused indenopyridine salt that was successfully neutralized by dilute hydrochloric acid.



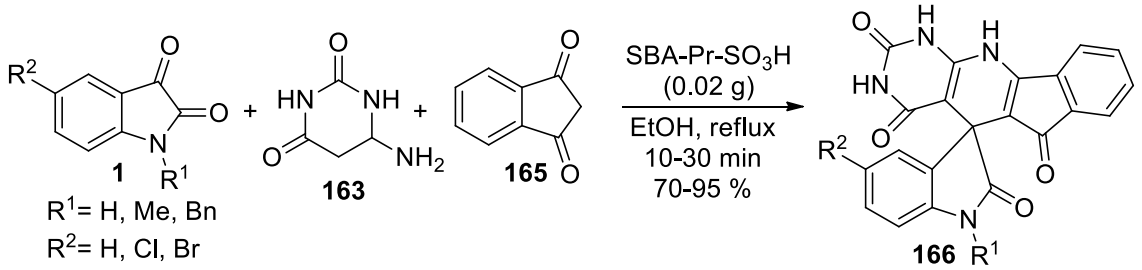
Scheme 60

Treatment of isatin derivatives **1** and barbituric acids **162** with 6-amino-1,3-dimethyl uracil **163** using SBA-15-Pr-SO_3H as a heterogeneous nano catalyst in one pot reaction, resulted in the formation of the spirooxindole dipyrimidine derivatives **164** in high yields (Scheme 61).[107]



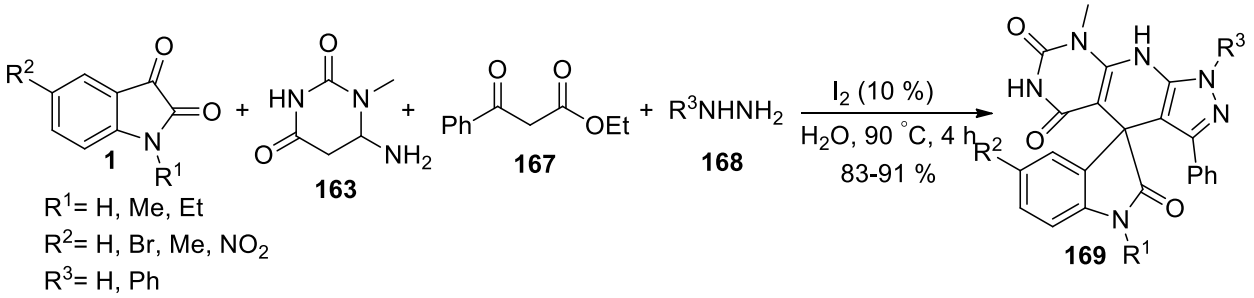
Scheme 61

In another study, Mohammadi Ziarani and co-workers reported a method for the synthesis of spiro indeno[1,2-*b*]pyrido[2,3-*d*]pyrimidine-5,3′-indolines **166** through the condensation reaction of isatins **1**, 6-aminouracil **163** and 1,3-indanedione 165 in the presence of SBA-15-Pr-SO_3H as a heterogeneous nano catalyst (Scheme 62).[108] The same authors also reported microwave irradiation condition for this reaction.[109]



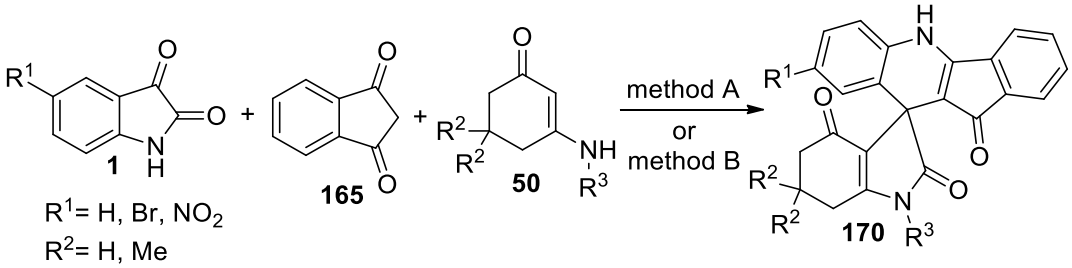
Scheme 62

Siddiqui's group prepared the pyrazolo-pyridopyrimidines **169** by the four-component reaction of isatins **1**, 6-amino-1-methyluracil **163**, β-ketoester **167** and hydrazines **168** in the presence of a catalytic amount of iodine (Scheme 63).[110]



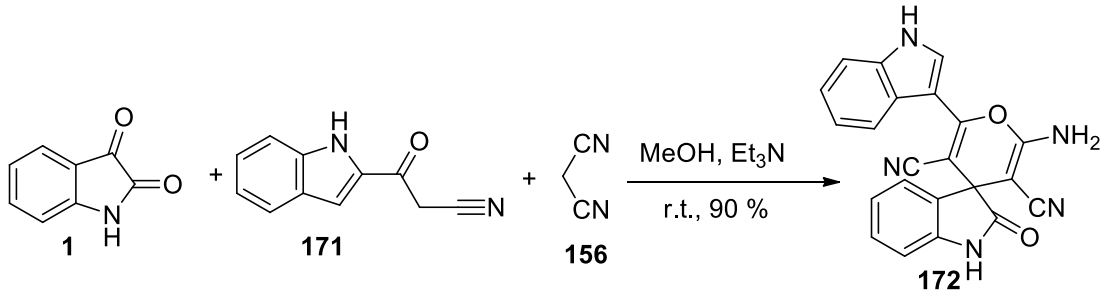
Scheme 63

An efficient methodology for the synthesis of substituted spiro[indolo-3,10'-indeno[1,2-*b*]quinoline]-2,4,11'-triones **170** by the reaction of isatins **1**, 1,3-indanedione **165**, and enaminones **50** using $La(OTf)_3$ as catalyst in PEG-400 under conventional heating and or ultrasonic irradiation was reported by Kumari *et al*. (Scheme 64).[111]



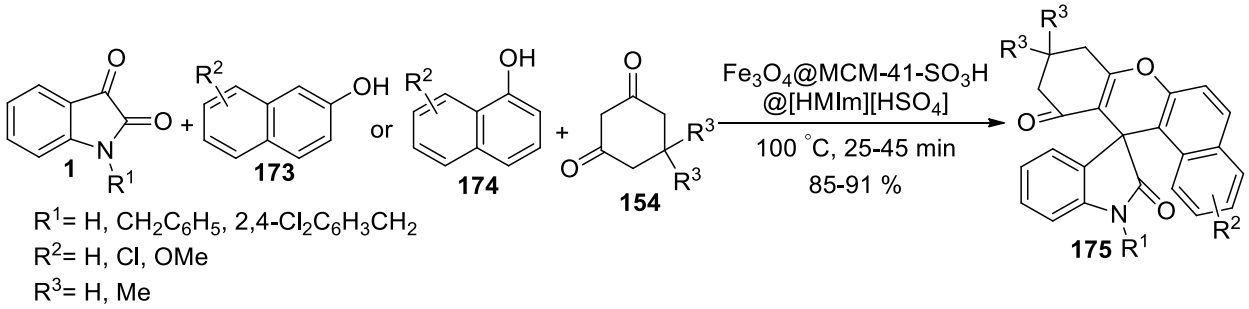
Scheme 64

Thanikachalam and co-workers prepared a spirooxindole compound namely 2'-amino-6'-(1*H*-indol-3-yl)-2-oxospiro[indole-3,4'-pyran]-3',5'-dicarbonitrile **172**, from the reaction of isatin **1**, 2-cyanoacetylindole **171** and malononitrile **156** (Scheme 65).[112]



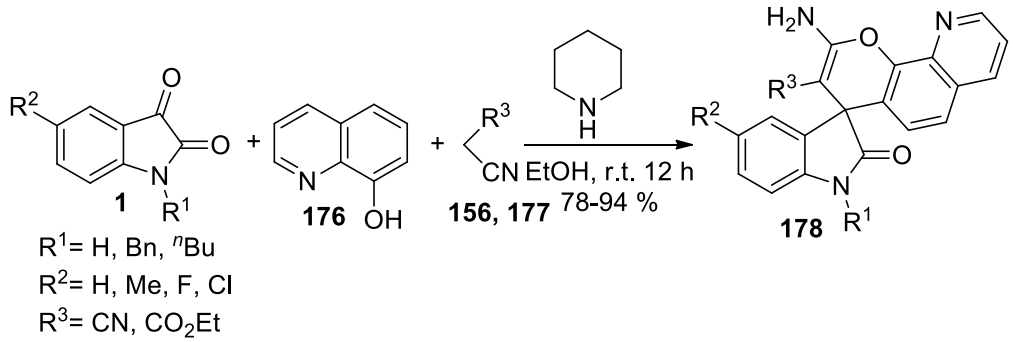
Scheme 65

The one-pot three-component condensation of isatins **1**, α or β-naphthols **173, 174**, and cyclic 1,3-dicarbonyl compounds **154** in the presence of Fe_3O_4@MCM-41-SO_3H@[HMIm][HSO_4] as catalyst was successfully established for the synthesis of new derivatives of spiro[benzoxanthene-indoline]diones **175** (Scheme 66).[113]



Scheme 66

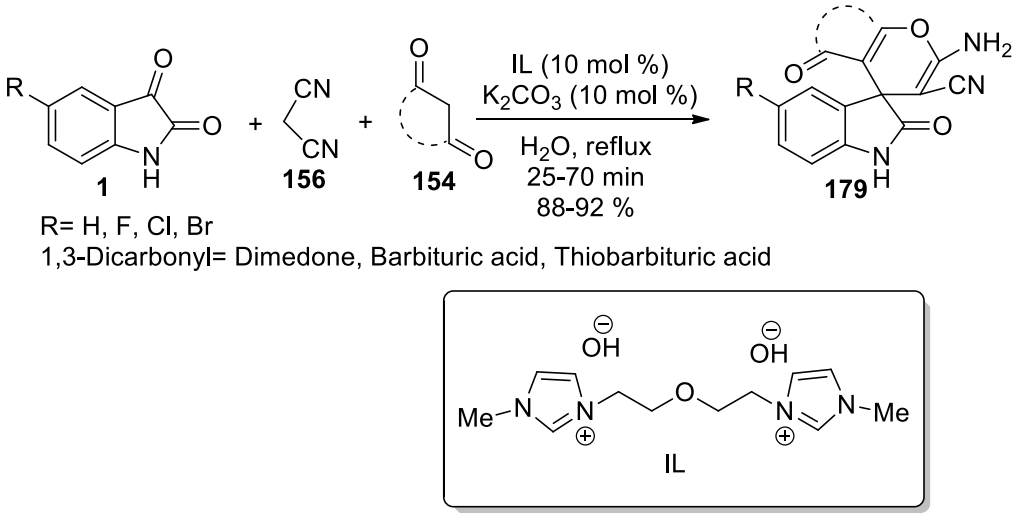
Shi and Yan reported a method for the synthesis of functionalized spiro[indoline-3,4'-pyrano[3,2-*h*]quinolines] **178** via the three-component condensation of isatins **1**, 8-hydroxyquinoline **176** and malononitrile **156** or ethyl cyanoacetate **177** (Scheme 67).[114]



Scheme 67

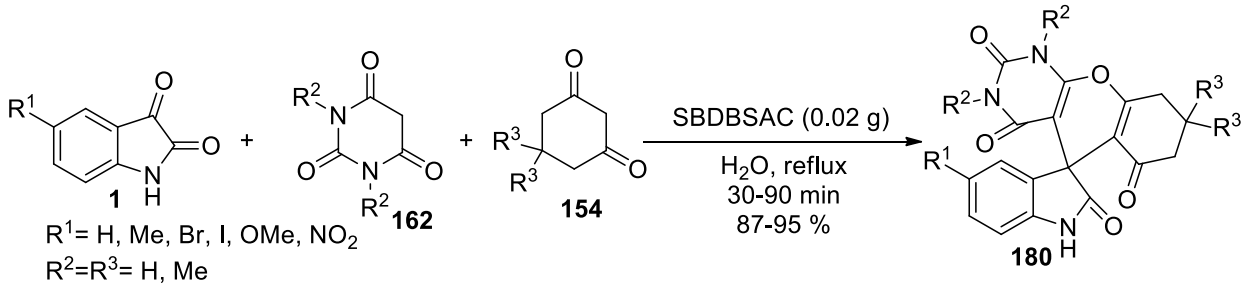
A dicationic ionic liquid (IL) and K_2CO_3 were used as an efficient catalytic system for the synthesis of 4*H*-pyrans **179** via the three-component condensation reaction of isatin derivatives **1**, malononitrile **156**, and 1,3-dicarbonyl compounds **154** in water (Scheme 68).[115] This reaction has been widely studied and different

catalysts such as [Amb]*L*-prolinate,[116] tetrabutylammonium bromide (TBAB),[117] boron nitride supported iron oxide (BN@Fe_3O_4),[118] Al-ITQ-HB,[119] [bmim]OH,[120] Fe_3O_4,[121] carbon nanotube (CNT),[122] NaOAc,[123] $CuFe_2O_4$ nanoparticles[124] and trisodium citrate dihydrate[125] were used in this reaction.



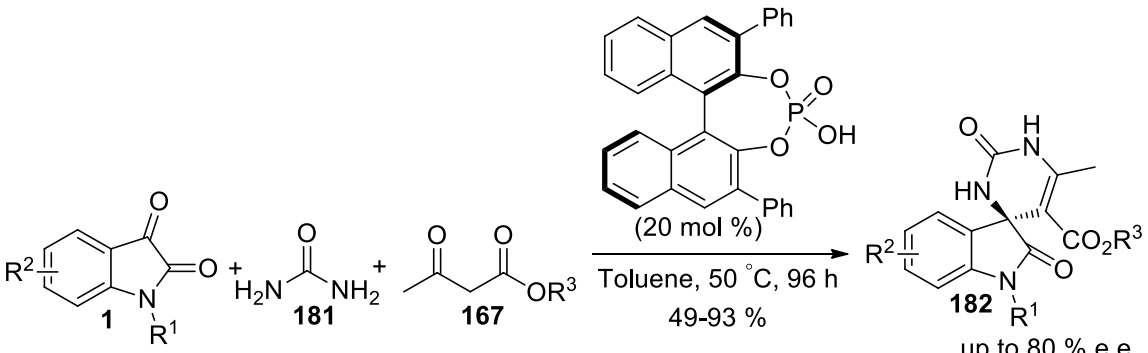
Scheme 68

The preparation of spiropyran derivatives **180** using silica-bonded 1,4-diazabicyclo[2.2.2]octane-sulfonic acid chloride (SBDBSAC) as a catalyst in multicomponent reaction of isatin derivatives **1**, barbituric acids **162**, and 1,3-dicarbonyl compounds **154** was reported by Moosavi-Zare and co-workers (Scheme 69).[126]



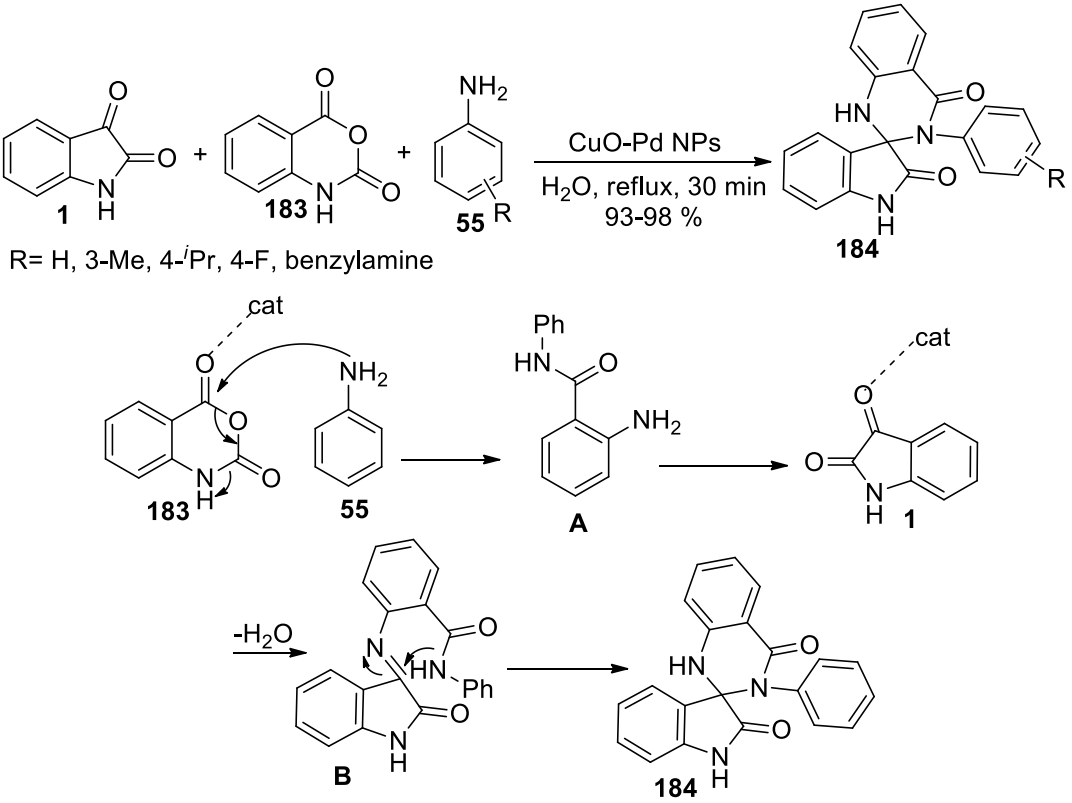
Scheme 69

The synthesis of chiral, enantioenriched spiro(indoline-pyrimidine)-dione derivatives **182** from the asymmetric, Biginelli-like reaction of *N*-substituted isatins **1**, urea **181** and β-ketoesters **167** using BINOL-derived phosphoric acid as a catalyst has been studied by Stucchi *et al*. (Scheme 70).[127]



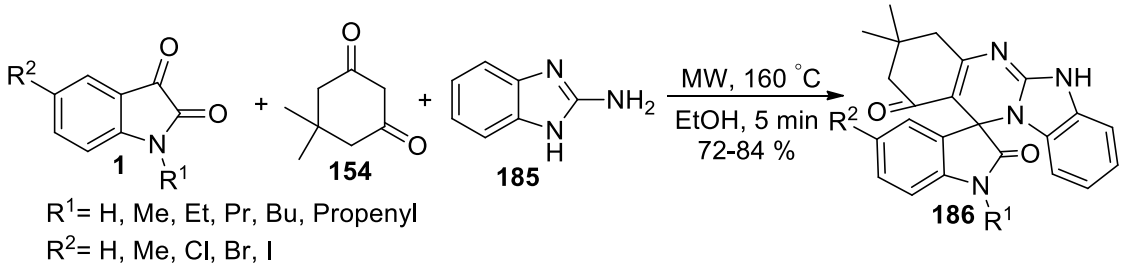
Scheme 70

A variety of spirooxindole derivatives **184** were synthesized by a facile one pot, three-component protocol using isatin **1**, isatoic anhydride **183** and amines **55** in the presence of CuO–Pd nanoparticles as catalyst. The nucleophilic addition of aniline **55** to isatoic anhydride **183**, in the presence of the CuO–Pd NPs, followed by decarboxylation, produced 2-aminobenzamide **A**. The condensation of **A** with isatin **1**, in the presence of CuO–Pd NPs, gave imine **B**, which on intramolecular cyclization gave the final product **184** (Scheme 71).[128]



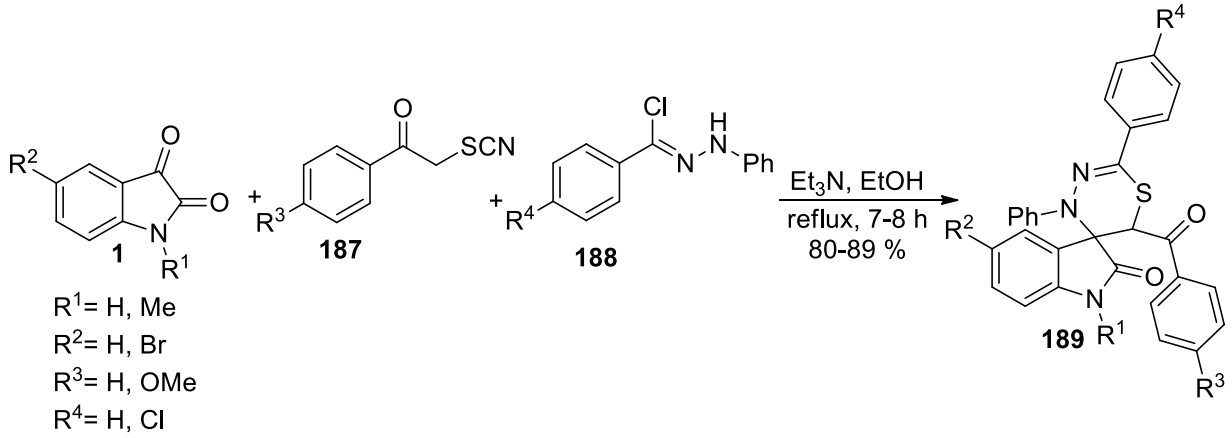
Scheme 71

Pardasani and co-workers studied a novel three-component reaction for the synthesis of spiro-benzimidazoquinazolinones **186** via the reaction of isatins **1**, dimedone **154** and 2-aminobenzimidazole **185** under microwave irradiation (Scheme 72).[129] This one-pot process involves the formation of one C–C and two C–N bonds during the synthesis of the spiro-compounds as confirmed by X-ray analysis.



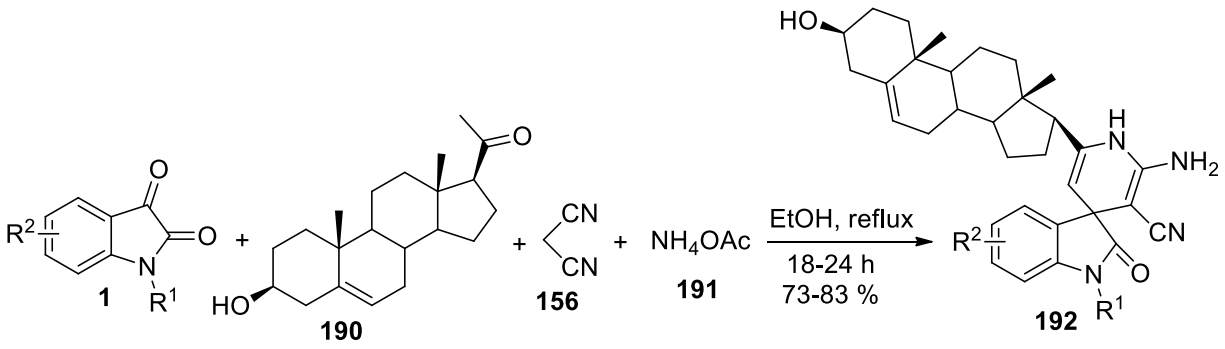
Scheme 72

Alizadeh and Moafi developed a three-component domino reaction of isatin derivatives **1**, 2-aryl-2-oxoethyl thiocyanates **187** and hydrazonoyl chlorides **188** that provides a convenient method for the synthesis of 4'*H*-spiro[indole-3,5'-[1,3,4]thiadiazin]-2(1*H*)-ones **189** (Scheme 73).[130]



Scheme 73

Novel steroidal dihydropyridinyl spirooxindoles **192** were synthesized by the multicomponent reaction of isatins **1**, pregnenolone (PREG) **190**, malononitrile **156** and ammonium acetate **191** (Scheme 74).[131] MTT assay indicated that some of these compounds exhibited moderate to excellent cytotoxic activity against the tested cancer cell lines. The cytotoxic activities varied greatly depending on the position and electronic nature of substituents on the isatin nucleus and *N*-benzyl moieties.

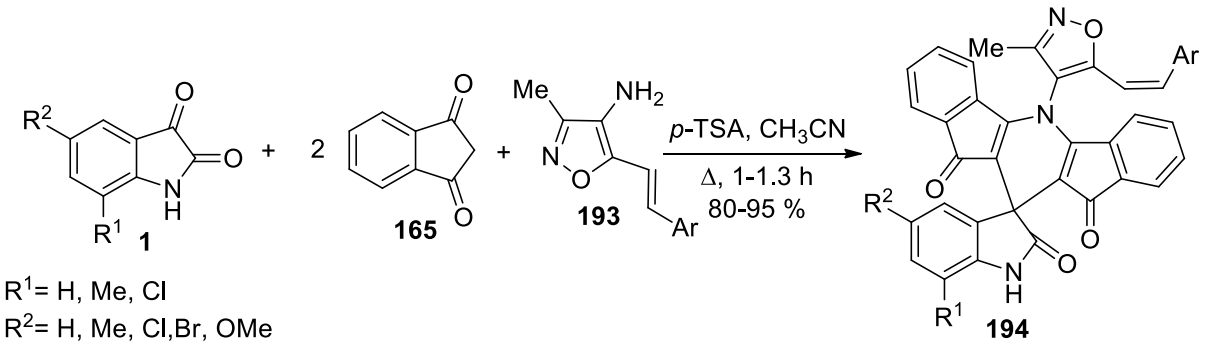


R^1= H, 2-$MeC_6H_4CH_2$, 3-$MeC_6H_4CH_2$, 4-$MeC_6H_4CH_2$, 2-$ClC_6H_4CH_2$, 4-$ClC_6H_4CH_2$, 3,4-$Cl_2C_6H_3CH_2$, 2-$FC_6H_4CH_2$, 3-$FC_6H_4CH_2$, 4-$FC_6H_4CH_2$, Propargyl

R^2= H, 5-F, 5-Cl, 5-Br, 7-Cl

Scheme 74

Rajanarendar *et al*. used *p*-toluene sulfonic acid (*p*-TSA) as an efficient catalyst in the reaction of isatin derivatives **1**, 1,3-indanedione **165** and 4-amino-3-methyl-5-styrylisoxazole **193** for the synthesis of isoxazolylspiro [diindeno[1,2-*b*;2',1'-*e*]pyridine-11,3'-indoline]-2',10,12-triones **194** (Scheme 75).[132]



R^1= H, Me, Cl

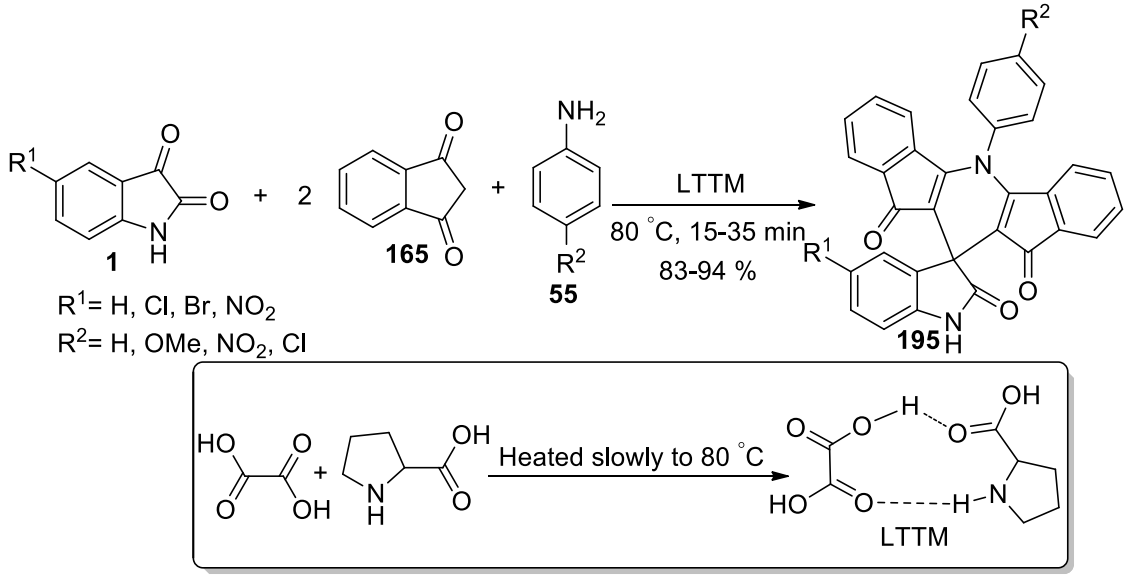
R^2= H, Me, Cl,Br, OMe

Ar= C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-BrC_6H_4, 2-ClC_6H_4, 2-$MeOC_6H_4$

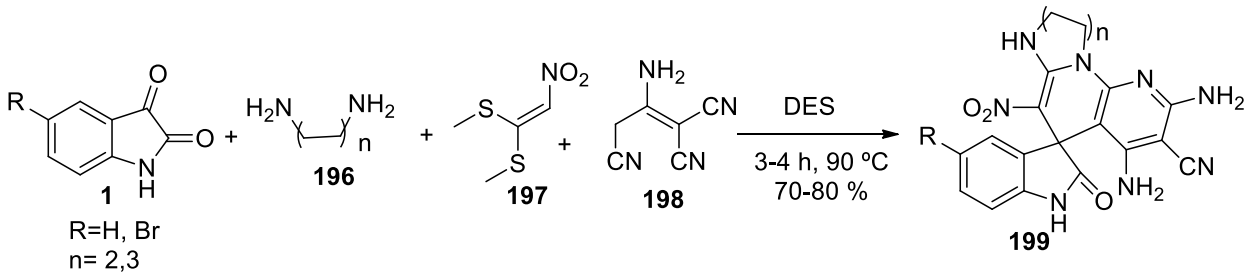
Scheme 75

Oxalic acid dihydrate: proline (LTTM) promoted the synthesis of spiro[diindeno[1,2-*b*:2',1'-*e*]pyridine-11,3'-indoline]-triones **195** in the reaction of isatins **1**, 1,3-indanedione **165** and anilines **55** as starting materials (Scheme 76).[133]

Shaabani *et al*. studied the synthesis of fully substituted naphthyridines **199** through the domino reaction of isatin derivatives **1**, diamines **196**, 1,1-bis(methylthio)-2-nitroethylene **197** and 2-aminoprop-1-ene-1,1,3-tricarbonitrile **198** using a deep eutectic solvent (DES) (Scheme 77).[134]

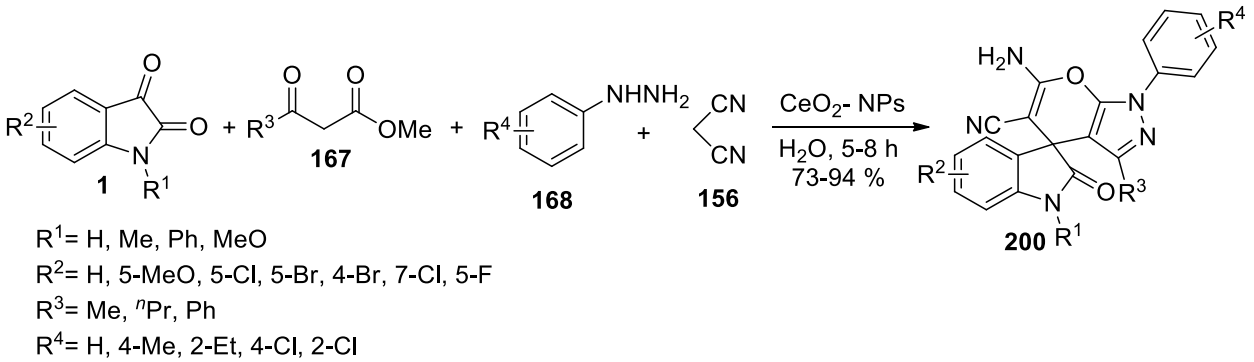


Scheme 76



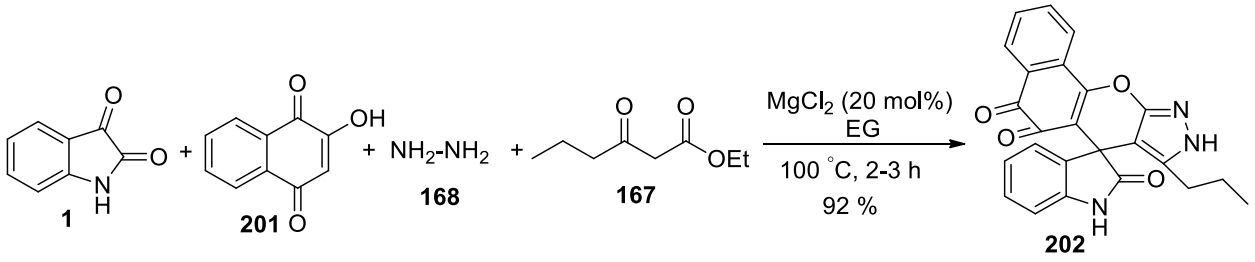
Scheme 77

Shrestha *et al.* reported a one-pot synthesis of biologically spiro[indoline-3,4'-pyrano[2,3-*c*]pyrazole] derivatives **200** using CeO_2 nanoparticle-catalyzed four-component reaction of isatins **1**, β-ketoesters **167**, phenylhydrazines **168** and malononitrile **156** in water (Scheme 78).[135] In another study, Fe_3O_4@SiO_2 was used as the catalyst of this reaction.[136]



Scheme 78

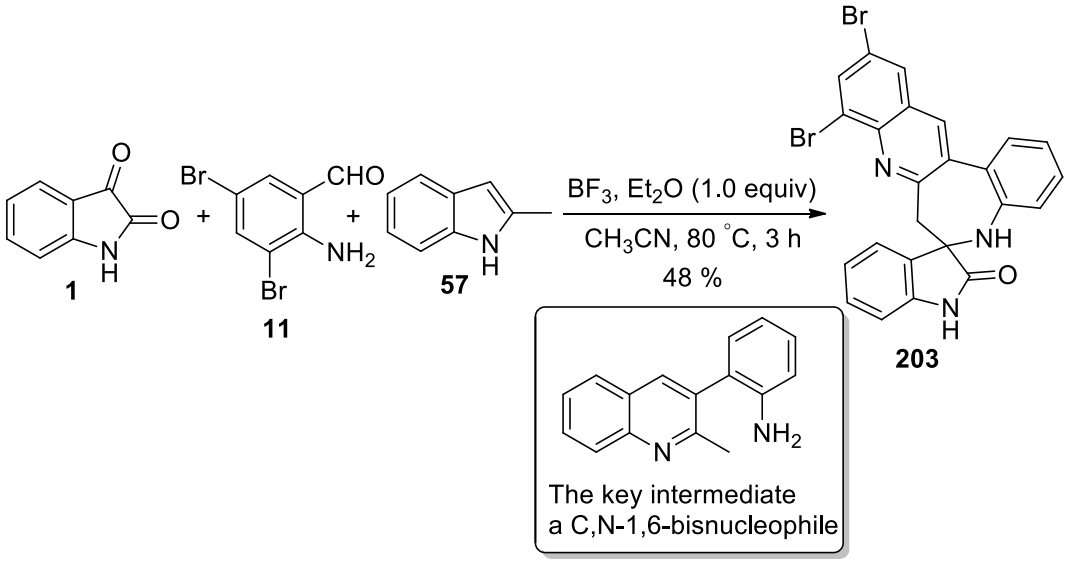
The synthesis of 2-hydroxy-3-[(5-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)(phenyl)methyl]-naphthalene-1,4-dione derivatives **202** has been developed through a one-pot, four-component reaction of isatin **1**, 2-hydroxy-1,4-naphthoquinone **201**, hydrazine **168** and β-ketoester **167** catalyzed by $MgCl_2$ in ethylene glycol (Scheme 79).[137]



Scheme 79

4.4. Seven-membered heterocycles

Condensation of isatin **1** with a C,N-1,6-binucleophile generated *in situ* from *o*-aminobenzaldehyde **11** and 2-methylindole **57** through a Mannich-type reaction was established for the synthesis of a quinoline-fused 1-benzazepine derivative **203** (Scheme 80).[138]

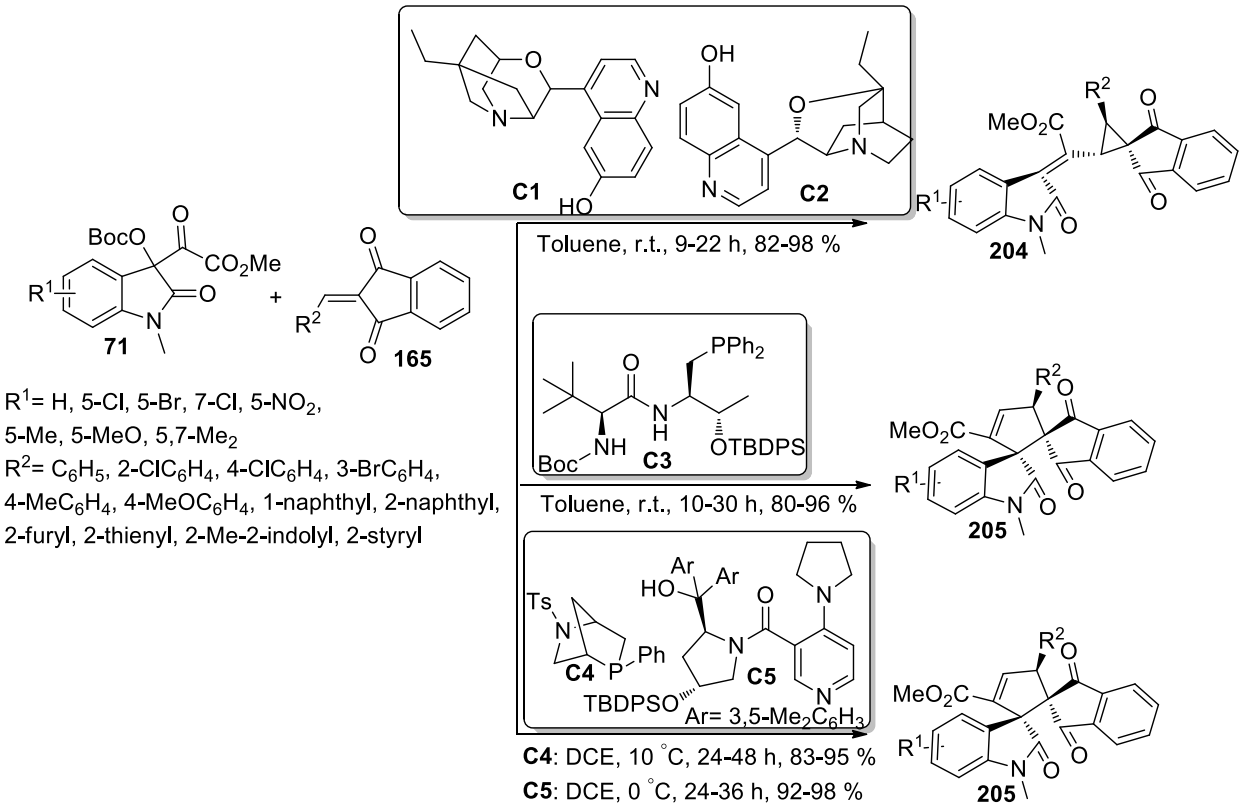


Scheme 80

5. Synthesis of Isatin-based Spiro-fused Carbocyclic Frameworks

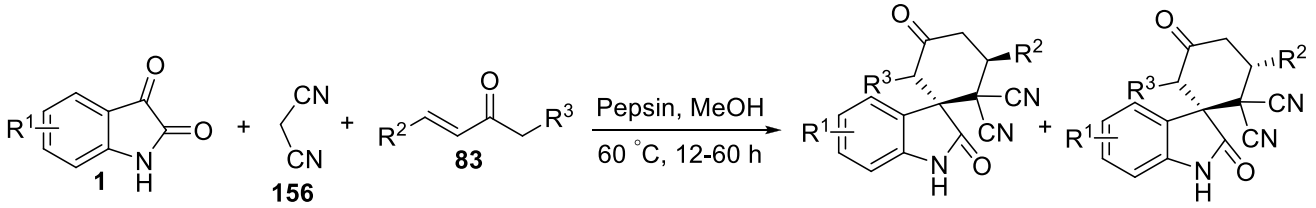
Zhan *et al.* investigated the asymmetric annulation reactions of Morita–Baylis–Hillman carbonates, derived from isatins **71** and 2-alkylidene-1*H*-indene-1,3(2*H*)-diones **165**, catalyzed by various chiral Lewis bases, which resulted in a switch in chemo- and diastereoselectivity. While [2 + 1] reactions catalyzed by chiral tertiary amines, derived from cinchona alkaloids, produced densely substituted cyclopropanes **204**, diastereodivergent

[3 + 2] annulations generated bis(spirocycl)ic oxindoles **205** by employing either a chiral phosphine or a DMAP-type catalyst (Scheme 81).[139]



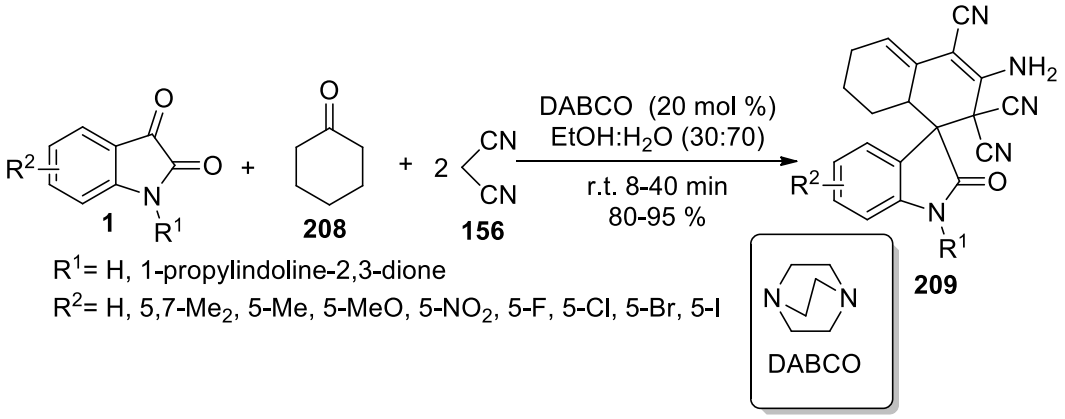
Scheme 81

Pepsin was used as a biocatalyst in the domino Knoevenagel/Michael/Michael reaction for the synthesis of spirooxindole derivatives in methanol. A wide range of isatins **1** and enones **83** in reaction with malononitrile **156** provided spirocyclic oxindoles **206** in yields of up to 99% and oxindoles **207** in trace yields with diastereoselectivity up to >99:1 dr (Scheme82).[140] Reactions with isatins bearing an electron-donating group in the 5-position gave better yields than those bearing a strong electron-withdrawing group in the 5-position. The position of substituents also had effects on the reaction yield. The isatins with a substituent in the 5-position gave higher yields than those with a substituent in the 1- or 7-position.



Scheme 82

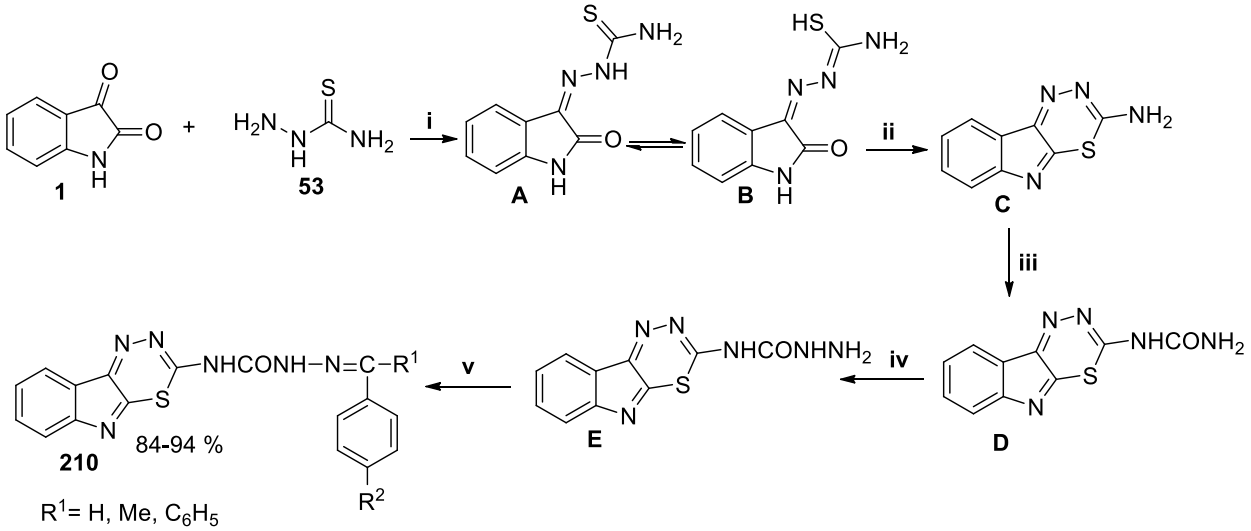
Hegade and co-workers developed an organocatalyzed pseudo four-component reaction of isatin derivatives **1**, cyclohexanone **208**, and malononitrile **156** in the presence of a catalytic amount of DABCO for the synthesis of functionalized spirooxindoles **209** (Scheme 83).[141]



Scheme 83

6. Miscellaneous Reactions

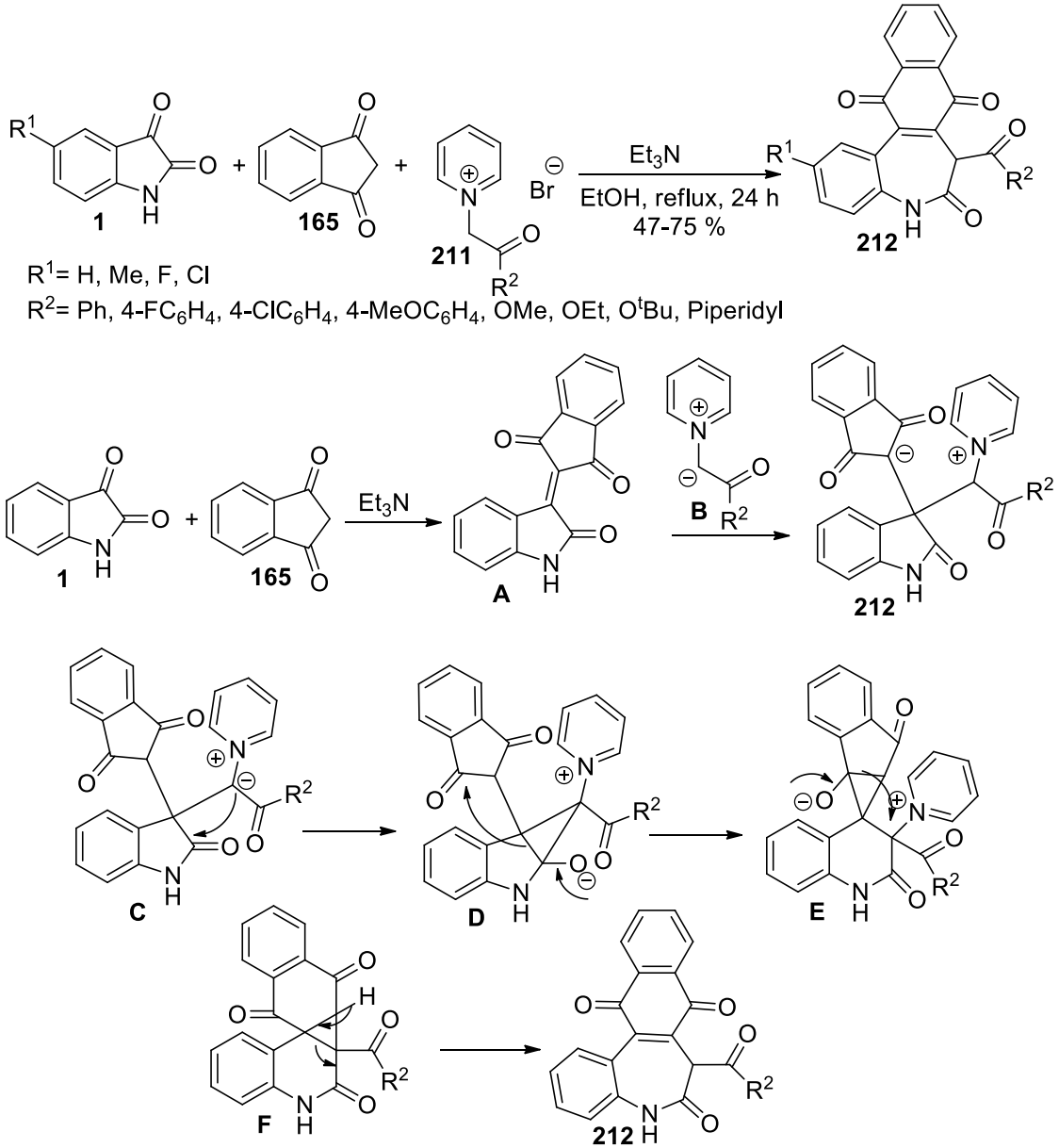
From the reaction of isatin **1** and thiosemicarbazide **53** through multiple steps (involving the intermediates **A-E**) a series of semicarbazones containing 1,3,4-thiadiazino and indole rings **210** were synthesized (Scheme 84).[142] All the newly synthesized compounds were investigated for anticonvulsant activity.



Scheme 84

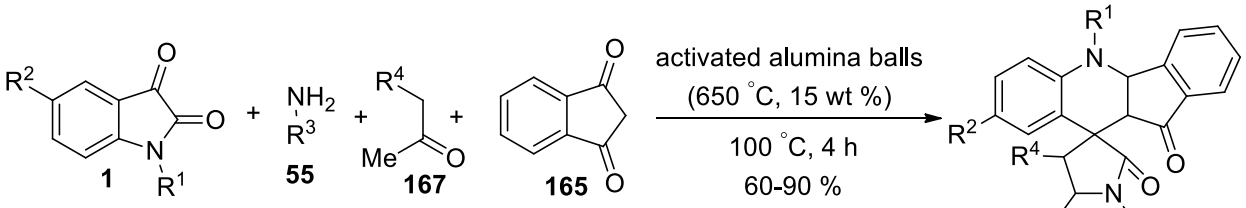
A unique two-carbon ring expansion of isatins **1** has been achieved to conveniently construct the functionalized dibenzo[*b,d*]azepin-6-one scaffolds **212** while one carbon atom is from the *N*-substituent of

pyridinium bromide **211** and the other is from indene-1,3-dione **165**. The possible reaction mechanism for two-carbon ring expansion has been shown in scheme 85. Pyridinium bromide **211** was first deprotonated to a pyridinium ylide under the basic conditions. The Michael addition of pyridinium ylide to the condensation product **A** resulted in the formation of zwitterion **B** without other regio-isomers, and this might have resulted from the more electron-deficient 3-position on the isatin **1** than the 2-position of indan-1,3-dione **165**. The following proton transfer gave a new zwitterion **C**, and the intramolecular nucleophilic addition of the carbon anion to the 2-carbonyl group of the isatinyl moiety afforded a cyclopropyl intermediate **D**. The less strong electron-withdrawing nature of R^2 groups such as *p*-nitrobenzyl makes this transfer hard to occur, and this multi-component reaction stops at this stage. The re-opening of cyclopropane oxide **D** leads to the attack of the newly generated carbon anion on the carbonyl group in the indene-1,3-dione **165**. The resulting cyclopropyl oxide **E** further re-opened and the removal of pyridine afforded cyclopropane **F**. The following cyclopropane reorganized to the ring-expanded product **212** (Scheme 85).[143]



Scheme 85

The spiro[pyrrolo-4,10'-indeno[1,2-*b*]quinolin]-3-carboxylate compounds **213** were obtained from the reaction of isatin derivatives **1**, amines **55**, β-ketoesters **167** and indane-1,3-dione **165** with activated alumina balls (3–5 mm diameter) as a catalyst under neat reaction conditions (Scheme 86).[144] Except for *n*-butylamine (which resulted in lower yields), the products were obtained in good to excellent yields (72–92%) whether there is an electron-donating or –withdrawing substituent on the aromatic ring. The substituted isatin derivatives with Cl and Br at the 5-position also reacted efficiently to give high yields.



R^1= H, Allyl, Bn, Me, CO_2Me, CO_2Et, ^{n}Bu
R^2= H, Cl, Br
R^3= H, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-ClC_6H_4, 3,4-$Me_2C_6H_3$, 3-$CO_2HC_6H_4$, 4-$CO_2HC_6H_4$, 3-MeC_6H_4, 2-*i*-PrC_6H_4, ^{i}Pr, ^{n}Bu
R^4= CO_2Et, CO_2Me

Scheme 86

7. Conclusions

Isatin is one of the important heterocyclic structures with special significance for the synthesis of organic compounds. Schiff bases of isatin, 3,3-disubstituted oxindoles and spirooxindoles are some important structures that can be synthesized using isatin as an starting material. More importantly, most of these compounds exhibit biological and pharmaceutical activities. In recent years, isatin has been widely used in the synthesis of a variety of organic compounds. Due to the widespread use of isatin in organic reactions and pursuant to our previous studies, herein we have an overview of recent applications of isatin in the synthesis of organic compounds up to June 2016.

Acknowledgements

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Abbreviations
DABCO: diazabicyclooctane
DBU: diazabicycloundecene
DCE: dichloroethane
DCM: dichloromethane
DMF: dimethylformamide
EG: ethylene glycol
MTBE: methyl tertiary-butyl ether

PEG: polyethylene glycol
TBAF: tetrabutylammonium fluoride
TBSOTf: tert-butyldimethylsilyl trifluoromethanesulfonate
TFA: trifluoroacetic acid
THF: tetrahydrofuran

References

1. Erdmann, O. L. *J. Prakt. Chem.* **1840**, *19*, 321. http://dx.doi.org/10.1002/ardp.18400720604
2. Laurent, A. *Ann. Chim. Phys.* **1840**, *3*, 393.
3. Jarrahpour, A. A.; Khalili, D. *Molbank* **2005**, *4*, M437. http://dx.doi.org/10.3390/M437
4. Fortt, R.; Smith, G.; Awais, R. O.; Luthra, S. K.; Aboagye, E. O. *Nucl. Med. Biol.* **2012**, *39*, 1000. http://dx.doi.org/10.1016/j.nucmedbio.2012.03.004
5. Ermut, G.; Karal, N.; Cetin, I.; Topcul, M.; Birteksoz, S. *Marmara Pharm. J.* **2013**, *17*, 147. http://dx.doi.org/10.12991/201317383
6. Kumar, M.; Ramasamy, K.; Mani, V.; Mishra, R. K.; Majeed, A. B. A.; Clercq, E. D.; Narasimhan, B. *Arabian J. Chem.* **2014**, *7*, 396. http://dx.doi.org/10.1016/j.arabjc.2012.12.005
7. Havrylyuk, D.; Zimenkovsky, B.; Vasylenko, O.; Gzella, A.; Lesyk, R. *J. Med. Chem.* **2012**, *55*, 8630. http://dx.doi.org/10.1021/jm300789g
8. Kumar, S. B.; Ravinder, M.; Kishore, G.; Rao, V. J.; Yogeeswari, P.; Sriram, D. *Med. Chem. Res.* **2014**, *23*, 1934. http://dx.doi.org/10.1007/s00044-013-0787-x
9. Kumar, K.; Kremer, S. C.; Kremer, L.; Gueerardel, Y.; Biot, C.; Kumar, V. *Organomet.* **2013**, *32*, 5713. http://dx.doi.org/10.1021/om301157z
10. Mondal, P.; Jana, S.; Balaji, A.; Ramakrishna, R.; Kanthal, L. *J. Young Pharm.* **2013**, *4*, 38. http://dx.doi.org/10.4103/0975-1483.93574
11. Raj, R.; Singh, P.; Singh, P.; Gut, J.; Rosenthal, P. J.; Kumar, V. *Eur. J. Med. Chem.* **2013**, *62*, 590. http://dx.doi.org/10.1016/j.ejmech.2013.01.032
12. Paul, B. K.; Ray, D.; Guchhait, N. *Phys. Chem. Chem. Phys.* **2013**, *15*, 1275. http://dx.doi.org/10.1039/C2CP42539D
13. Kiran, G.; Maneshwar, T.; Rajeshwar, Y.; Sarangapani, M. *J. Chem.* **2013**, *2013*, 1. http://dx.doi.org/10.1155/2013/192039
14. Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. http://dx.doi.org/10.1002/adsc.201000161
15. Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. http://dx.doi.org/10.2174/157340709787580900
16. Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 758.
17. Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. http://dx.doi.org/10.1021/cr300135y
18. Borad, M. A.; Bhoi, M. N.; Prajapati, N. P.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 897. http://dx.doi.org/10.1080/00397911.2013.843196

19. Borad, M. A.; Bhoi, M. N.; Prajapati, N. P.; Patel, H. D. *Synth. Commun.* **2014**, *44*, 1043. http://dx.doi.org/10.1080/00397911.2013.858361
20. Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. http://dx.doi.org/10.1039/C2OB25184A
21. Flores, M.; Pena, J.; García, P. G.; Garrido, N. M.; Díez, D. *Curr. Org. Chem.* **2013**, *17*, 1957. http://dx.doi.org/10.2174/13852728113179990092
22. Liu, Y.; Wang, H.; Wan, J. *Asian J. Org. Chem.* **2013**, *2*, 374. http://dx.doi.org/10.1002/ajoc.201200180
23. Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. *Arkivoc* **2016**, (*i*), 1. http://dx.doi.org/10.3998/ark.5550190.p009.385
24. Lashgari, N.; Mohammadi Ziarani, G. *Arkivoc* **2012**, (*i*), 277. http://dx.doi.org/10.3998/ark.5550190.0013.108
25. Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. *Tetrahedron: Asymmetry* **2015**, *26*, 517. http://dx.doi.org/10.1016/j.tetasy.2015.04.011
26. Yadav, G. D.; Singh, S. *Tetrahedron: Asymmetry* **2016**, *27*, 123. http://dx.doi.org/10.1016/j.tetasy.2015.12.005
27. Yadav, G. D.; Singh, S. *Tetrahedron: Asymmetry* **2016**, *27*, 463. http://dx.doi.org/10.1016/j.tetasy.2016.04.008
28. Sanjeeva Kumar, A.; Santosh Kumar, G.; Babu Nanubolu, J. *RSC Adv.* **2016**, *6*, 1705. http://dx.doi.org/10.1039/C5RA14714J
29. Huang, Y.; Huang, R.-Z.; Zhao, Y. *J. Am. Chem. Soc.* **2016**, *138*, 6571. http://dx.doi.org/10.1021/jacs.6b02372
30. Chen, Q.; Tang, Y.; Huang, T.; Liu, X.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 5286. http://dx.doi.org/10.1002/anie.201600711
31. Singh, V. K.; Upadhyay, A.; Singh, R. K. P. *Tetrahedron Lett.* **2017**, *58,* 156. http://dx.doi.org/10.1016/j.tetlet.2016.11.124c
32. Pandey, G.; Khamrai, J. *Asian J. Chem.* **2016**, *5*, 621. http://dx.doi.org/10.1002/ajoc.201600101
33. Xu, N.; Gu, D.-W.; Zi, J.; Wu, X.-Y.; Guo, X.-X. *Org. Lett.* **2016**, *18*, 2439. http://dx.doi.org/10.1021/acs.orglett.6b00971
34. Wang, G.; Liu, X.; Chen, Y.; Yang, J.; Li, J.; Lin, L.; Feng, X. *ACS Catal.* **2016**, *6,* 2482. http://dx.doi.org/10.1021/acscatal.6b00294
35. He, Q.; Zhan, G.; Du, W.; Chen, Y. C. *Beilstein J. Org. Chem.* **2016**, *12*, 309. http://dx.doi.org/10.3762/bjoc.12.33
36. Senwar, K. R.; Reddy, T. S.; Thummuri, D.; Sharma, P.; Naidu, V. G. M.; Srinivasulu, G.; Shankaraiah, N. *Eur. J. Med. Chem.* **2016**, *118*, 34. http://dx.doi.org/10.1016/j.ejmech.2016.04.025
37. Shaker, S. A.; Marzouk, M. I. *Molecules* **2016**, *21*, 155. http://dx.doi.org/10.3390/molecules21020155
38. Kondoh, A.; Takei, A.; Terada, M. *Synlett* **2016**, *27*, 1848. http://dx.doi.org/10.1055/s-0035-1561859
39. Nazish, M.; Jakhar, A.; Noor-ul, H. K.; Verma, S.; Kureshy, R. I.; Abdi, S. H.; Bajaj, H. C. *Appl. Catal., A* **2016**, *515*, 116.

http://dx.doi.org/10.1016/j.apcata.2015.12.037
40. Su, L.; Xu, M.-H. *Synthesis* **2016**, *48*, 2595. http://dx.doi.org/10.1055/s-0035-1561426
41. Menapara, T.; Choudhary, M. K.; Tak, R.; Kureshy, R. I.; Noor-ul, H. K.; Abdi, S. H. *J. Mol. Catal. A: Chem.* **2016**, *421*, 161. http://dx.doi.org/10.1016/j.molcata.2016.05.021
42. Amr, F. I.; Vila , C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2016**, *358*, 1583. http://dx.doi.org/10.1002/adsc.201600036
43. Vila, C.; Amr, F. I.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Chem. Asian J.* **2016**, *11*, 1532. http://dx.doi.org/10.1002/asia.201600325
44. Yanagisawa, A.; Yamafuji, S.; Sawae, T. *Synlett* **2016**, *27*, 2019. http://dx.doi.org/10.1055/s-0035-1561450
45. Chen, T.; Cai, C. *Org. Biomol. Chem.* **2016**, *14*, 5019. http://dx.doi.org/10.1039/C6OB00551A
46. He, Q.; Wu, L.; Kou, X.; Butt, N.; Yang, G.; Zhang, W. *Org. Lett.* **2016**, *18*, 288. http://dx.doi.org/10.1021/acs.orglett.5b03458
47. Li, X.; Su, J.; Liu, Z.; Zhu, Y.; Dong, Z.; Qiu, S.; Wang, J.; Lin, L.; Shen, Z.; Yan, W. *Org. Lett.* **2016**, *18*, 956. http://dx.doi.org/10.1021/acs.orglett.5b03566
48. Elghamry, I.; Al-Faiyz, Y. *Tetrahedron Lett.* **2016**, *57*, 110. http://dx.doi.org/10.1016/j.tetlet.2015.11.070
49. Yogi, P.; Ashid, M.; Hussain, N.; Khan, S.; Joshi, A. *Asian J. Chem.* **2016**, *28*, 927. http://dx.doi.org/10.14233/ajchem.2016.19603
50. Kumar, M.; Kaur, B. P.; Chimni, S. S. *Chem. Eur. J.* **2016**, *22*, 9948. http://dx.doi.org/10.1002/chem.201601222
51. Sharma, S.; Banerjee, B.; Brahmachari, G.; Kant, R.; Gupta, V. K. *Crystallogr. Rep.* **2016**, *61*, 225. http://dx.doi.org/10.1107/S2052520616005060
52. Nikoofar, K.; Khalili, Z. *Z. Naturforsch. B Chem. Sci.* **2016**, *71*, 31. http://dx.doi.org/10.1515/znb-2015-0111
53. Hassani, H.; Nasseri, M. A.; Zakerinasab, B.; Rafiee, F. *Appl. Organomet. Chem.* **2016**, *30*, 408. http://dx.doi.org/10.1002/aoc.3447
54. Cheng, D.; Ling, F.; Zheng, C.; Ma, C. *Org. Lett.* **2016**, *18*, 2435. http://dx.doi.org/10.1021/acs.orglett.6b00964
55. Bejjam, M. B.; Kumar, G. S.; Swetha, A.; Meshram, H. *RSC Adv.* **2016**, *6*, 13820. http://dx.doi.org/10.1039/C5RA24127H
56. Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. http://dx.doi.org/10.1021/ar020229e
57. Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832. http://dx.doi.org/10.7164/antibiotics.49.832
58. Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175. http://dx.doi.org/10.1002/1522-2675(20000607)83:6<1175::AID-HLCA1175>3.0.CO;2-D
59. Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186. http://dx.doi.org/10.1002/(SICI)1521-3773(19991102)38:21<3186::AID-ANIE3186>3.0.CO;2-E
60. Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477.

http://dx.doi.org/10.1021/ja980786p
61. Hajra, S.; Aziz, S. M.; Jana, B.; Mahish, P.; Das, D. *Org. Lett.* **2016**, *18*, 532. http://dx.doi.org/10.1021/acs.orglett.5b03564
62. Pace, V.; Castoldi, L.; Mamuye, A. D.; Langer, T.; Holzer, W. *Adv. Synth. Catal.* **2016**, *358*, 172. http://dx.doi.org/10.1002/adsc.201500840
63. Wang, K.-K.; Jin, T.; Huang, X.; Ouyang, Q.; Du, W.; Chen, Y.-C. *Org. Lett.* **2016**, *18*, 872. http://dx.doi.org/10.1021/acs.orglett.6b00189
64. Zhao, B.-L.; Du, D.-M. *Chem. Commun.* **2016**, *52*, 6162. http://dx.doi.org/10.1039/C6CC00705H
65. Zhao, K.; Zhi, Y.; Li, X.; Puttreddy, R.; Rissanen, K.; Enders, D. *Chem. Commun.* **2016**, *52*, 2249. http://dx.doi.org/10.1039/C5CC10057G
66. Kumar, K.; Sankar, M. G.; Garcia-Castro, M.; Golz, C.; Strohman, C. *RSC Adv.* **2016**, *6*, 56537. http://dx.doi.org/10.1039/C6RA12387B
67. Cheng, P.; Guo, W.; Chen, P.; Liu, Y.; Du, X.; Li, C. *Chem. Commun.* **2016**, *52*, 3418. http://dx.doi.org/10.1039/C5CC10292H
68. Cui, H.-L.; Chouthaiwale, P. V.; Yin, F.; Tanaka, F. *Org. Biomol. Chem.* **2016**, *14*, 1777. http://dx.doi.org/10.1039/C5OB02393A
69. Cui, H. L.; Chouthaiwale, P. V.; Yin, F.; Tanaka, F. *Asian J. Org. Chem.* **2016**, *5*, 153. http://dx.doi.org/10.1002/ajoc.201500412
70. Rong, X.; Yao, H.; Xia, W.; Du, Y.; Zhou, Y.; Liu, H. *ACS Comb. Sci.* **2016**, *18*, 220. http://dx.doi.org/10.1021/acscombsci.5b00197
71. Zhu, L.; Yu, C.; Li, T.; Wang, Y.; Lu, Y.; Wang, W.; Yao, C. *Org. Biomol. Chem.* **2016**, *14*, 1485. http://dx.doi.org/10.1039/C5OB02160J
72. Han, J. L.; Chang, C. H. *Chem. Commun.* **2016**, *52*, 2322. http://dx.doi.org/10.1039/C5CC08883F
73. Li, Y.; Hu, Y.; Zhang, S.; Sun, J.; Li, L.; Zha, Z.; Wang, Z. *J. Org. Chem.* **2016**, *81*, 2993. http://dx.doi.org/10.1021/acs.joc.5b02780
74. Mane, M. M.; Pore, D. M. *J. Chem. Sci.* **2016**, *128*, 657. http://dx.doi.org/10.1007/s12039-016-1047-7
75. Kumarswamyreddy, N.; Kesavan, V. *Org. Lett.* **2016**, *18*, 1354. http://dx.doi.org/10.1021/acs.orglett.6b00287
76. Wang, S.; Jiang, Y.; Wu, S.; Dong, G.; Miao, Z.; Zhang, W.; Sheng, C. *Org. Lett.* **2016**, *18*, 1028. http://dx.doi.org/10.1021/acs.orglett.6b00155
77. Kumar, D.; Sharma, L. K.; Sharma, K.; Jain, R. *J. Heterocycl. Chem.* **2017**, *54*, 570. http://dx.doi.org/10.1002/jhet.2623
78. Liu, J.-Y.; Lu, H.; Li, C.-G.; Liang, Y.-M.; Xu, P.-F. *Synlett* **2016**, *27*, 1287. http://dx.doi.org/10.1055/s-0035-1560600
79. Domling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083. http://dx.doi.org/10.1021/cr100233r
80. González-López, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164. http://dx.doi.org/10.1021/cr8002714
81. Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. *Chem. Rev.* **2014**, *114*, 8323. http://dx.doi.org/10.1021/cr400615v

82. Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300. http://dx.doi.org/10.1002/chem.200802140
83. Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. http://dx.doi.org/10.1016/j.tetasy.2007.03.002
84. Liu, H.; Dou, G.; Shi, D. *J. Comb. Chem.* **2010**, *12*, 292. http://dx.doi.org/10.1021/cc900195t
85. Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. *Chem. Commun.* **2016**, *52*, 9044. http://dx.doi.org/10.1039/c6cc00057f
86. Parmar, B. D.; Sutariya, T. R.; Brahmbhatt, G. C.; Parmar, N. J.; Kant, R.; Gupta, V. K. *J* **2016**, *81*, 4955. http://dx.doi.org/10.1021/acs.joc.6b00107
87. Liu, X.-W.; Yao, Z.; Yang, J.; Chen, Z.-Y.; Liu, X.-L.; Zhao, Z.; Lu, Y.; Zhou, Y.; Cao, Y. *Tetrahedron* **2016**, *72*, 1364. http://dx.doi.org/10.1016/j.tet.2016.01.029
88. Liu, X.-L.; Yang, C.; Zhang, W.-H.; Zhou, G.; Ma, X.-T.; Lin, B.; Zhang, M.; Zhou, Y.; Feng, T.-T. *Tetrahedron Lett.* **2016**, *57*, 1385. http://dx.doi.org/10.1016/j.tetlet.2016.02.074
89. Sumesh, R. V.; Muthu, M.; Almansour, A. I.; Suresh Kumar, R.; Arumugam, N.; Athimoolam, S.; Jeya Yasmi Prabha, E. A.; Kumar, R. R. *ACS Comb. Sci.* **2016**, *18*, 262. http://dx.doi.org/10.1021/acscombsci.6b00003
90. Cores, Á.; Estévez, V.; Villacampa, M.; Menéndez, J. C. *RSC Adv.* **2016**, *6*, 39433. http://dx.doi.org/10.1039/C6RA06317A
91. Nayak, S.; K Mishra, S.; Bhakta, S.; Panda, P.; Baral, N.; Mohapatra, S.; S Purohit, C.; Satha, P. *Lett. Org. Chem.* **2016**, *13*, 11. http://dx.doi.org/10.2174/1570178612666151030213735
92. George, R. F.; Panda, S. S.; Shalaby, E. S. M.; Srour, A. M.; Farag, I. S. A.; Girgis, A. S. *RSC Adv.* **2016**, *6*, 45434. http://dx.doi.org/10.1039/C6RA07061B
93. Uma Rani, G.; Vivek Kumar, S.; Bharkavi, C.; Menéndez, J. C.; Perumal, S. *ACS Comb. Sci.* **2016**, *18*, 337. http://dx.doi.org/10.1021/acscombsci.6b00011
94. Mathusalini, S.; Arasakumar, T.; Lakshmi, K.; Lin, C.-H.; Mohan, P. S.; Ramnath, M. G.; Thirugnanasampandan, R. *New J. Chem.* **2016**, *40*, 5164. http://dx.doi.org/10.1039/c6nj00534a
95. Hamama, W. S.; Hassanien, A. E.; El-Fedawy, M. G.; Zoorob, H. H. *J. Heterocycl. Chem.* **2017**, *54*, 859. http://dx.doi.org/10.1002/jhet.2646
96. Sankar, U.; Surya Kumar, C. V.; Subramanian, V.; Balasubramanian, K. K.; Mahalakshimi, S. *J. Org. Chem.* **2016**, *81*, 2340. http://dx.doi.org/10.1021/acs.joc.5b02845
97. Ramesh, P.; Rao, K. S.; Trivedi, R.; Kumar, B. S.; Prakasham, R.; Sridhar, B. *RSC Adv.* **2016**, *6*, 26546. http://dx.doi.org/10.1039/C6RA00613B
98. Shi, G.; He, X.; Shang, Y.; Xie, M. *RSC Adv.* **2016**, *6*, 10412. http://dx.doi.org/10.1039/c5ra23860a
99. Wang, Y.-M.; Zhang, H.-H.; Li, C.; Fan, T.; Shi, F. *Chem. Commun.* **2016**, *52*, 1804. http://dx.doi.org/10.1039/C5CC07924A

100. Safaei-Ghomi, J.; Zahedi, S. *Tetrahedron Lett.* **2016**, *57*, 1071. http://dx.doi.org/10.1016/j.tetlet.2016.01.073
101. Preetam, A.; Nath, M. *Tetrahedron Lett.* **2016**, *57*, 1502. http://dx.doi.org/10.1016/j.tetlet.2016.02.079
102. Rajeswari, M.; Kumari, S.; Khurana, J. M. *RSC Adv.* **2016**, *6*, 9297. http://dx.doi.org/10.1039/C5RA26093K
103. Mali, P. R.; Rao, L. C.; Bangade, V. M.; Shirsat, P. K.; George, S. A.; Babu, N. J.; Meshram, H. M. *New J. Chem.* **2016**, *40*, 2225. http://dx.doi.org/10.1039/C5NJ02126J
104. Kumari, S.; Singh, H.; Khurana, J. M. *Tetrahedron Lett.* **2016**, *57*, 3081. http://dx.doi.org/10.1016/j.tetlet.2014.11.046
105. Maryamabadi, A.; Hasaninejad, A.; Nowrouzi, N.; Mohebbi, G.; Asghari, B. *Bioorg. Med. Chem.* **2016**, *24*, 1408. http://dx.doi.org/10.1016/j.bmc.2016.02.019
106. Shakibaei, G. I.; Bazgir, A. *RSC Adv.* **2016**, *6*, 22306. http://dx.doi.org/10.1039/C6RA00869K
107. Mohammadi Ziarani, G.; Aleali, F.; Lashgari, N.; Badiei, A. R. *Iran. J. Chem. Chem. Eng.* **2016**, *35*, 17.
108. Mohammadi Ziarani, G.; Asadi, S.; Badiei, A. R.; Sharifi, A.; Amanlou, M. *Iran. J. Pharm. Res.* **2016**, *15*, 55.
109. Mohammadi Ziarani, G.; Hassanzadeh, Z.; Gholamzadeh, P.; Soorki, A. A. *Rev. Roum. Chim.* **2016**, *61*, 77.
110. Sagir, H.; Rai, P.; Tiwari, S.; Siddiqui, I. *J. Heterocycl. Chem.* **2017**, *54*, 397. http://dx.doi.org/10.1002/jhet.2596
111. Kumari, S.; Rajeswari, M.; Khurana, J. M. *Synth. Commun.* **2016**, *46*, 387. http://dx.doi.org/10.1080/00397911.2016.1141427
112. Nalini, G.; Jayachandramani, N.; Thanikachalam, V.; Jayabharath, J.; Manikandan, G.; Suresh, R. *Can. Chem. Trans.* **2016**, *4*, 62. http://dx.doi.org/10.13179/canchemtrans.2016.04.01.0248
113. Kefayati, H.; Bazargard, S. J.; Vejdansefat, P.; Shariati, S.; Kohankar, A. M. *Dyes Pigm.* **2016**, *125*, 309. http://dx.doi.org/10.1016/j.dyepig.2015.10.034
114. Shi, R.-G.; Yan, C.-G. *Chin. Chem. Lett.* **2016**, *27*, 575. http://dx.doi.org/10.1016/j.cclet.2016.02.016
115. Niknam, K.; Khataminejad, M.; Zeyaei, F. *Tetrahedron Lett.* **2016**, *57*, 361. http://dx.doi.org/10.1016/j.tetlet.2015.12.034
116. Keshavarz, M. *J. Iran. Chem. Soc.* **2016**, *13*, 553. http://dx.doi.org/10.1007/s13738-015-0765-y
117. Ramadoss, H.; Saravanan, D.; Sudhan, S. P. N.; Sheik Mansoor, S. *Der Pharma Chemica* **2016**, *8*, 94.
118. Molla, A.; Hussain, S. *RSC Adv.* **2016**, *6*, 5491. http://dx.doi.org/10.1039/C5RA21969H
119. Garcia-Garcia, P.; Moreno, J. M.; Diaz, U.; Bruix, M.; Corma, A. *Nat. Commun.* **2016**, *7*, 10835. http://dx.doi.org/10.1038/ncomms10835
120. Padvi, S. A.; Tayade, Y. A.; Wagh, Y. B.; Dalal, D. S. *Chin. Chem. Lett.* **2016**, *27*, 714. http://dx.doi.org/10.1016/j.cclet.2016.01.016
121. Molla, A.; Hussain, S. *Synfacts* **2016**, *12*, 0426. http://dx.doi.org/10.1055/s-0035-1561789

122. Rashidi, A.; Tavakoli, Z.; Tarak, Y.; Khodabakhshi, S.; Abbasabadi, M. K. *J. Chin. Chem. Soc.* **2016**, *63*, 399. http://dx.doi.org/10.1002/jccs.201500508
123. Elinson, M. N.; Ryzhkov, F. V.; Zaimovskaya, T. A.; Egorov, M. P. *Monatsh. Chem.* **2016**, *147*, 755. http://dx.doi.org/10.1007/s00706-015-1617-2
124. Baghernejad, M.; Khodabakhshi, S.; Tajik, S. *New J. Chem.* **2016**, *40*, 2704. http://dx.doi.org/10.1039/C5NJ03027G
125. Brahmachari, G.; Banerjee, B. *Asian J. Org. Chem.* **2016**, *5*, 271. http://dx.doi.org/10.1002/ajoc.201500465
126. Moosavi-Zare, A. R.; Zolfigol, M. A.; Noroozizadeh, E.; Moratab, R. S.; Zarei, M. *J. Mol. Catal. A: Chem.* **2016**, *420*, 246. http://dx.doi.org/10.1016/j.molcata.2016.04.021
127. Stucchi, M.; Lesma, G.; Meneghetti, F.; Rainoldi, G.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2016**, *81*, 1877. http://dx.doi.org/10.1021/acs.joc.5b02680
128. Mishra, K.; Basavegowda, N.; Lee, Y. R. *RSC Adv.* **2016**, *6*, 27974. http://dx.doi.org/10.1039/C6RA03883B
129. Maloo, P.; Roy, T. K.; Sawant, D. M.; Pardasani, R. T.; Salunkhe, M. M. *RSC Adv.* **2016**, *6*, 41897. http://dx.doi.org/10.1039/C6RA05322J
130. Alizadeh, A.; Moafi, L. *Synlett* **2016**, *27*, 595. http://dx.doi.org/10.1055/s-0035-1560905
131. Zhang, Y.-L.; Li, Y.-F.; Wang, J.-W.; Yu, B.; Y.-K., S.; Liu, H.-M. *Steroids* **2016**, *109*, 22. http://dx.doi.org/10.1016/j.steroids.2016.03.005
132. Rajanarendar, E.; Thirupathaiah, K.; Ramakrishna, S.; Nagaraju, D.; Kishore, B. *J. Heterocycl. Chem.* **2017**, *54*, 889. http://dx.doi.org/10.1002/jhet.2650
133. Chandam, D. R.; Mulik, A. G.; Patil, D. R.; Patravale, A. P.; Kumbhar, D. R.; Deshmukh, M. B. *J. Mol. Liq.* **2016**, *219*, 573. http://dx.doi.org/10.1016/j.molliq.2016.02.101
134. Shaabani, A.; Hooshmand, S. E.; Tabatabaei, A. T. **2016**, *57*, 351. http://dx.doi.org/10.1016/j.tetlet.2015.12.017
135. Shrestha, R.; Sharma, K.; Lee, Y. R.; Wee, Y.-J. *Mol. Divers.* **2016**, *20*, 847. http://dx.doi.org/10.1007/s11030-016-9670-2
136. Alemi-Tameh, F.; Safaei-Ghomi, J.; Mahmoudi-Hashemi, M.; Teymuri, R. *Res. Chem. Intermed.* **2016**, *42*, 6391. http://dx.doi.org/10.1007/s11164-016-2470-6
137. Fu, Z.; Qian, K.; Li, S.; Shen, T.; Song, Q. *Tetrahedron Lett.* **2016**, *57*, 1104. http://dx.doi.org/10.1016/j.tetlet.2016.01.089
138. Min, L.; Pan, B.; Gu, Y. *Org. Lett.* **2016**, *18*, 364. http://dx.doi.org/10.1021/acs.orglett.5b03287
139. Zhan, G.; Shi, M. L.; He, Q.; Lin, W. J.; Ouyang, Q.; Du, W.; Chen, Y. C. *Angew. Chem., Int. Ed.* **2016**, *55*, 2147. http://dx.doi.org/10.1002/anie.201510825
140. He, Y.-H.; He, T.; Guo, J.-T.; Li, R.; Xiang, Y.; Yang, D.-C.; Guan, Z. *Catal. Sci. Tech.* **2016**, 6, 2239. http://dx.doi.org/10.1039/C5CY00987A

141. Hegade, P. G.; Chinchkar, S. D.; Pore, D. M. *Monatsh. Chem.* **2016**, *147*, 1243. http://dx.doi.org/10.1007/s00706-015-1637-y
142. Deshmukh, R.; S Thakur, A.; K Jha, A.; Kumar, P. *Cent. Nerv. Syst. Agents Med. Chem.* **2016**, *16*, 29. http://dx.doi.org/10.2174/1871524915666150623091716
143. Shi, R.-G.; Wang, X.-H.; Liu, R.; Yan, C.-G. *Chem. Commun.* **2016**, *52*, 6280.
http://dx.doi.org/10.1039/C6CC00525J
144. Mondal, A.; Banerjee, B.; Bhaumik, A.; Mukhopadhyay, C. *Chem. Cat. Chem.* **2016**, *8*, 1185. http://dx.doi.org/10.1002/cctc.v8.6

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