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Transition metal-catalyzed synthesis of spirooxindoles

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Spirooxindole is a principal bioactive agent and is observed in several natural products including alkaloids. They are broadly studied in the pharmaceutical field and have a significant role in the evolution of drugs such as anti-viral, anti-cancer, anti-microbial *etc.* In organic chemistry, an indispensable role is presented by transition metal catalysts. An effective synthetic perspective to spirooxindoles is the use of transition metals as the catalyst. This review discusses the synthesis of spirooxindoles catalyzed by transition metals and covers literature up to 2020.

1 Introduction

Compounds having at least two molecular rings with one common atom are called spiro compounds. They can be heterocyclic or fully carbocyclic. The spiro atom is the one which connects the two or three rings. These compounds are useful in the synthesis of various novel therapeutic agents.

Spirooxindole is a type of spiro compound which has a prominent role in synthetic and pharmaceutical chemistry. Several natural products such as horsfiline,[1] alantrypinone,[2] elacomine and isoelacomine[3] contain spirooxindole framework in their structure. Spirooxindoles have wide applications as anti-cancer,[4,5] anti-inflammatory,[6] anti-microbial,[7,8] anti-oxidant,[9,10] anti-viral,[11] and anti-malarial[12] agents (Fig. 1).

Spirooxindole synthesis is a rapidly developing research area wherein the strategies towards enantioselective synthesis is undergoing large-scale investigations.[13–15] Methyleneindolinones,[16] isatin derivatives[17] *etc.* are widely employed as the starting materials for spirooxindole synthesis. Expeditious development occurred in the field of spirooxindole synthesis from 2012 to 2020.[18–20]

The synthesis of spirooxindoles catalyzed by different reagents has been reported which includes iodine/H_2O_2,[21] amine,[22] β-cyclodextrin,[23] L-proline,[24] ethylenediaminediacetate,[25] imidazole,[26] citric acid[27] and many others. Transition metals are efficient catalysts, as they are facile in losing and gaining of electrons, and most of them are malleable, ductile and easily available. In organic synthesis, transition metal-catalyzed reactions have advantages

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like gentle reaction conditions and are compatible with an extensive span of functionalities. Consequently, transition metal-catalyzed approaches are deliberated most assiduously. Ligand exchange, elimination, coordination *etc.* are the different modes through which the transition metal catalyst can stimulate the starting materials. Ligand alteration is a suitable pathway for changing the selectivities of these catalysts. Recently, investigations in the transition metal-catalyzed synthesis of spirooxindoles are advancing rapidly.

Previously, reviews were reported on the synthesis of spirooxindole *via* green protocols.[28] In addition, several other reviews are available on the catalytic asymmetric synthesis of spirooxindole.[29–31] In the present review, we highlight the transition metal-catalyzed synthesis of spirooxindoles up to 2020. For better conception, the review is categorized based on the transition metal catalyst used and subcategorized according to the starting materials.

2 Ag-catalyzed spirooxindole synthesis

Silver has helped in the development of novel reactions at a much lower cost compared to platinum and gold. The construction of both intramolecular and intermolecular bonds can be intermediated by Ag catalysts.[32] Silver can manifest Ag(I)/Ag(III) redox chemistry[33] and can function as one-electron oxidant. Several of the silver catalyst can effectively activate C–H bond present in the substrate to generate various useful organic scaffolds.

Spirooxindoles containing pyrrolidine and nitrile were synthesized by utilizing various silver catalysts from 2011 to 2018. Among the various silver catalysts used, Ag nanoparticle-catalyzed reactions are economic because the catalyst can be separated effortlessly and there is no necessity for any ligands. Large surface area is an assisting factor in their activity and selectivity. The other catalysts employed include – AgOAc, AgF and bimetallic catalyst of Ag(I) with Pd(0).

2.1 Reaction involving oxoindoline derivatives

Wang *et al.* proposed a method for the building up of spirooxindole-pyrrolidines **3** carrying four vicinal stereogenic centers from azomethine ylides **1** and 2-oxoindolin-3-ylidene **2** which are *N*-unprotected, through 1,3-dipolar cycloaddition catalyzed by AgOAc/TF-BiphamPhos complexes.[34] They could attain finer diastereo-, enantio- and regioselectivity with the catalyst. The reaction involved 15 mol% of triethylamine, 5 mol% of AgOAc/(*S*)-TF-BiphamPhos (**L1**) in dichloromethane at room temperature (Scheme 1). High to excellent yields of adducts with enantioselectivities 50–71% and diastereoselectivities >98 : <2 were obtained *via* the reaction between 2-

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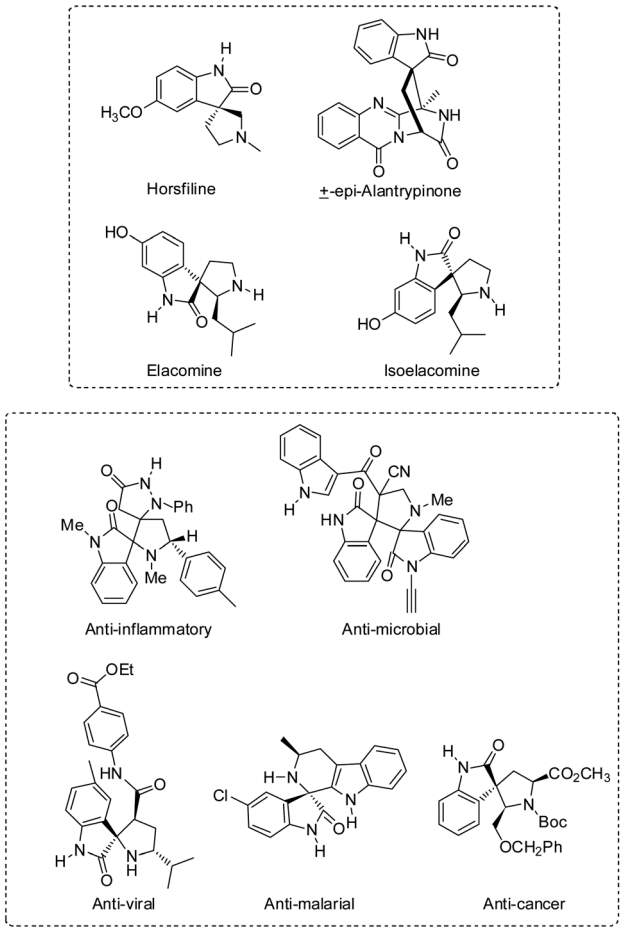
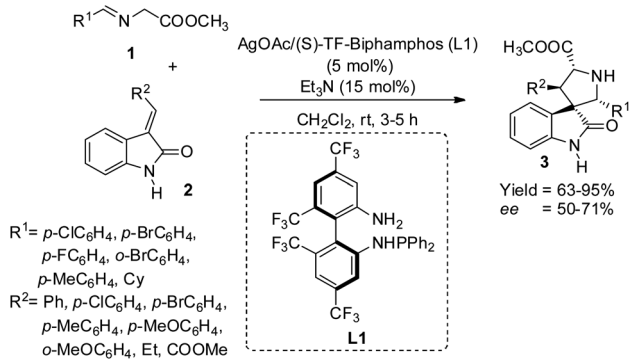


Fig. 1 Examples of natural products and bioactive molecules containing a spirooxindole core.

oxoindolin-3-benzylidene and imino esters gained from aromatic aldehydes. The enantioselectivities were not significantly affected by the electronic and positional properties of aromatic ring substituents. 92% of adduct with 50% ee were afforded by imino esters derived from aliphatic cyclohexane carbaldehyde. Good yields and diastereo- and enantioselectivities were attained with electron-deficient and electron-rich substituents on the benzene ring of 2-oxoindolin-3-ylidenes.



Scheme 1 Synthesis of spirooxindole-pyrrolidines from azomethine ylides and derivatives of *N*-unprotected 2-oxoindoline-3-ylidene.

R	R^1	R^2	R^3	Yield (%), *dr*
H	Me	t-Bu	Me	61, 1.1:1
5-Br	Me	Me	Me	65, 1.2:1
5-Me	Me	Me	Me	51, 1.1:1
H	Me	Me	Ph	51, 1.1:1
H	Me	Me	^{t}Bu	0

Scheme 2 Yield and diastereomeric ratio for the synthesis of nitrile-containing spirooxindoles through AgF mediated dialkylation.

Moderate enantioselectivity and high diastereo- and regioselectivity were afforded by the adduct from methyl oxoindolylidene acetate derived from Wittig reagent and isatin.

Wide substrate scope was a major highlight of the reaction involving oxoindoline derivatives.

2.2 Reaction involving alkene derivatives

A novel method for the synthesis of nitrile-containing spirooxindoles **5** mediated by AgF was developed by Liu and co-worker.[35] Activated alkenes **4** were dialkylated with acetonitrile as solvent, 4 equiv. of AgF as catalyst in an atmosphere of nitrogen at 110 °C in which the C–H bond of acetonitrile was activated by AgF (Scheme 2). Moderate yield with diastereoselectivities 1.1–1.2 : 1 were obtained when indoles having alkyl groups on nitrogen were used as the substrates. The corresponding products were not yielded by substrates with electron-deficient indole or with simple indole. Moderate yield was obtained with substrate in which the linked nitrogen bears a ^{t}Bu group. The yield of the product was not significantly affected by the aromatic ring substituents. When ^{t}Bu was on alkene moiety the product was not obtained, but phenyl group gave 51% of product. The diastereomeric ratio could be increased to 4–4.9 : 1 when 0.2 mmol K_2CO_3 was added at a lowered reaction temperature of 80 °C (Scheme 3).

Further explorations in this field of spirooxindole synthesis using alkene as starting materials did not expand much after 2014.

2.3 Reactions involving isatin derivatives

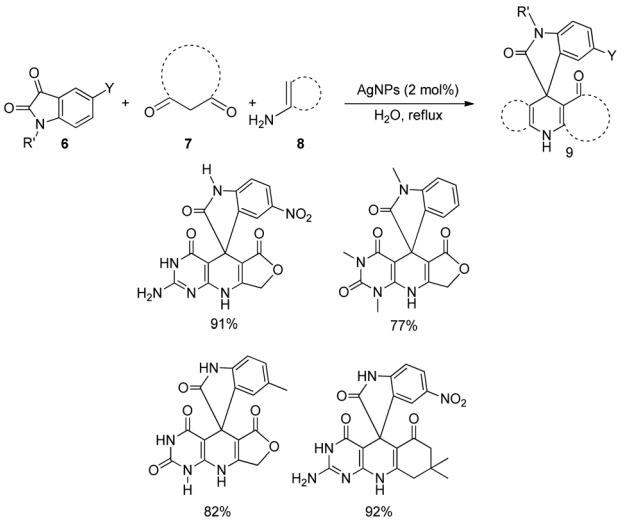
A method for the synthesis of spirooxindoles catalyzed by silver nanoparticles was established.[36] It is a green approach in which the aqueous extract of the leaves of *Ferula latisecta* was used to make up Ag nanoparticles. A series of spirooxindoles **9** were synthesised using the condensation reaction between isatin **6**, β-diketone **7** and enamines **8**, catalyzed by Ag nanoparticles in water as solvent at 90 °C (Scheme 4). Spirooxindoles were obtained in a reaction time of 15–30 minutes in high to excellent yields.

R	R^1	R^2	Yield (%), *dr*
H	Et	Me	64, 4:1
H	Me	^{t}Bu	67, 4.9:1
5-Br	Me	Me	61, 4.4:1
6-Me	Me	Me	64, 3.7:1

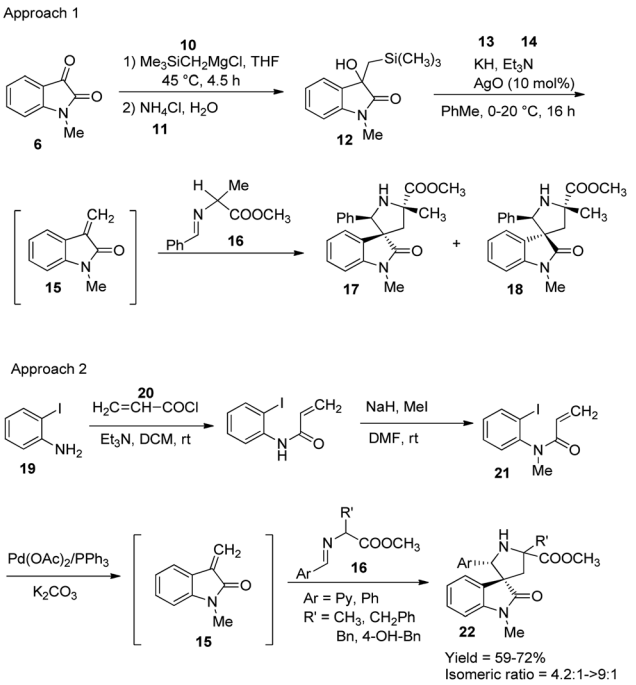
Scheme 3 Yield and diastereomeric ratio for the synthesis of nitrile-containing spirooxindoles with the addition of K_2CO_3 at 80 °C.

Millington and co-workers reported a bimetallic Pd(0)/Ag(I)-catalyzed synthesis of spirooxindoles, *epi*-spirotryprostatin A and its analogues.[37] There are two approaches in which the first one, produces spirooxindoles *via* Peterson olefination followed by 1,3-dipolarcycloaddition. Here initially, a β-hydroxysilane **12** was obtained by the reaction between trimethylsilylmethyl magnesium chloride **10** and *N*-methyl isatin **6** followed by the addition of NH_4Cl solution **11**. In the second step, the β-hydroxysilane **12** was treated with potassium hydride **13** and triethylamine **14**, in the presence of 10 mol% AgO to form an intermediate **15**. Mixture of stereoisomers of spirooxindoles (**17** and **18**) were obtained in a 1 : 2 ratio by the reaction between the intermediate and the imine **16**. The cycloaddition was catalyzed by Ag(I)oxide in Et_3N, KH and toluene at 0–20 °C.

In the second approach, reaction between acryloyl chloride **20** and *o*-iodoaniline **19** was succeeded by an *N*-methylation to give precursor **21**, which then underwent intra-molecular Heck reaction using $Pd(OAc)_2/PPh_3$. Spirooxindoles **22** were obtained with



Scheme 4 Synthesis of spirooxindoles catalyzed by silver nanoparticles.



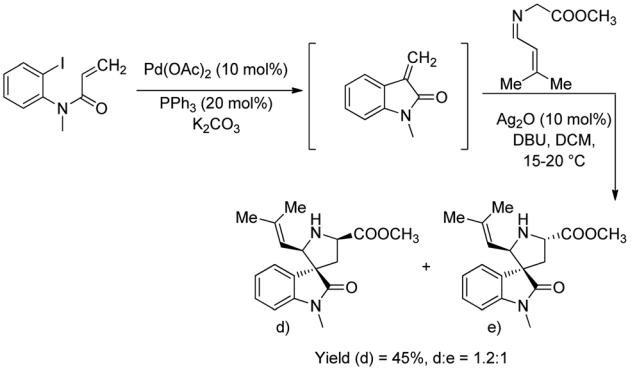
Scheme 5 Synthesis of spirooxindole *via* Peterson olefination/1,3-dipolar cycloaddition and intramolecular Heck/1,3-dipolar cycloaddition.

endo-selectivity with isomer ratios 4.2 : 1 to >9 : 1 through cycloaddition cascade process between the intermediate **15** and imine **16**, catalyzed by Ag(I). Both the approaches are portrayed in Scheme 5.

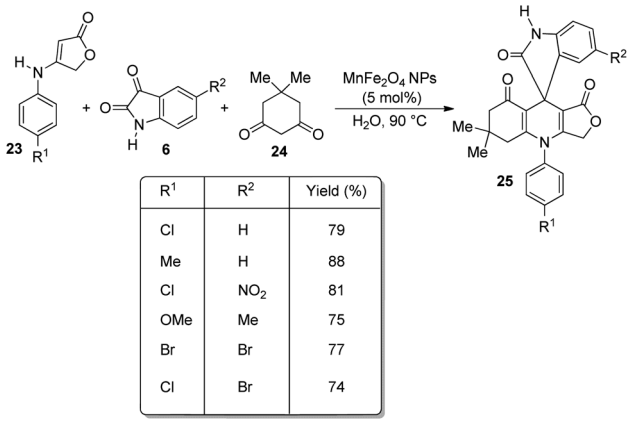
The group also synthesised *epi*-spirotryprostatin A and its analogues using the second approach. The products were obtained as a stereoisomeric mixture in which the product of cycloaddition of *syn*-dipole led to the minor isomer (Scheme 6).

3 Mn-catalyzed spirooxindole synthesis

Manganese is an excellent candidate as a catalyst due to its earth-abundance, cheapness and non-toxicity. In organic reactions, catalyst derived from manganese could gain a ubiquitous role because



Scheme 6 Synthesis of *epi*-spirotryprostatin A and its analogues.



R^1	R^2	Yield (%)
Cl	H	79
Me	H	88
Cl	NO_2	81
OMe	Me	75
Br	Br	77
Cl	Br	74

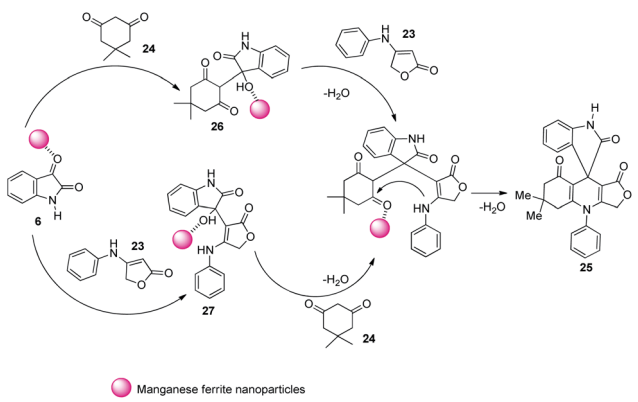
Scheme 7 Scope of the condensation reaction between anilinolactone, isatin and dimedone.

of the higher activity and cost-effectiveness. The electrophilic trait in starting materials, can be raised by some Mn catalysts because of their Lewis acidic nature.[38] Immense electron mobility could be observed in many of the manganese derived catalysts.

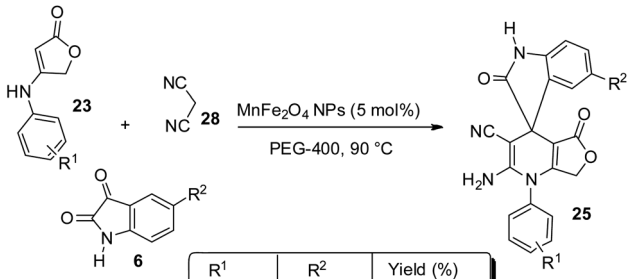
Various reports for the synthesis of spirooxindoles from isatin derivatives, catalyzed by manganese were published in 2013 and 2014. In all these cases, the catalyst used was manganese ferrite nanoparticles. The importance of this catalyst lies in its uncomplicated recoverability and reusability up to many cycles of reaction.

3.1 Reactions involving isatin derivatives

In 2013, Naeimi and co-workers demonstrated an environmentally benign method for the construction of novel spirooxindoles **25** by means of a one-pot procedure.[38] The reaction was effected by the condensation between anilinolactone **23**, isatin **6** and dimedone **24** with 5 mol% of $MnFe_2O_4$ NPs as catalyst, water as solvent at 90 °C (Scheme 7). The most important advantage of this procedure is that, the catalyst is green, can be recovered magnetically and can be reused. The reaction time was high in the case of anilinolactones having electron-deficient substituents on the aryl ring compared to electron-rich ones. The yield was not significantly affected by the nature of substituents on isatin.



Scheme 8 Plausible mechanism for spirooxindole synthesis by condensation between anilinolactone, isatin and dimedone [reproduced with permission from ref. 38].



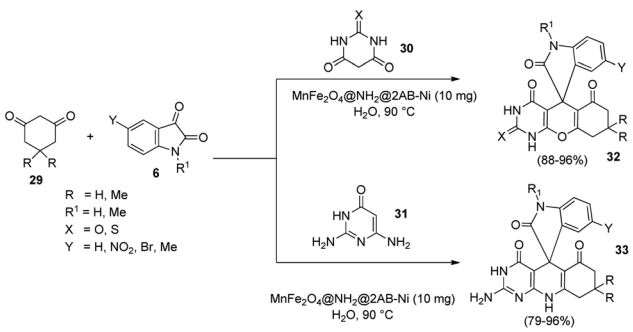
R^1	R^2	Yield (%)
p-Cl	H	80
m-Cl	H	77
o,*p*-diCl	H	79
o-Me	Br	76
p-Br	NO_2	84
m-Cl	NO_2	75

Scheme 9 Synthesis of spirooxindole by condensation between anilinolactone, isatin and dicyanomethane in PEG-400.

Two mechanistic pathways were suggested for the reaction (Scheme 8). In the first approach Lewis acid sites present in nano $MnFe_2O_4$ caused activation of isatin **6** and further nucleophilic addition occurred between activated isatin and dimedone **24**. The intermediate **26** so obtained reacted with anilinolactone **23** and subsequent cyclization gave the required product **25**. The second step was also catalyzed by $MnFe_2O_4$. According to the second pathway, anilinolactone **23** reacted with isatin **6** generating an intermediate **27**. Next step was the nucleophilic addition between dimedone **24** and the intermediate **27**. The spirooxindole product **25** was obtained *via* intramolecular ring closing step. In this approach also all the steps were catalyzed by nano $MnFe_2O_4$.

This method was further explored and was reported by the same group in the next year.[39] Here, anilinolactone **23**, isatin **6** and dicyanomethane **28** undergo one-pot reaction in PEG-400 as solvent, catalyzed by 5 mol% of $MnFe_2O_4$ nanoparticles at 90 °C (Scheme 9). The activity of the catalyst was not diminished even after five cycles of reaction. Recyclability of the catalyst and PEG-400 and the green conditions are the significances of this method.

An eco-friendly methodology for the production of spirooxindoles catalyzed by $MnFe_2O_4$@NH_2@2AB-Ni was established.[40]



Scheme 10 Synthesis of spirooxindole catalyzed by $MnFe_2O_4$@NH_2@2AB-Ni.

It is a nanocatalyst, the surface of which was functionalised with amino group and then a nickel complex was immobilized on it. Under the optimized conditions, derivatives of spirooxindole **32**, **33** were produced by the condensation reaction between barbituric acid **30** or 2,6-diaminopyrimidine-4(3*H*)-one **31**, cyclic 1,3-diketone **29** and different isatins **6** in the presence of water at 90 °C, and the reaction was catalyzed by 10 mg of $MnFe_2O_4$@NH_2@2AB-Ni (Scheme 10).

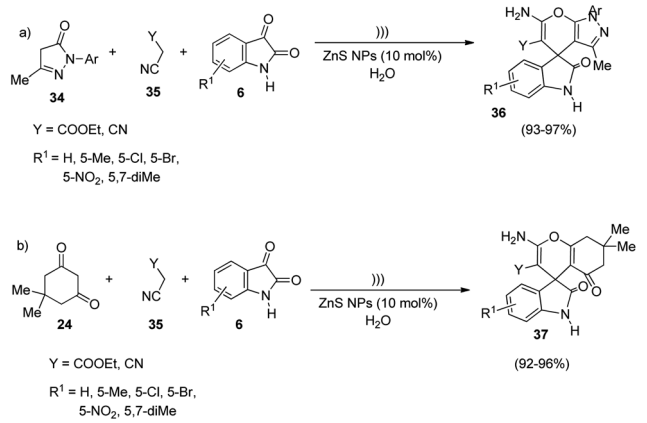
4 Zn-catalyzed spirooxindole synthesis

The biological relevance, abundance and unique capabilities of Zn aided in the application of it as a substitute for metals like Rh, Ir *etc.* Numerous reports are accessible on organic transformations attained by employing catalytic quantities of Zn.[41,42] A pair of electrons can be accepted by Zn^{2+} by acting as Lewis acid but it is deficient in redox properties due to the filled d^{10} configuration. The zinc ion can function as redox-stable Lewis acid catalyst.

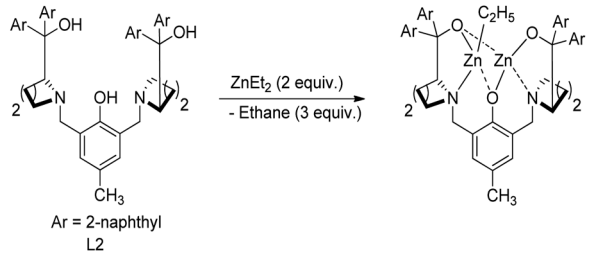
Diverse Zn catalysts like zinc sulphide nanoparticles, zinc triflates *etc.* were applied for the synthesis of spirooxindoles bearing frameworks such as dihydrofuran, tetrahydrofuran and so on. Metal triflates are having Lewis acidic properties and are generally eco-friendly. Typical chemical and physical characteristics are exhibited by ZnS nanoparticles in comparison with ZnS in bulk and this property adds to their catalytic efficiency.

4.1 Reactions involving isatin derivatives

In an interesting work put forth by Dandia and co-workers, spirooxindole derivatives were synthesized using ZnS NPs as catalyst.[43] The reaction follows a green procedure through which derivatives of spiro[chromene-4,3′-indoline] **37** and spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] **36** were generated by means of Knoevenagel condensation followed by Michael addition. The optimized reaction conditions include water as solvent, 10 mol% of ZnS NPs as catalyst under ultrasonic irradiation. Under the optimized reaction conditions, 3-methyl-1-phenyl-2-pyrazolidin-5-one **34**, activated methylene compound **35**



Scheme 11 ZnS nanoparticles-catalyzed synthesis of (a) spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole]; (b) spiro[chromene-4,3′-indoline].

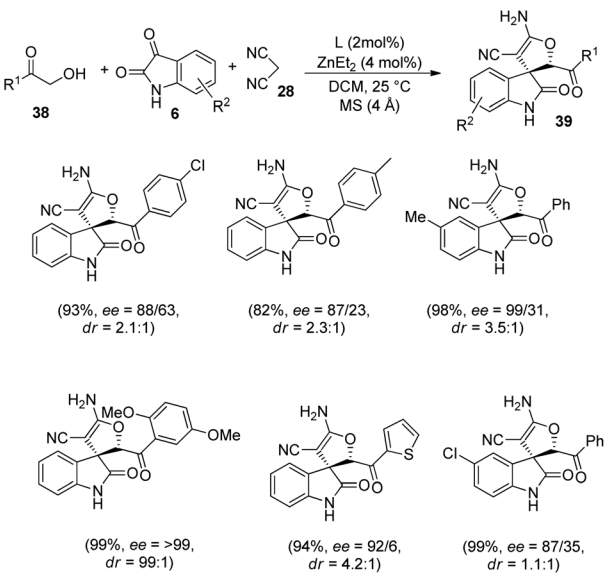


Scheme 12 Generation of dinuclear zinc catalyst.

and different isatins **6** were reacted to afford derivatives of spiro[indoline-3,4′-pyrano[2,3-*c*]pyrazole] **36.** Derivatives of spiro[chromene-4,3′-indoline] **37** were produced by utilizing dimedone **24**, activated methylene compound **35** and isatins 6 (Scheme 11). The reaction components bearing different substituents underwent the reaction evenly and rendered excellent yields.

Wang and co-workers developed a novel procedure for the synthesis of 3,3′-dihydrofuran spirooxindoles **39** with excellent yields and diastereo- and enantioselectivities, utilizing a dinuclear zinc catalyst, in 2019.[44] The reaction proceeds through Knoevenagel/Michael/Pinner/Isomerization path, *via* condensation between α-hydroxy ketones **38**, substituted isatins **6** and dicyanomethane **28** catalyzed by dinuclear zinc generated *in situ* by reaction between 2 mol% of ligand **L2** and 4 mol% of diethyl zinc (Scheme 12). The optimized reaction conditions include DCM as solvent at a temperature of 25 °C (Scheme 13).

In the case of α-hydroxy ketones **38**, substituents R′ such as benzene rings which are *o*-, *m*- and *p*-substituted, α-heteroaromatic ring and β-naphthyl ring afforded good to excellent yields and enantioselectivities. The ee values of 29% and >99% were obtained by using 2-hydroxy acetone and α-hydroxy-2,5-dimethoxy acetophenone respectively. Excellent yields and ee values were observed in the case of isatin bearing electron-



Scheme 13 Synthesis of 3,3′-dihydrofuran spirooxindoles using dinuclear zinc catalyst.

releasing as well as electron-deficient substituents. Relatively higher enantioselectivities were afforded by isatins having electron-rich groups compared to electron-poor ones. A gram scale reaction between the three components was also performed *via* the protocol, and they could regain the yield and stereoselectivity.

4.2 Reactions involving isothiocyanatooxindole derivatives

Alkenes with electron-deficient groups and carbonyl compounds were excellent cyclization partners for isothiocyanatooxindole derivatives which were adaptable under the conditions of transition metal-catalyzed synthesis of spirooxindoles. In the case of reaction with the electrophiles, the isothiocyanatooxindoles performed as excellent donors.

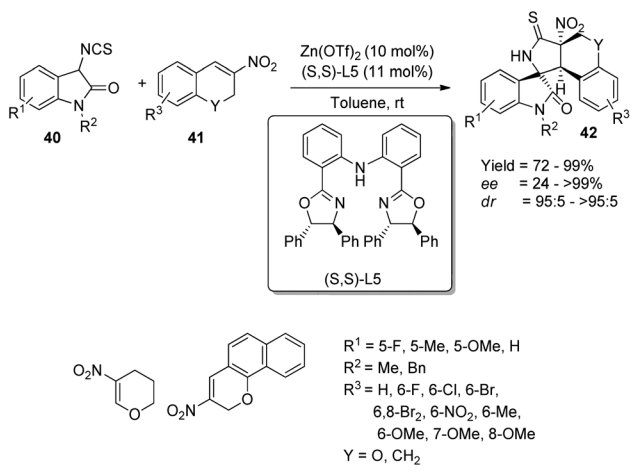
Xiao *et al.* demonstrated a method for the emergence of polycyclic spirooxindoles **42** *via* Michael addition/cyclization cascade utilizing $Zn(OTf)_2$/bis(oxazoline) complex, where the ligand is having a chiral center.[45] The reaction between 3-isothiocyanato oxindole **40** and 3-nitro-2*H*-chromene **41** was optimized by using 11 mol% of ligand (*S*,*S*)-**L5** and 10 mol% of $Zn(OTf)_2$ in toluene at room temperature (Scheme 14). The substrate scope investigations were carried out by using differently substituted 3-isothiocyanato oxindoles **40** and 3-nitro-2*H*-chromenes **41**. Great enantio- and high diastereoselectivities and good to efficient yields were obtained with different 3-nitro-2*H*-chromenes **41** irrespective of the electronic nature and position of the substituents. Excellent stereoselectivity and yield were afforded by 3-nitro-2*H*-benzo[*h*]chromene, but the enantioselectivity was less with reactive alkyl substrates. Excellent stereoselectivity and yield were also obtained when the methylene group was substituted for 3-nitro-2*H*-chromene oxygen atom. In the case of 3-isothiocyanato oxindoles **40**, very good stereoselectivities and yields were gained when the 5th position bears substituents OMe, F and Me. The reaction exhibited tolerance towards substrates which are benzyl protected. β-Nitro styrene and β-methyl-β-nitrostyrene instead of 3-nitro-2*H*-chromenes underwent the reaction giving respective yields of 29% and 82%.

A method for the formation of derivatives of polycyclic spirooxindoles **44** employing $Zn(OTf)_2$/diphenylamine linked bis(oxazoline) complex, which is a chiral catalyst was proposed by Yuan and co-workers.[46] The Michael/cyclization reaction between 3-nitroindoles **43** and 3-isothiocyanato oxindoles **40** was catalyzed by 10 mol% $Zn(OTf)_2$ with 11 mol% ligand **L4** in presence of toluene at 50 °C (Scheme 15). 95–99% of the products were provided by 3-nitroindoles with different substituents on the benzene ring irrespective of their electronic nature. Various N1-substituted 3-nitroindoles also underwent the reaction except the one bearing methyl. The outcomes were high to excellent with different substituents at the benzene ring and N1-position of 3-isothiocyanato oxindoles. They also compared the metal catalyst with the organocatalyst in their previous work and could demonstrate the superiority of metal catalyst.

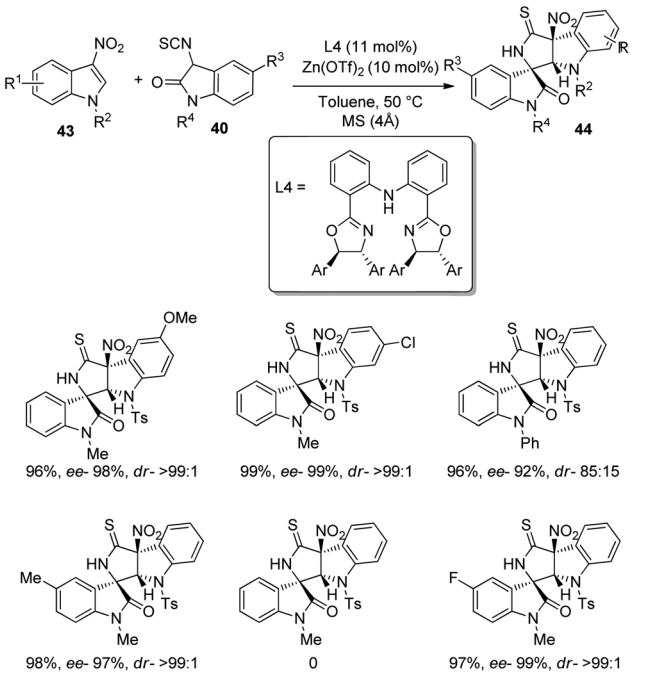
4.3 Reaction involving β,γ-unsaturated-α-ketoamide derivatives

In 2020, Wang and team produced chiral tetrahydrofuran spirooxindoles **47** by using a dinuclear zinc catalyst.[47] Here, it is a two-step reaction in which Michael/Hemiketalization is followed by Friedel–Crafts reaction. In the first step, α-hydroxyaryl ketone (derivative of **38**) is reacted with β,γ-unsaturated-α-ketoamide **45** in CH_2Cl_2 solvent at 20 °C catalyzed by dinuclear zinc which was formed *in situ* by the reaction between 20 mol% of diethyl zinc and 10 mol% of ligand **L3**. In the second step, trifluoroacetic acid **46** was added and the reaction was carried out at room temperature for 60 min.

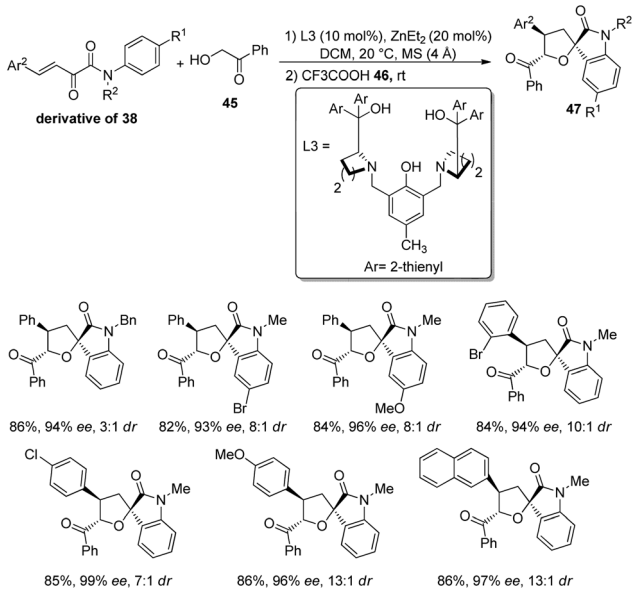
For the substrate scope assessment, α-hydroxyacetophenone was reacted with a series of β,γ-unsaturated-α-ketoamides **45** (Scheme 16). It afforded 80–85% of products with 8 : 1 to 13 : 1 dr values when the *N*-aromatic ring at the *p*-position bears either electron-rich or electron-poor groups. Substrates with benzyl, ethyl and methyl as the *N*-substituents were tolerated. In



Scheme 14 Synthesis of spirooxindole derivatives catalyzed by $Zn(OTf)_2$/bis(oxazoline) complex.



Scheme 15 Synthesis of polycyclic spirooxindoles catalyzed by $Zn(OTf)_2$/diphenylamine linked bis(oxazoline) complex.

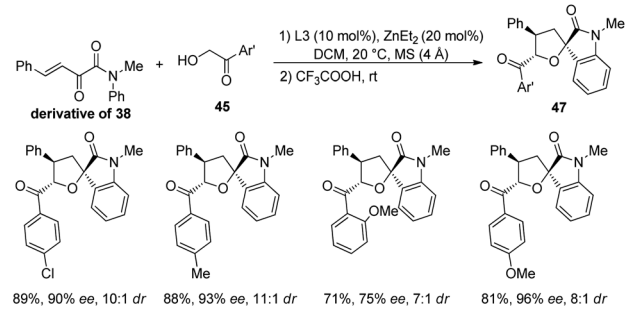


Scheme 16 Synthesis of tetrahydrofuran-spirooxindoles with α-hydroxy acetophenone and β,γ-unsaturated-α-ketoamides.

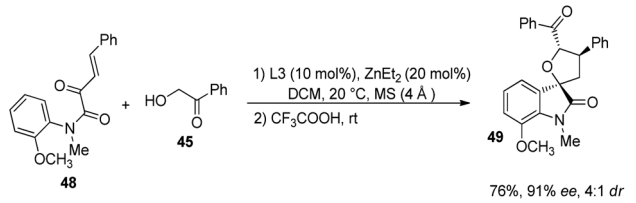
the case of Ar^2 groups at the *p*-position, good dr values and yields were observed and the ee value was relatively higher for Cl. Excellent ee was obtained when *o*- or *m*-position of Ar^2 is having Br and the *p*-position is having electron-releasing substituents. The products were also afforded by fused and heterocyclic ring substrates.

Further the influence of substituents on α-hydroxyaryl ketones (derivative of **38**) were also assessed (Scheme 17). Electron-releasing as well as electron-deficient groups on the aryl group provided good stereoselectivities for the corresponding spirooxindoles. 2-Methoxy substituted and 4-methoxy substituted α-hydroxyaryl ketones afforded the products with ee values 75% and 96% respectively. Then, 76% of the tetrahydrofuran spirooxindole **49** with 91% ee and 4 : 1 dr value was gained by the implementation of substrate **48** which has an *N*-aromatic ring *ortho*-substituted by OMe group (Scheme 18). Wang and co-workers could also synthesise tetrahydrofuran spirooxindoles by using this protocol on gram scale.

Efficient enantioselectivities and good diastereoselectivities were afforded by β,γ-unsaturated-α-ketoamide derivatives in the synthesis of spirooxindole.



Scheme 17 Synthesis of tetrahydrofuran-spirooxindoles with β,γ-unsaturated-α-ketoamide and a series of α-hydroxy aryl ketones.



Scheme 18 Synthesis of tetrahydrofuran-spirooxindole corresponding to substrate having *N*-aromatic ring *ortho*-substituted by OMe group.

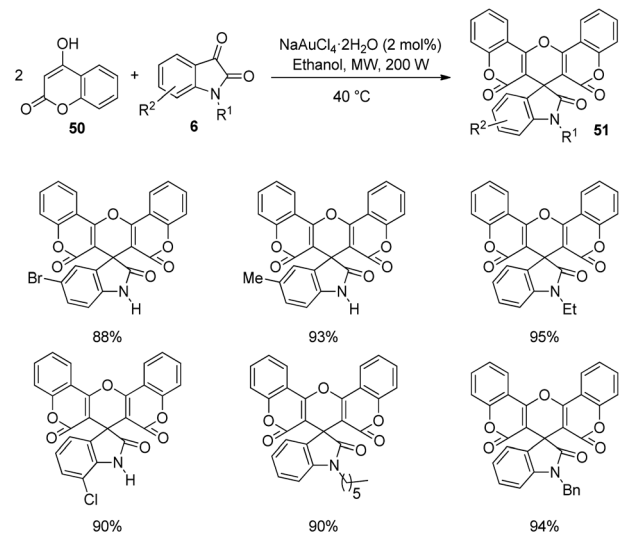
5 Au-catalyzed spirooxindole synthesis

Gold-catalyzed organic transformations developed notably in the past years. Gold shows greater resistance towards oxidation. High selectivities and activities are exhibited by most of the Au catalysts. Gold(I) catalysts being more stable are widely employed in reactions than gold(III).[48] But, gold(III) catalysts also play function like activating unsaturated bonds through electrophilic π-activation.[49]

Gold-catalyzed spirooxindole synthesis was not well explored and only two works-one in 2016 and another in 2018 were reported. The strategies employed sodium tetrachloroaurate and JohnphosAu(CH_3CN)SbF_6 as the catalyst respectively.

5.1 Reaction involving isatin derivatives

Praveen and co-workers devised a procedure for the construction of spirooxindoles catalyzed by gold(III) and studied the cytotoxic and antimicrobial characters.[50] A series of spirooxindoles **51** were produced by reacting 4-hydroxycoumarin **50** and isatins **6** which were *N*-substituted. The reaction was catalyzed by 2 mol% $NaAuCl_4 \cdot 2H_2O$ in ethanol solvent at 40 °C under microwave (Scheme 19). The yield of the desired product was good to



Scheme 19 Substrate scope for the gold-catalyzed spirooxindole synthesis.

excellent with different substituents on the isatin. Based on this strategy, they could build bis-spirooxindole system also.

Here, isatin **6** was activated by gold catalyst which acted as Lewis acid. An intermediate **52** was produced *via* the nucleophilic addition between isatin **6** and 4-hydroxycoumarin **50.** The catalyst coordinates with carbonyl oxygen of second intermediate **53** which was formed through elimination of water molecule from first intermediate **52**. Third intermediate **54** was generated through the addition of 4-hydroxycoumarin **50** to second intermediate **53.** The desired spirooxindole product **51** was achieved by means of cyclization followed by dehydration. The scheme furnishes the possible mechanism for the reaction (Scheme 20).

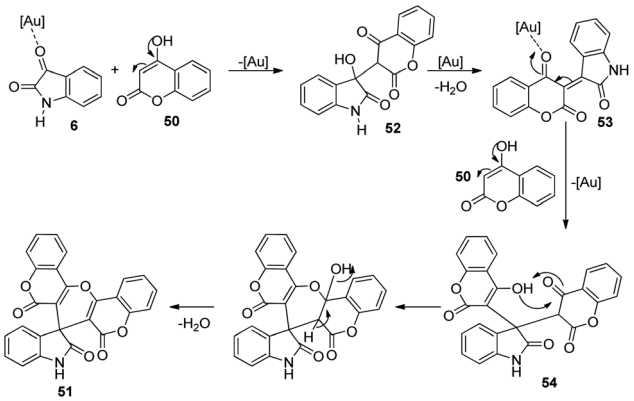
5.2 Reaction involving diaryl alkyne derivatives

A strategy for the development of derivatives of spirooxindoles using gold catalyst *via* diaryl alkyne bicyclization was reported by Xu *et al.*[51] In the first step, fused indoles **56** were formed from diaryl alkyne **55** by making use of gold catalyst JohnphosAu(CH_3CN)SbF_6 in 1,2-dichloroethane at 60 °C for 12 h (Scheme 21). Electron-deficient and electron-releasing groups on the diaryl alkynes **55** rendered fused indoles **56** without significant electronic and steric effects. Substrate containing naphthyl group afforded two isomers of the corresponding product. The yield was 75% with substrate bearing an alkynyl substituent. In the second step the substrates **56** thus obtained were protected with $(Boc)_2O$ **57** and converted into spirooxindoles **59** *via* oxidation with PCC **58** in dichloromethane (Scheme 22).

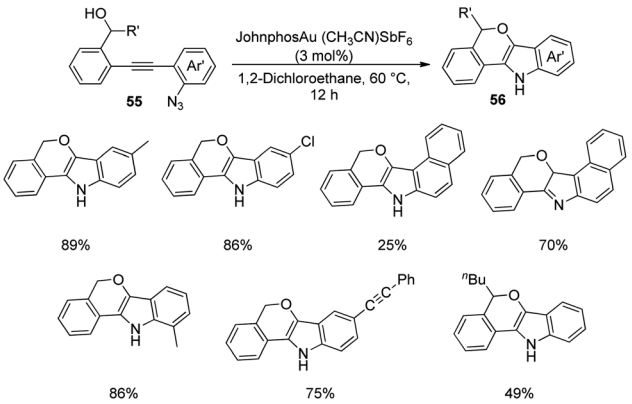
This protocol is found to be highly atom-economic with an added advantage of gentle reaction conditions.

6 Ni-catalyzed spirooxindole synthesis

Nickel is admirable in terms of catalyst cost compared to metals like Pt, Rh and so on. Great variability of oxidation states are exhibited by nickel catalysts. Reactants can be activated and the conversion to products can be achieved effortlessly. Most of the nickel catalysts exhibit great affinity to unsaturated molecules.



Scheme 20 Proposed mechanism for the construction of spirooxindoles [reproduced with permission from ref. 50].



Scheme 21 Formation of fused indoles from diaryl alkenes catalyzed by gold.

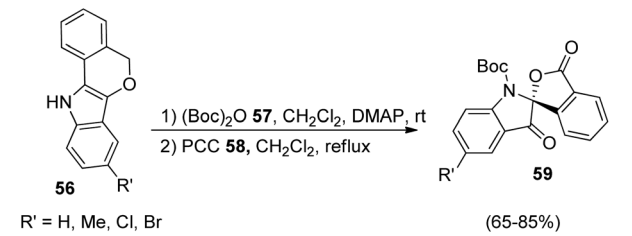
Hence they can easily coordinate to alkynes and alkenes and can activate them.[52]

The generation of spirooxindoles by means of nickel-catalyzed approaches were reported from 2011 to 2020, most of them based upon isatin derivatives. Pyrazolophthalazinyl-, pyrazolopyrridine-, thiochromanyl-spirooxindoles *etc.* were built by availing catalysts including nickel chloride, nickel oxide and nickel(II)acetate. In most of these protocols, the mostly employed catalyst was NiO nanoparticle which is superior in terms of catalytic activities and environmental benignity.

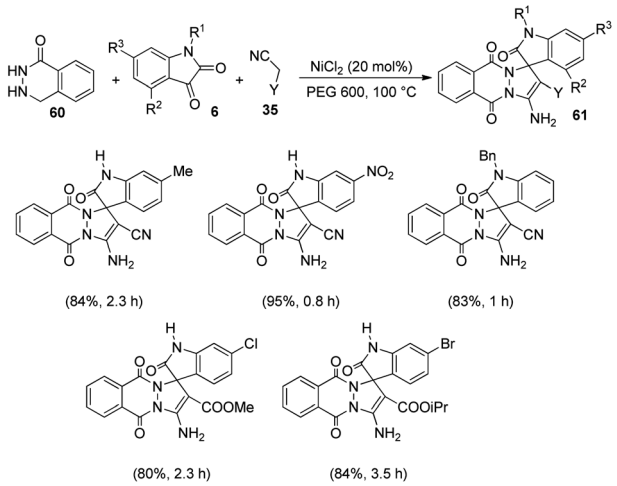
6.1 Reactions involving isatin derivatives

Zhang and co-workers established a plan for the evolution of pyrazolophthalazinyl spirooxindoles **61** by applying nickel chloride as catalyst.[53] The reaction between phthalhydrazide **60**, isatin **6** and activated methylene compound **35** was optimized in PEG 600 as the solvent, $NiCl_2$ as catalyst at 100 °C (Scheme 23). The product yield was slightly higher for dicyanomethane compared with cyanoacetic esters. Both electron-deficient and electron-rich group substituted isatins afforded the products in excellent yields (80–95%). A large scale reaction offered 88% yield of the product.

The reaction follows a Knoevenagel condensation/Michael addition/cycloaddition/isomerization sequence in which the conversion of cyano group into amine was activated by $NiCl_2$. In the first step an adduct **62** was formed by the Knoevenagel condensation of activated methylene compound **35** with isatin



Scheme 22 PCC oxidation of Boc-protected fused indoles to produce spirooxindoles.

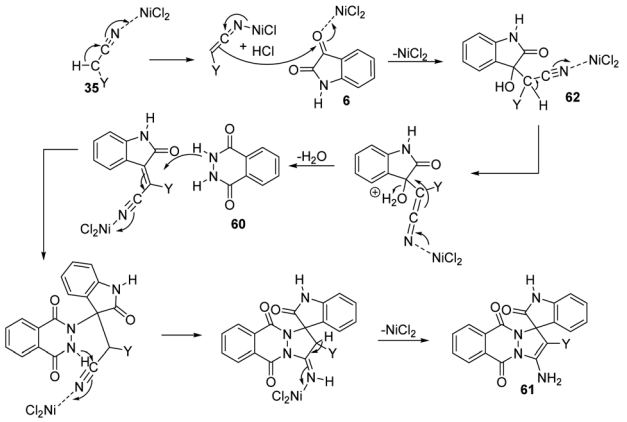


Scheme 23 $NiCl_2$ catalyzed synthesis of pyrazolophthalazinyl spirooxindoles.

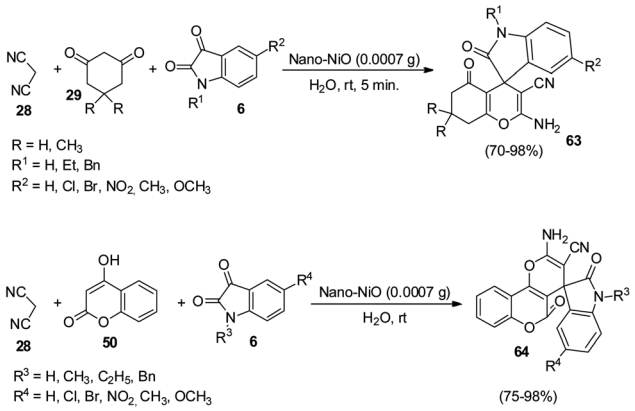
6. Then there occurs a Michael addition between the carbon–carbon double bond of the adduct **62** and phthalhydrazide **60**. The required product **61** was achieved in the next step which involves cycloaddition and isomerization. The suggested mechanism is depicted in Scheme 24.

An environmentally-benign strategy for the synthesis of spirooxindoles by employing NiO NPs was demonstrated by Nasseri and co-workers.[54] The optimized reaction condition includes 0.0007 g of nano-NiO in aqueous medium at room temperature in which dicyanomethane **28**, cyclic 1,3-diketone **29** and isatins **6** reacted to formulate derivatives of spirooxindole **63**. High to excellent yields were given by different cyclic 1,3-diketones and isatins. Due to the presence of electron-releasing Me groups, dimedone reacted rapidly relative to 1,3-cyclohexadione. Further, the authors could also extend the reaction by employing 4-hydroxycoumarine **50** as an alternative to 1,3-cyclohexadione and obtained the corresponding spirooxindole **64** (Scheme 25).

A strategy for the synthesis of spirooxindole-fused pyrazolo pyridine derivatives **66** utilizing silica supported NiO



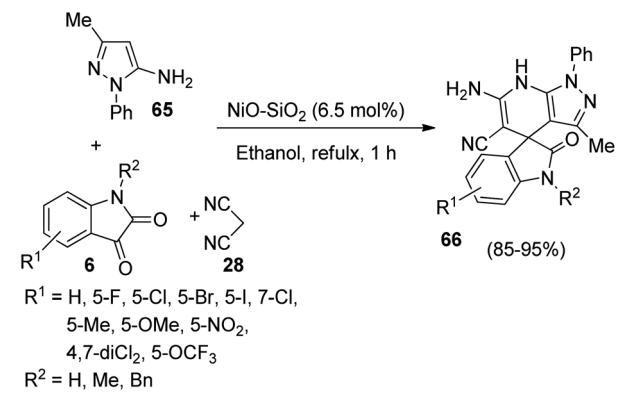
Scheme 24 The suggested mechanism for the synthesis of pyrazolophthalazinyl spirooxindole utilizing $NiCl_2$ as the catalyst [reproduced with permission from ref. 53].



Scheme 25 Synthesis of spirooxindoles using dicyanomethane, dicarbonyl compounds/4-hydroxycoumarine and isatins.

nanoparticles as catalyst was put forth by Yagnum *et al.* in which they also studied the anti-microbial activities of the novel compounds.[55] The one-pot reaction between three components-dicyanomethane **28**, isatin **6** and 3-methyl-1-phenyl-1*H*-pyrazole-5-amine **65** was advanced in ethanol, 6.5 mol% of NiO–SiO_2 at reflux temperature (Scheme 26). Isatins with electron-withdrawing and electron-releasing groups were tolerated in the reaction. The yield was a little higher for 5-substituted and 7-substituted isatins relative to 4,7-disubstituted ones. There was no prominent role for steric and electronic factors. According to the suggested mechanism, the reaction follows a Knoevenagel condensation/Michael addition/cyclization/isomerization sequence. Anti-fungal and anti-bacterial properties were displayed by most of the spirooxindole derivatives so-obtained.

A green methodology for the building up of derivatives of spirooxindoles **68, 63, 64** by applying another NiO based catalyst was designed by Moqadam *et al.*[56] Here the catalyst was NiO@g-C_3N_4, in which nanosheets of graphitic carbon nitride was used to carry NiO nanoparticles, through which the catalytic activity was enhanced by decreasing the nanoparticle aggregation. The reaction between dicyanomethane **28**, isatin **6** and 4-hydroxycoumarin **50** (or 1,3-diketoester **67** or cyclic 1,3-diketone **29**) was catalyzed by 50 mg of NiO@g-C_3N_4 in ethanol at 80 °C



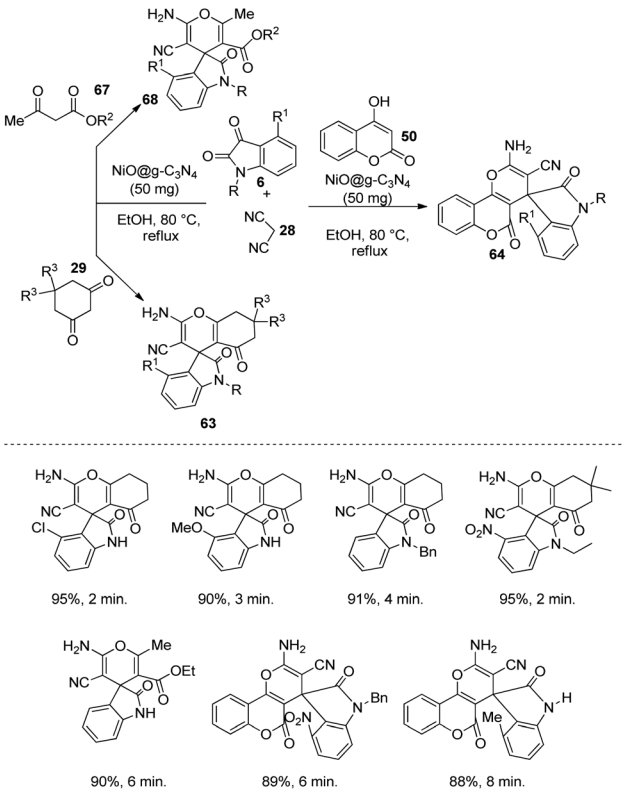
Scheme 26 Synthesis of spirooxindole fused pyrazolo pyrrolidine using NiO–SiO_2 catalyst.

under reflux (Scheme 27). The starting materials with diverse substituents were used to explore the scope of this reaction. The reactivity and outcomes were best for dimedone relative to 4-hydroxycoumarin, 1,3-diketoesters and 1,3-cyclohexadione. In the case of isatins, better upshots were obtained with electron-withdrawing substituents on the aromatic ring. The development of products was diminished with electron-releasing groups on the N atom of isatin.

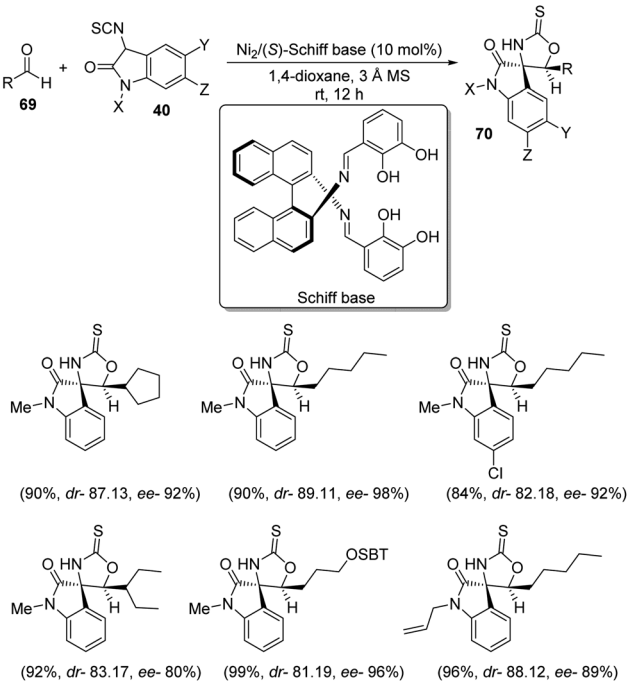
6.2 Reaction involving isothiocyanatooxindole derivatives

A scheme for the development of spirooxindoles **70** catalyzed by dinuclear nickel Schiff base was proposed by Matsunaga *et al.*[57] The reaction between aldehydes **69** and 3-isothiocyanato oxindoles **40** was effected by Ni_2/Schiff base in 1,4-dioxane at room temperature (Scheme 28). The enantioselectivity was a bit lower for α-branched aldehydes compared to the linear aliphatic ones. The diastereoselectivity, yield and enantioselectivity were 81 : 19, 99% and 96% respectively for aldehyde having silyl ether component. The outcomes were poor in the case of aromatic aldehydes. Isothiocyanato oxindoles bearing electron-releasing and electron-withdrawing substituents on aromatic ring underwent the reaction and those containing allyl as the *N*-protecting group also gave good results.

Spirooxindoles with three stereocenters were achieved from isothiocyanatooxindole derivatives *via* catalysis by zinc and nickel. The other substrate for the reaction was: 3-nitro-2*H*-chromenes and aldehydes in the case of zinc- and nickel-catalyzed approaches respectively. Enantioselectivity was slightly higher for the zinc-catalyzed reaction in comparison to the nickel-catalyzed one.



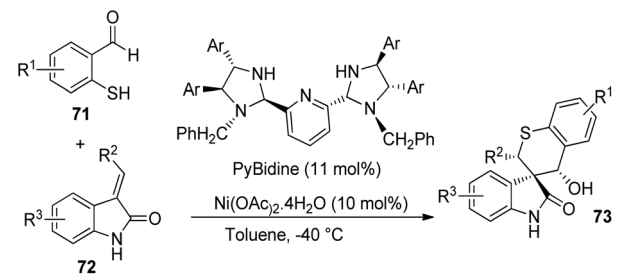
Scheme 27 NiO@g-C_3N_4-catalyzed synthesis of spirooxindoles.



Scheme 28 Synthesis of spirooxindoles using Ni_2/(*S*)-Schiff base as the catalyst.

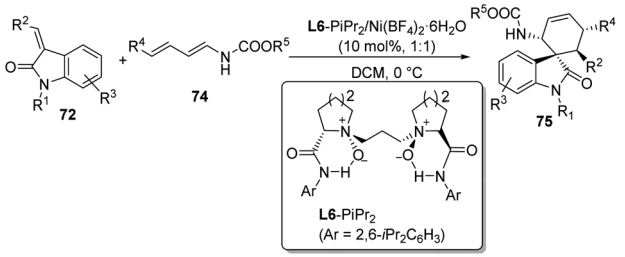
6.3 Reactions involving methyleneindolinone derivatives

Arai *et al.* presented a plan for the formation of chiral thiochromanyl-spirooxindoles **73** by using bis-(imidazolidine)



R^1	R^2	R^3	Yield (%)	*dr*	*ee* (%)
H	Ph	H	99	93/2/5	88
H	4-BrC_6H_4	H	94	93/2/5	69
H	4-MeC_6H_4	H	89	80/16/4	81
H	2-BrC_6H_4	H	>99	98/2/-	93
H	^{n}propyl	H	>99	92/8/-	89
H	Ph	5-Cl	>99	97/2/1	94
H	Ph	5-Me	>99	87/7/6	87
6-Cl	Ph	H	>99	95/2/3	82
6-^{t}Bu	Ph	H	73	98/1/1	90

Scheme 29 PyBidine-Ni(OAc)$_2$ catalyzed thiochromanyl spirooxindole synthesis.



R^1	R^2	R^3	R^4	R^5	Yield/*ee*
Boc	COOMe	H	H	Cbz	99%/98%
Boc	COPh	H	H	Cbz	99%/96%
Boc	COO*t*Bu	5-F	H	Cbz	91%/95%
Boc	COO*t*Bu	6-Cl	H	Cbz	92%/96%
Boc	COO*t*Bu	7-Br	H	Cbz	90%/99%
Boc	COO*t*Bu	5-Me	H	Cbz	97%/99%
Boc	COO*t*Bu	H	H	Boc	99%/99%
Boc	COO*t*Bu	H	Me	Cbz	94%/99%
Cbz	COO*t*Bu	H	H	Cbz	97%/92%

Scheme 30 Substrate scope for the Diels–Alder reaction between 1,3-dienylcarbamates and methyleneindolinones.

pyridine-Ni(OAc)$_2$ catalyst.[58] Here, spirooxindoles were evolved from thiosalicylaldehydes **71** and methyleneindolinones **72** *via* Michael/Aldol pathway. Various substrates reacted in the optimized conditions of 11 mol% PyBidine and 10 mol% Ni(OAc)$_2$.4H$_2$O in toluene at −40 °C (Scheme 29). Moderate to efficient yields were provided by thiosalicylaldehydes with different substituents. High diastereoselectivities and yields were endowed by methyleneindolinones bearing different substituents on the aromatic ring. Good yield and enantioselectivity were afforded by methyleneindolinone substituted with alkyl group and those with substituents on indolinone ring.

Feng and co-workers introduced a procedure for the fabrication of spirooxindole cyclohexaneamides **75** catalyzed by *N*,*N*′-dioxide/nickel(II) complex.[59] 1,3-Dienyl carbamates **74** underwent a Diels–Alder reaction with methyleneindolinones **72**. The reaction proceeded in DCM at 0 °C applying 10 mol% of **L6**-PiPr$_2$/Ni(BF$_4$)$_2$·6H$_2$O as the catalyst (Scheme 30). 87–99% yield, 93–99% ee and 93 : 7 to >95 : 5 dr were acquired from diverse substituents on the aromatic ring of methyleneindolinones. The result was also excellent with different substituents R^2 on methyleneindolinones. When R^4 = methyl, only one diastereoisomer with four chiral centers was obtained.

Further, the reaction between 1,2-dihydropyridine **76** and methyleneindolinone **72** was conducted to access the corresponding spirooxindole **77** (Scheme 31). Efficient ee and dr values and high to excellent yield were brought by different protecting groups on N of 1,2-dihydropyridine. Excellent yield, ee and dr values were obtained when R^8 = Ph, Me and Bn. Due to the steric effect between methyleneindolinone and methyl group (R^9), the product was contributed only in tinge. The Diels–Alder reaction was also done on gram scale. The group could also confirm that the reaction followed a concerted pathway.

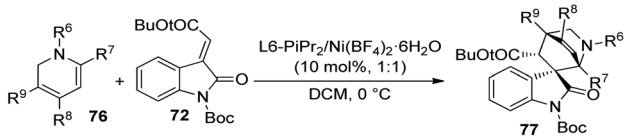
7 Fe-catalyzed spirooxindole synthesis

Iron is superior to majority of the transition metals in terms of non-toxicity, earth abundance, cost-effectiveness and environmental benignity. Its redox potential range is broad and can exhibit variable electronic states. These properties led it to become a promising candidate as a catalyst in organic reactions. Fe catalysts keep the oxidation state varying from −2 to +6. Consequently, they are functional in both oxidation and reduction reactions.[60] By changing the ligands, the Lewis acidity can be tuned, it is also dependent on the oxidation state.

Different iron catalysts: $FeCl_3$, $Fe(OTf)_2$, $CoFe_2O_4$- and Fe_3O_4-nanoparticles with various modifications were used for the synthesis of spirooxindoles. The modifications in terms of morphology, size and shape is a way of tuning the activities of nano sized catalysts. Among the diverse synthetic approaches adopted, those dependent on isatin derivatives prevailed over others.

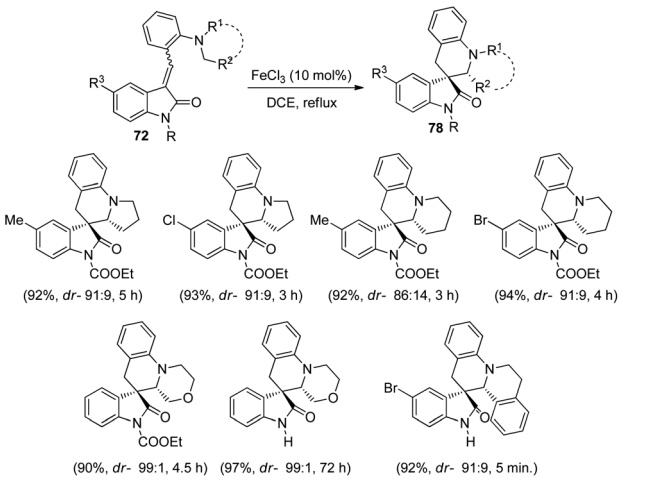
7.1 Reaction involving methyleneindolinone derivatives

Yuan and co-workers formulated a procedure for the generation of novel spirooxindole tetrahydroquinolines **78** by applying

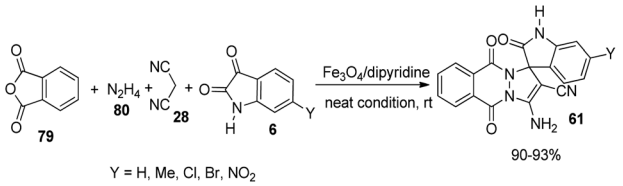


R^6	R^7	R^8	R^9	Yield/*ee*
COOMe	H	H	H	87%/99%
COOiBu	H	H	H	96%/99%
Cbz	H	H	H	91%/99%
COOPh	Me	H	H	95%/99%
COOPh	H	Me	H	99%/99%
COOPh	H	Ph	H	95%/92%
COOPh	H	H	Me	trace

Scheme 31 Substrate scope for the Diels–Alder reaction between 1,2-dihydropyridines and methyleneindolinone.



Scheme 32 Synthesis of spirooxindole derivatives catalyzed by $FeCl_3$.



Scheme 33 Fe_3O_4/dipyridine MPs catalyzed synthesis of pyrazolophthalazinyl spirooxindoles.

$FeCl_3$ as catalyst.[61] The reaction occurs through a 1,5-hydride transfer followed by ring closure in 1,2-dichloroethane with $FeCl_3$ (10 mol%) (Scheme 32). The reaction was carried out using different methyleneindolinone substrates **72** including tetrahydroisoquinoline, morpholine, piperidine and pyrrolidine derivatives. High to efficient yields and diastereoselectivities were ensued from unprotected and protected methyleneindolinones bearing different substituents on the aromatic ring of oxindole. Piperidine derivatives manifested 87–94% yield and up to 91 : 9 dr values. The *N*-protected morpholines reacted rapidly than the unprotected ones. The dr values and yields were adequate with substrates derived from tetrahydroisoquinoline also.

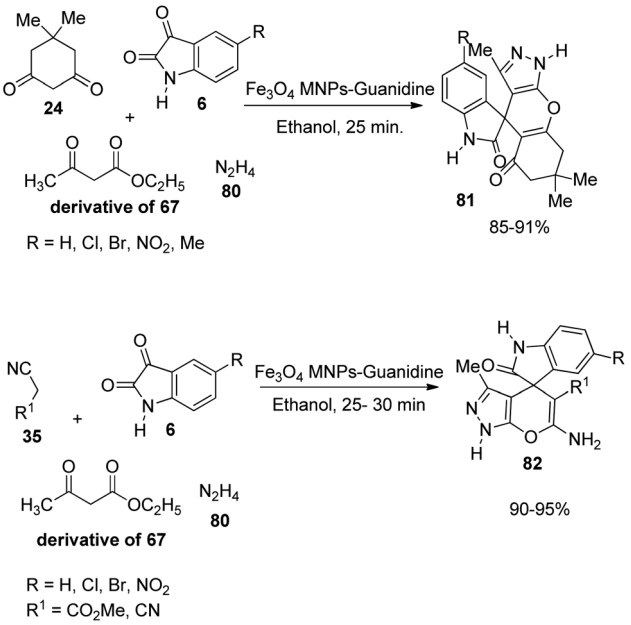
7.2 Reactions involving isatin derivatives

A green strategy for the production of pyrazolophthalazinyl spirooxindoles **61** catalyzed by surface functionalized Fe_3O_4 was worked out.[62] The catalyst was prepared by the treatment of Fe_3O_4 NPs with tetraethyl orthosilicate which was further treated with 3-chloropropyltriethoxy silane and finally dipyridine-2-ylmethanol was employed for the base group loading on the surface. The reaction between hydrazine **80**, malonic dinitrile **28**, isatin **6** and phthalic anhydride **79** was effected by 0.0008 g of Fe_3O_4/dipyridine magnetic particles (MPs) in solvent free-condition at rt (Scheme 33). Isatins with various substituents resulted in high to excellent yields without notable electronic effects. The group could reuse the catalyst with almost similar efficiency.

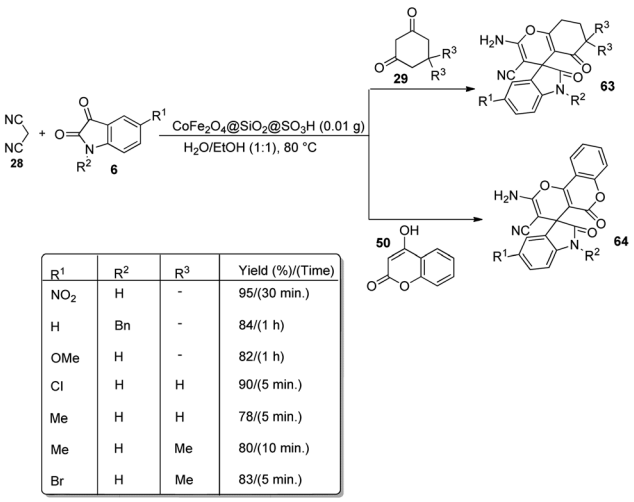
Safaei-Ghomi *et al.* described a proposal for the emergence of spirooxindoles **81**, **82** catalyzed by guanidine-functionalized Fe_3O_4 magnetic NPs.[63] It is an eco-friendly procedure which involves a multi-component reaction between isatin, ethyl acetoacetate, hydrazine hydrate and active methylene compound or dimedone in ethanol. First the reaction of acetoacetic ester-derivative of **67**, hydrazine **80** and dimedone **24** was carried out with variously substituted isatins **6**. Then the reaction was done using active methylene compound **35** instead of dimedone (Scheme 34). High to efficient yields were provided by isatins with both electron-releasing and -withdrawing substituents.

A design for the formation of derivatives of spirooxindoles **63**, **64** catalyzed by $CoFe_2O_4$@SiO_2 nanoparticles was confirmed by Hemmat *et al.*[64] The catalyst was produced by coating silica on the surface of cobalt ferrite nanoparticles by the application of tetraethylorthosilicate, which helped to prevent the aggregation of $CoFe_2O_4$ NPs. Optimization of the reaction between cyanoacetonitrile **28**, isatins **6** and cyclic 1,3-diketone **29** or 4-hydroxycoumarin **50** was carried out in water/ethanol mixture with 0.01 g of catalyst at 80 °C (Scheme 35). Good to excellent yields were given by different isatins and cyclic 1,3-diketones. The yield was slightly low for electron-releasing groups than electron-withdrawing ones on the aromatic ring of isatin. It was also observed that, 1,3-dicarbonyl compounds reacted rapidly than 4-hydroxycoumarin.

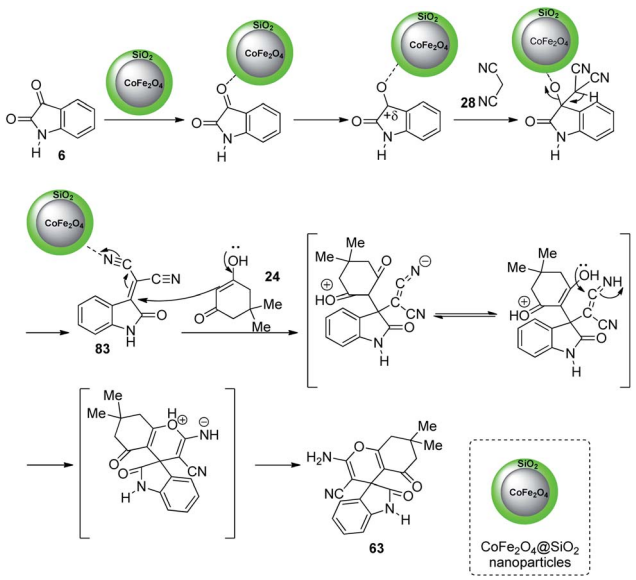
The mechanistic studies suggest that cyanoacetonitrile **28** underwent a nucleophilic addition with isatin **6** whose carbonyl group was triggered by silica nanoparticles. Further, a Knoevenagel condensation occurred and the intermediate **83** thus formed was reacted with dimedone **24** to give the desired product **63**. The mechanism is depicted in Scheme 36.



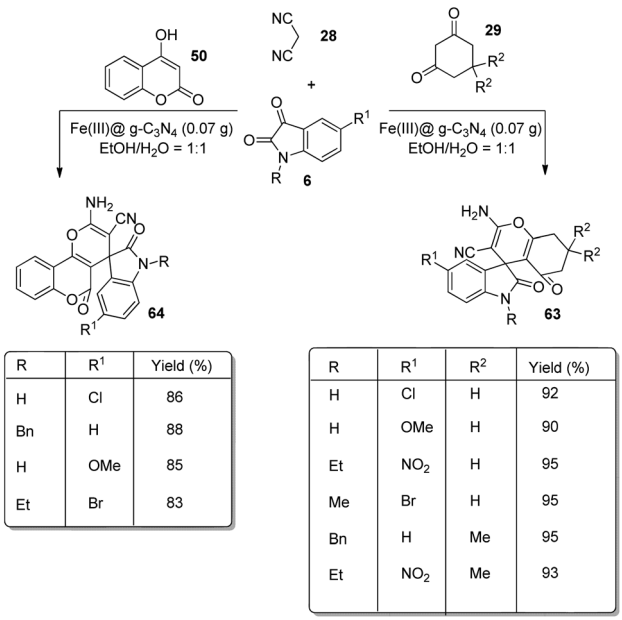
Scheme 34 Multi-component reaction between acetoacetic ester, hydrazine hydrate, dimedone/active methylene compound and isatins catalyzed by Fe_3O_4 MNPs-guanidine.



Scheme 35 $CoFe_2O_4$@SiO_2-catalyzed spirooxindole synthesis.



Scheme 36 Suggested mechanism for the synthesis of spirooxindoles with $CoFe_2O_4$@SiO_2 as catalyst [reproduced with permission from ref. 64].



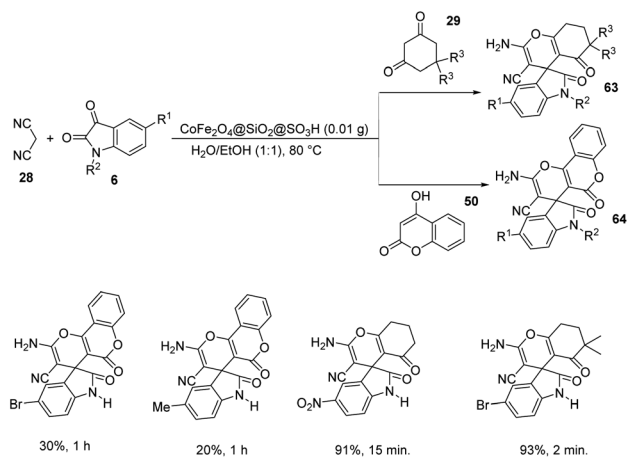
R	R^1	Yield (%)
H	Cl	86
Bn	H	88
H	OMe	85
Et	Br	83

R	R^1	R^2	Yield (%)
H	Cl	H	92
H	OMe	H	90
Et	NO_2	H	95
Me	Br	H	95
Bn	H	Me	95
Et	NO_2	Me	93

Scheme 38 Substrate scope for spirooxindole synthesis with Fe(III)@g-C_3N_4.

In the same year Zamani-Ranjbar-Garmroodi and co-workers used the same approach for the development of spirooxindoles by making use of slightly modified $CoFe_2O_4$@SiO_2@SO_3H as the catalyst,[65] which was prepared by treatment of $CoFe_2O_4$ with tetraethylorthosilicate which was further treated with chlorosulphonic acid. The one-pot reaction with the same substrates proceeded under the same conditions and provided almost similar results with respect to reactivity and electronic effects (Scheme 37).

An environmentally benign approach for the development of derivatives of spirooxindoles **63**, **64** by working with Fe(III)@graphitic carbon nitride was established by Allahresani *et al.*[66] Substituted isatins **6**, dicyanomethane **28** and 4-hydroxycoumarin **50** or cyclic 1,3-diketone **29** reacted in the optimized conditions of 0.07 g of Fe(III)@g-C_3N_4 in a mixture of water and ethanol in 1 : 1 ratio (Scheme 38). Various isatins afforded 70–98% of the products without significant effect on the electronic nature of the substituents. In the case of 4-hydroxycoumarin, the reaction time was longer and the yield was lower relative to 1,3-dicarbonyls. This approach shows benefits including short reaction time, eco-friendly reaction media and the catalyst can be reused without significant loss of efficiency.

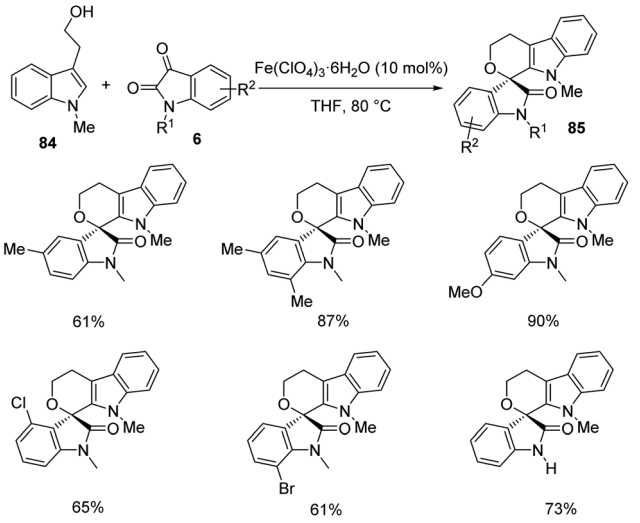


Scheme 37 $CoFe_2O_4$@SiO_2@SO_3H-catalyzed spirooxindole synthesis.

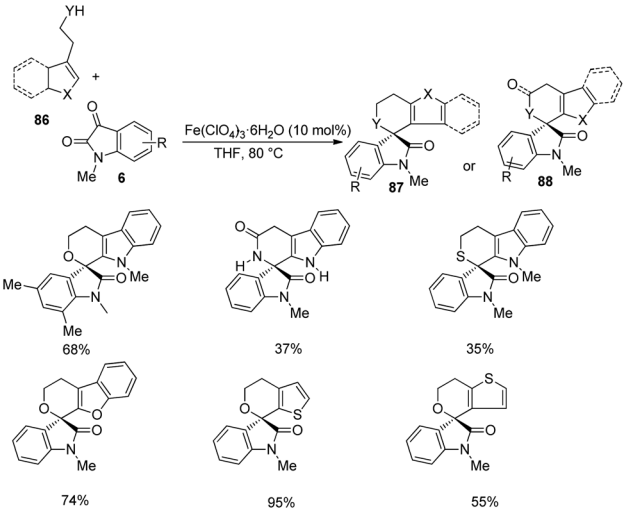
An idea for the growth of polyheterocyclic spirooxindoles **85** by utilizing environment friendly $Fe(ClO_4)_3 \cdot 6H_2O$ as the catalyst was established by Pan *et al.*[67] The product formation occurs through a hetero-Pictet–Spengler reaction. The reaction between variously substituted tryptophols **84** and isatins **6** was optimized under the conditions of $Fe(ClO_4)_3 \cdot 6H_2O$ (10 mol%) with tetrahydrofuran as the solvent at 80 °C. First, *N*-methyl tryptophol-derivative of **84** was reacted with different isatins **6** (Scheme 39). Electronic nature of the substituents was not very noticeable with respect to product formation. The reaction was also promoted by disubstituents on the phenyl ring.

Then various tryptophols **84** were reacted with *N*-methyl isatin-derivative of **6** and rendered moderate to excellent yields (Scheme 40). The concept was further extended to produce a series of polyheterocyclic spirooxindoles **87**, **88** by applying different substrates **86**: 2-(benzofuran-3-yl)ethanol, 2-(thiophene-2-yl)ethanol, 2-(indole-3-yl)acetamide *etc.* with substituted isatins **6** (Scheme 41).

Kavyani and Baharfar developed a concept for the generation of spirooxindole-dihydropyridines **90** catalyzed by Fe_3O_4/GO/Au–Ag.[68] It was a novel catalyst made by the assembly of Au–Ag alloy NPs on the surface of Fe_3O_4/graphene oxide spheres. The optimized reaction conditions include water as solvent and Fe_3O_4/GO/Au–Ag as catalyst at room temperature, under which derivatives of barbituric acids **30**, derivatives of isatin **6** and 6-amino uracil **89** underwent a one-pot reaction to afford spirooxindole products **90** in 81–93% yields (Scheme 42). The catalyst remained effective without losing its activity and chemical composition up to five cycles of reaction.



Scheme 39 Synthesis of polyheterocyclic spirooxindoles using *N*-methyl tryptophols and substituted isatins.

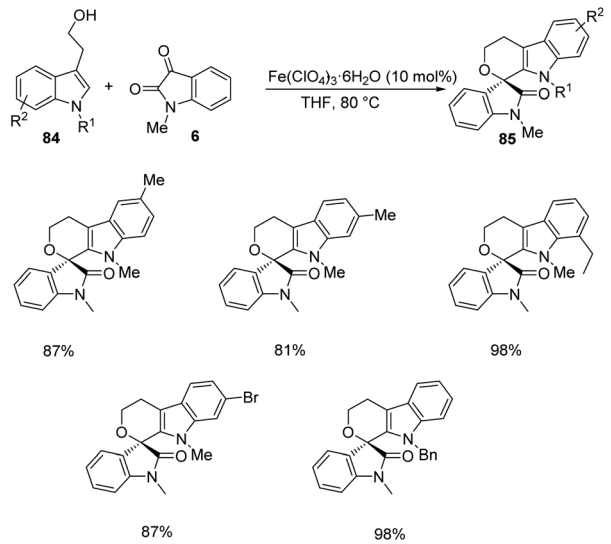


Scheme 41 Substrate scope investigation for the synthesis of polyheterocyclic spirooxindoles catalyzed by $Fe(ClO_4)_3 \cdot 6H_2O$.

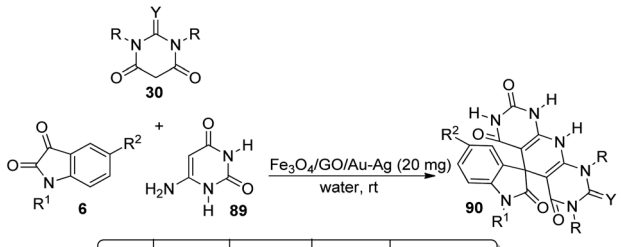
7.3 Reactions involving oxindole derivatives

An approach for the formation of derivatives of imidazolidinyl spirooxindoles **93** was reported by Wang and co-workers.[69] Here, $Fe(OTf)_2$, which is a Lewis acid, was used as the catalyst in the three-component reaction between diazo-oxindoles **91** and 1,4-oxazepins **92**. The reaction was optimized with 10 mol% $Fe(OTf)_2$ in tetrahydrofuran as the solvent at rt. This approach was evaluated by employing differently substituted diazo-oxindoles and 1,4-oxazepins. First, dibenzo[*b*,*f*][1,4]oxazepin-derivative of **92** was reacted with substituted diazo-oxindoles **91** (Scheme 43). Electron-releasing and electron-withdrawing groups at different positions on the aromatic ring of diazo-oxindoles underwent the reaction and the products were acquired in 80–91% yield. Different *N*-protecting groups were well tolerated in this reaction. Then, 3-diazoindoline-2-one, derivative of **91** was reacted with substituted dibenzo[*b*,*f*][1,4] oxazepins **92** (Scheme 44). Electron-rich and electron-deficient substituents and disubstituted dibenzo[*b*,*f*][1,4]oxazepins also underwent the reaction and afforded 80–89% of the corresponding product.

A novel procedure for the synthesis of spirooxindolo-2-iminothiazolines **96** catalyzed by $FeCl_3$ was established.[70] It involves a [3 + 2] cycloaddition reaction between aryl/alkyl isothiocyanates **94** and 1,3-dipoles produced from spirooxindole aziridines **95**. The one-pot reaction proceeded with $FeCl_3$ (10 mol%) in dichloromethane at −20 °C (Scheme 45). The substrate scope investigation was carried out utilizing different aryl/alkyl isothiocyanates and spirooxindole aziridines. The recovered yield of product was less with electron-deficient groups on the aromatic ring of oxindole relative to electron-

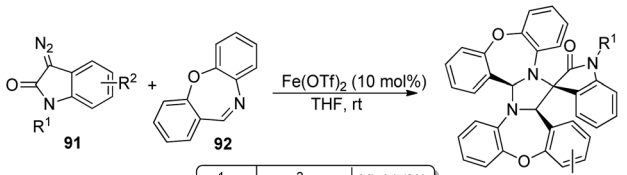


Scheme 40 Synthesis of polyheterocyclic spirooxindoles using *N*-methyl isatin and substituted tryptophols.



Y	R	R^1	R^2	Yield (%)
S	H	H	H	91
O	Me	H	H	89
O	H	Me	H	90
O	H	H	Cl	92
S	H	Bn	H	84
S	H	H	Cl	93

Scheme 42 Fe_3O_4/GO/Au–Ag catalyzed spirooxindole-dihydropyridine synthesis.



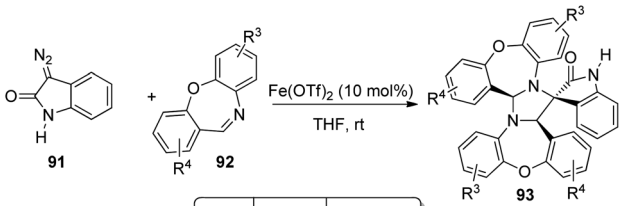
R^1	R^2	Yield (%)
H	H	86
Bn	H	89
Bz	H	87
Boc	H	90
Me	5-Me	81
Me	7-Cl	85
Me	6-Br	83
Me	5-OMe	91
Me	5,7-diMe	88

Scheme 43 Synthesis of spirooxindoles using dibenzo[*b*,*f*][1,4]oxazepins and substituted diazo-oxindoles.

rich groups. Compared to ethyl and benzyl protection on oxindole N, the yield was better for methyl substitution. Both aryl and alkyl isothiocyanates underwent the reaction without electronic and steric effect of the substituents on the aryl ring. Isothiocyanates which are non-aromatic and aliphatic were also compliant to the reaction. They could also obtain 72% of the products by employing the reaction on gram scale.

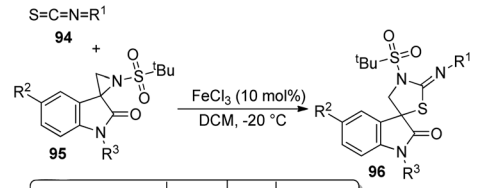
8 Pd-catalyzed spirooxindole synthesis

Pd catalysts are used in reactions like Wacker process,[71] carbon–carbon bond forming reactions[72,73] *etc.* and are still obtaining popularity in novel reactions. In organic transformations, palladium plays ubiquitous role among other transition metals. In most of the Pd-catalyzed reactions, the usual steps involved are two-electron reductive elimination and oxidative addition.



R^1	R^2	Yield (%)
8-Cl	H	82
8-Me	H	87
7-Cl	H	85
H	4-Cl	84
7-Me	H	89
8-Me	4-Cl	85
8-^{t}Bu	4-Cl	84

Scheme 44 Synthesis of spirooxindoles using diazo-oxindole and substituted dibenzo[*b*,*f*][1,4]oxazepins.



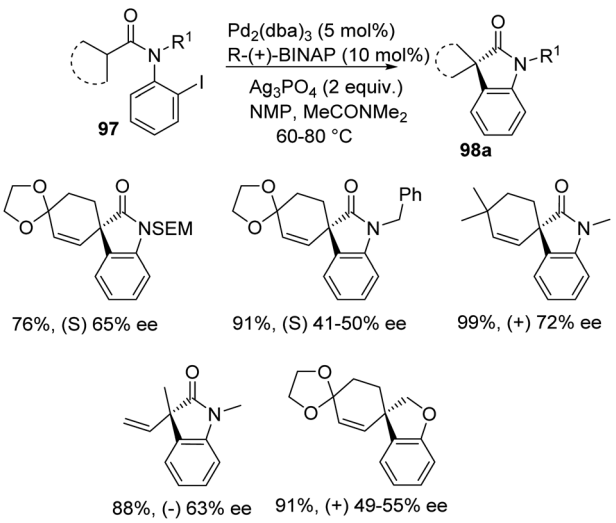
R^1	R^2	R^3	Yield (%)
Ph	Me	Me	84
4-MeC_6H_4	Me	Me	93
4-FC_6H_4	H	Me	74
4-EtC_6H_4	Cl	Me	74
^{n}Bu	H	Bn	71
Cy	H	Bn	64

Scheme 45 Synthesis of spirooxindolo-2-iminothiazolidines with $FeCl_3$ as catalyst.

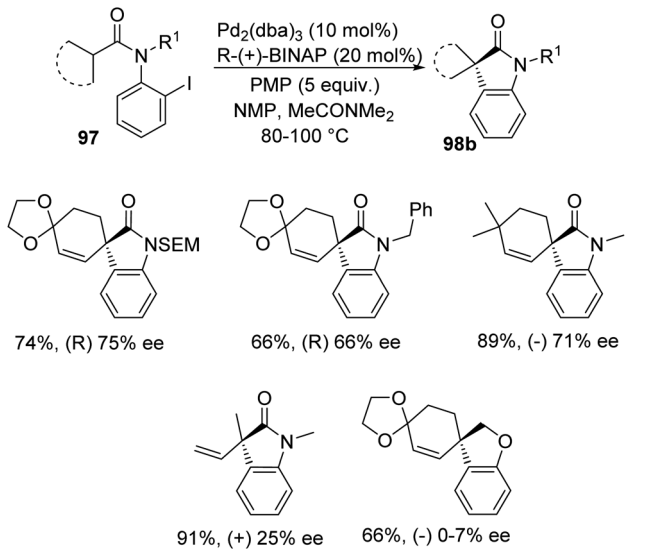
Spiropyrrolidinyl oxindoles, spirocyclooxindoles, cyclopropane-fused spirooxindoles *etc.* were produced by employing diverse Pd catalysts like $Pd_2(dba)_3$, $Pd(OAc)_2$, $PdCp(\eta^3\text{-}C_3H_5)$, $Pd(PPh_3)_4$ and so on. In most of the reports palladium(II)acetate was used as the catalytic species owing to its higher reactivity.

8.1 Reactions involving aryl iodide derivatives

Overman *et al.* disclosed a pathway for the synthesis of spirooxindoles **98** facilitated by palladium catalyst with a diphosphine ligand.[74] They used two different reaction conditions and they could obtain the two enantiomers of the product **98** from one enantiomer of the chiral ligand (*R*)-(+)-BINAP. Aryl iodides **97** were used as the substrates which underwent Heck reaction to give either enantiomer of the products. The (*S*)-enantiomer **98a** was produced by providing the conditions of 5 mol% of tris(dibenzylidene acetone)dipalladium, 10 mol% of the ligand, *N*,*N*-dimethylacetamide and Ag_3PO_4 (2 equiv.) at 60–80 °C (Scheme 46). In order to obtain the (*R*)-enantiomer **98b**, the



Scheme 46 Asymmetric synthesis of (*S*)-enantiomer of spirooxindole derivative utilizing palladium and *R*-(+)-BINAP.



Scheme 47 Asymmetric synthesis of (*R*)-enantiomer of spirooxindole derivatives utilizing Pd and *R*-(+)BINAP.

following reaction conditions were used: 10 mol% of tris(dibenzylidene acetone)dipalladium, 20 mol% of the ligand, *N*,*N*-dimethylacetamide and 1,2,2,6,6-pentamethylpiperidine (5 equiv.) at 80–100 °C (Scheme 47). In both the cases, *N*-methyl-2-pyrrolidinone was used as the solvent and high to good yields were observed.

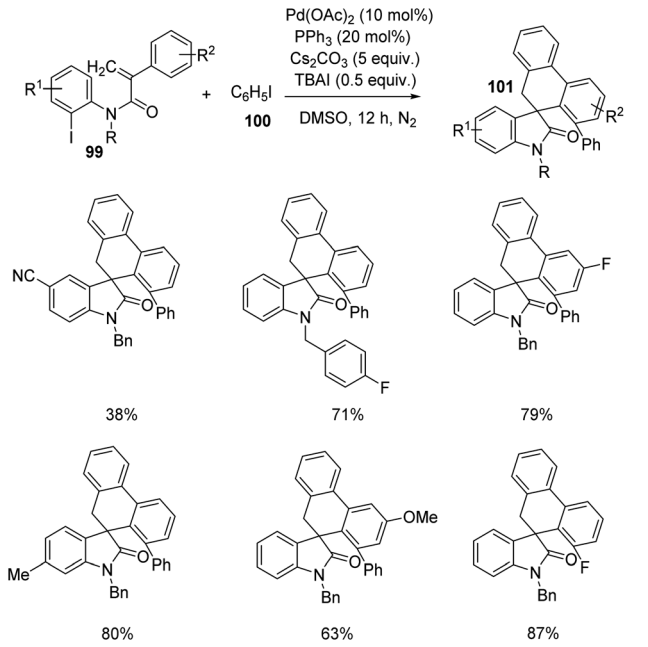
Yang *et al.* designed a process which involves palladium-catalyzed triple C–H bond activation for the formation of spirooxindoles[75] **101**, using diverse iodobenzene **100**. The reaction between iodobenzene-derivative of **100** and substituted acrylamides **99** was optimized using 10 mol% of palladium(II) acetate, 20 mol% triphenylphosphine, 5 equiv. of caesium carbonate and 0.5 equiv. of TBAI in dimethyl sulfoxide as the solvent under N_2 atmosphere at 120 °C (Scheme 48). Acrylamides with 4-methylbenzyl, 4-fluorobenzyl, benzyl and ethyl substituents on nitrogen underwent the reaction, but those with tosyl group and H atom on nitrogen were unable to perform the reaction. Electron-deficient and -rich groups on the 2-iodophenyl moiety was tolerated but the yield was lower with cyano substitution. Moderate to good yields were also afforded by various substituents on the benzene ring associated with double bond.

Then the reaction was carried out with diverse iodobenzenes **100** under the same conditions (Scheme 49). The electronic nature of the substituents was insignificant in case of iodobenzenes with *p*-substitution. With an increased reaction time, 65% spirooxindole was obtained from substrate bearing two methyl substituents on the meta-position.

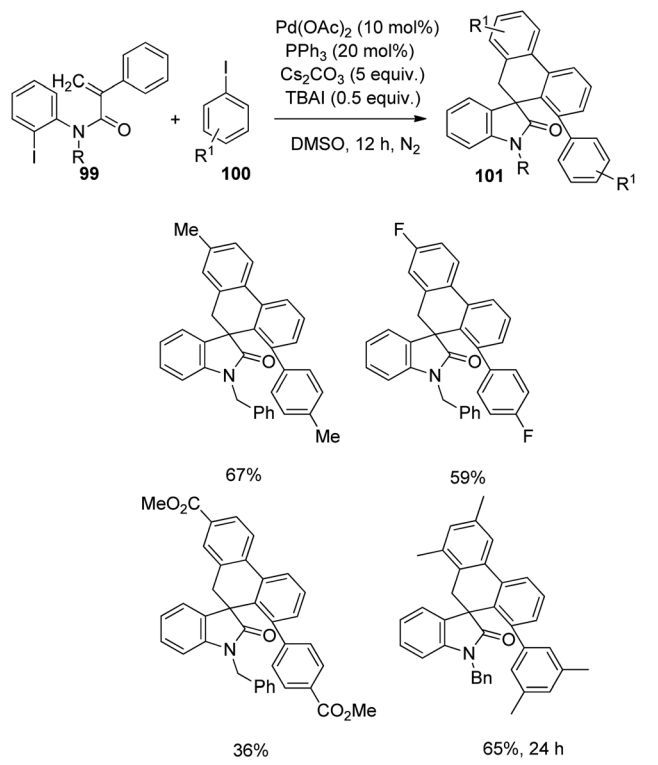
Aryl iodide derivatives were used along with palladium catalysts $Pd_2(dba)_3$ and $Pd(OAc)_2$ which furnished the spirooxindole product with up to 99% and 87% yields respectively.

8.2 Reactions involving isatin derivatives

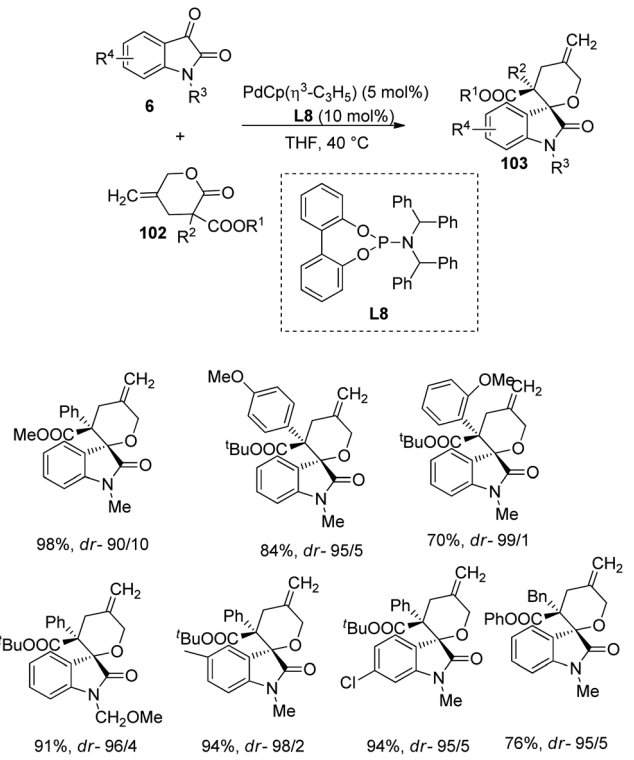
A strategy for the formation of derivatives of spirooxindole **103** from γ-methylidene-δ-valerolactones **102** and isatins **6** catalyzed by a palladium complex was devised by Hayashi and co-workers.[76] Here γ-methylidene-δ-valerolactones **102** underwent decarboxylative [4 + 2] cycloaddition with isatin **6** to afford spirooxindoles **103** which are highly stereoselective. The



Scheme 48 Synthesis of spirooxindoles from substituted *N*-(2-iodophenyl)-2-phenyl acrylamides and iodobenzene.



Scheme 49 Synthesis of spirooxindole from substituted iodobenzenes and *N*-(2-iodophenyl)-2-phenyl acrylamides.



Scheme 50 Substrate scope for the synthesis of spirooxindoles *via* decarboxylative cyclization catalyzed by Pd complex.

reaction between various isatins and γ-methylidene-δ-valerolactones was catalyzed with $PdCp(\eta^3\text{-}C_3H_5)$ (5 mol%) and phosphoramidite ligand (**L8**) (10 mol%) in tetrahydrofuran at 40 °C (Scheme 50).

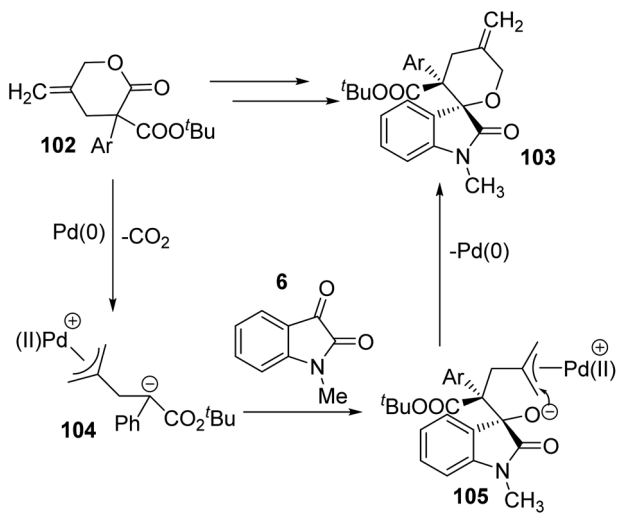
Isatins with different groups on N atom and on aromatic ring were tolerated and rendered high to efficient yields and dr values. In the case of γ-methylidene-δ-valerolactone, better dr values were achieved from ^{t}Bu compared to methyl as the ester groups. α-(Hetero)aryl-γ-methylidene-δ-valerolactones and α-alkyl lactones also underwent the reaction but in the case of α-alkyl lactones satisfactory yield was obtained only when phenyl was used as the ester group. They expanded the strategy to other ketones including diethylketomalonate. Scheme 51 provides the catalytic cycle for the reaction.

The allyl ester group of γ-methylidene-δ-valerolactone **102** underwent oxidative addition to Pd(0). A 1,4-zwitterionic species **104** was generated *via* subsequent elimination of a CO_2 molecule. An intermediate **105** was developed by the attack of anionic C of zwitterion **104** to electrophilic C of N-methyl isatin, derivative of **6**. In the intermediate **105**, the π-allyl palladium was attacked by nucleophilic O to give the spirooxindole product **103**. Here, the catalyst was restored.

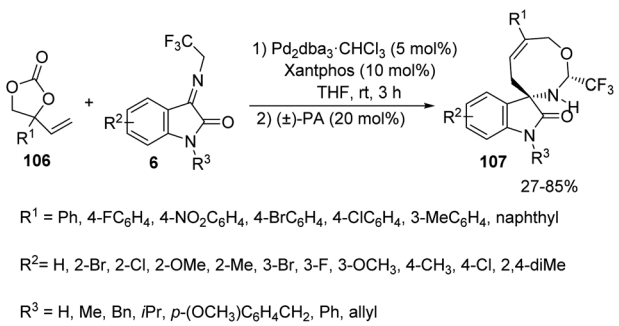
Synthesis of spirooxindoles **107** by the formal [5 + 3] cycloaddition reaction between aryl substituted vinylethylene carbonates **106** and α-(trifluoromethyl)imines derived from isatin **6** was established by Shi and co-workers.[77] Making use of the conditions given in the Scheme 52, they synthesised spirooxindole fused with an 8-membered ring as individual diastereoisomer. 66–82% of the products were afforded by isatin-derived α-(trifluoromethyl)imines with various substituents on the aryl ring without significant electronic and positional effects. Diverse groups such as Me, Bn and ^{i}Pr on the nitrogen atom of isatin underwent the reaction but the yield was only 27% without protection. The substrate scope for vinylethylene carbonates was also probed and moderate to good yields were contributed by those with electron-deficient and electron-donating groups on aromatic ring. The yield was 0 and 85% for vinylethylene carbonates without any substitution and with naphthyl substituent respectively. A chiral phosphine ligand was used to perform the asymmetric version of the [5 + 3] cycloaddition reaction.

8.3 Reactions involving oxindole derivatives

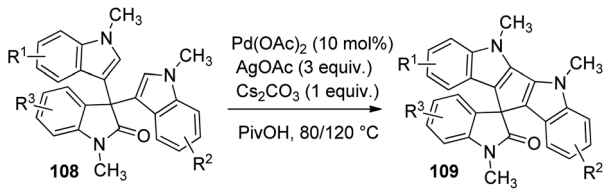
A procedure for the formation of spirocyclooxindoles through the synthesis of 3-cyanomethyloxindoles was executed by Jaegli *et al.*[78] Here spirocyclopropyl-, spiropiperidinyl- and spiropyrrolidinyl oxindoles were produced from 3′-alkyl-3-cyanomethyl-2-oxindoles which were made *via* Heck/cyanation catalyzed by palladium. Different heterocycles were further prepared by the functionalization of the products thus



Scheme 51 Possible catalytic cycle for the decarboxylative cyclization catalyzed by Pd [reproduced with permission from ref. 76].

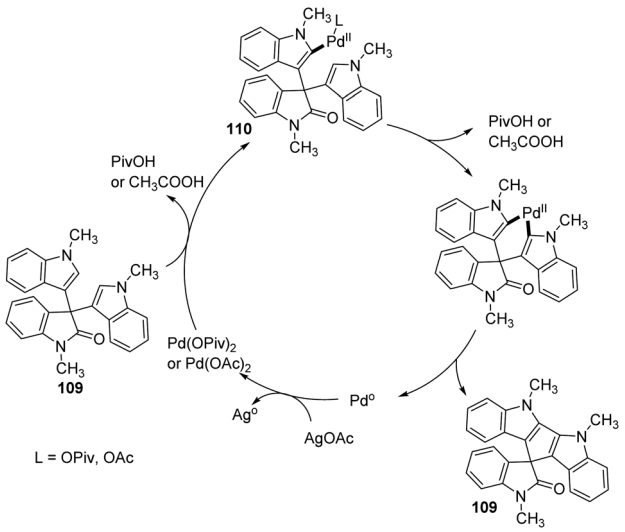


Scheme 52 Synthesis of spirooxindoles through formal [5 + 3] cycloaddition using Pd catalyst.



R^1	R^2	R^3	Yield (%)
H	H	5-Cl	88
H	H	5-OMe	86
H	H	5,7-diMe	82
H	5-OMe	H	67
5-Me	5-OMe	H	87
5-OMe	5-OMe	H	58

Scheme 53 Substrate scope for cyclopentadiindolyl spirooxindoles syntheses catalyzed by palladium.



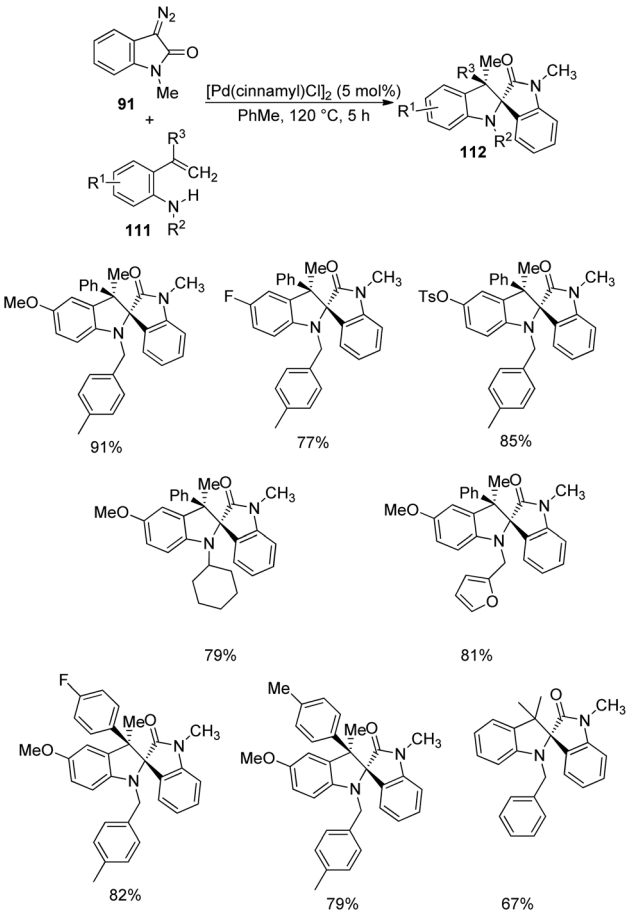
Scheme 54 Plausible mechanism for the oxidative coupling reaction with Pd catalyst [reproduced with permission from ref. 79].

achieved, through Buchwald–Hartwig *N*-arylation, *N*-sulfonylation, *N*-acylation and so on.

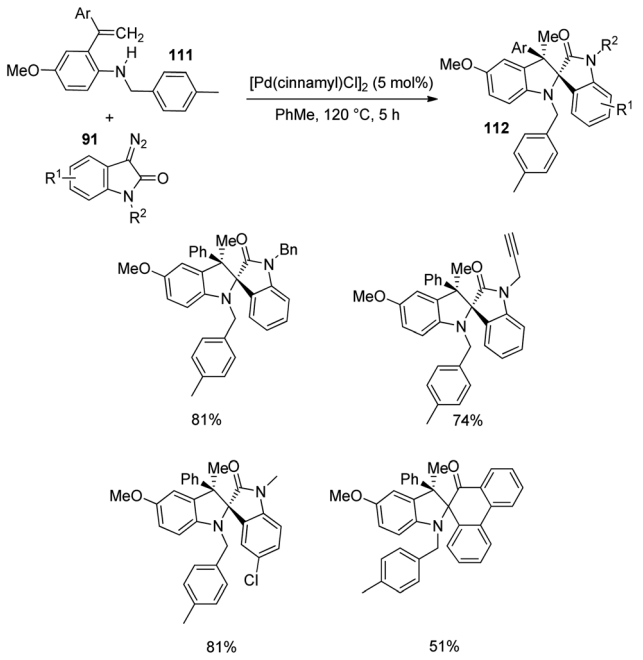
A procedure for the generation of cyclopentadiindolyl spirooxindoles **109** catalyzed by palladium through oxidative coupling reaction was reported by Kim *et al.*[79] 3,3-Diindolyl-2-oxindoles **108** upon treatment with 10 mol% $Pd(OAc)_2$ as the catalyst, 3 equiv. AgOAc as the oxidant and 1 equiv. caesium carbonate as the base in pivalic acid at 120 °C afforded cyclopentadiindolyl spirooxindoles (Scheme 53). Good yields were furnished by *N*-methylisatins with electron-poor and electron-rich groups with mono- and disubstitution. Indoles with Me and OMe group on fifth position offered 58–87% of spirooxindoles. Low reaction temperature (80 °C) was used with dimethoxy derivative in order to avoid decomposition.

According to the mechanism an intermediate **110** was generated by the electrophilic palladation of 3,3-diindolyl-2-oxindole **108** with $Pd(OPiv)_2$ or $Pd(OAc)_2$. Next electrophilic palladation took place in the intermediate **110** intramolecularly and subsequent reductive elimination provided the required cyclopentadiindolyl spirooxindole **109**. The palladium catalyst was regenerated by silver acetate. The proposed reaction path is depicted in Scheme 54.

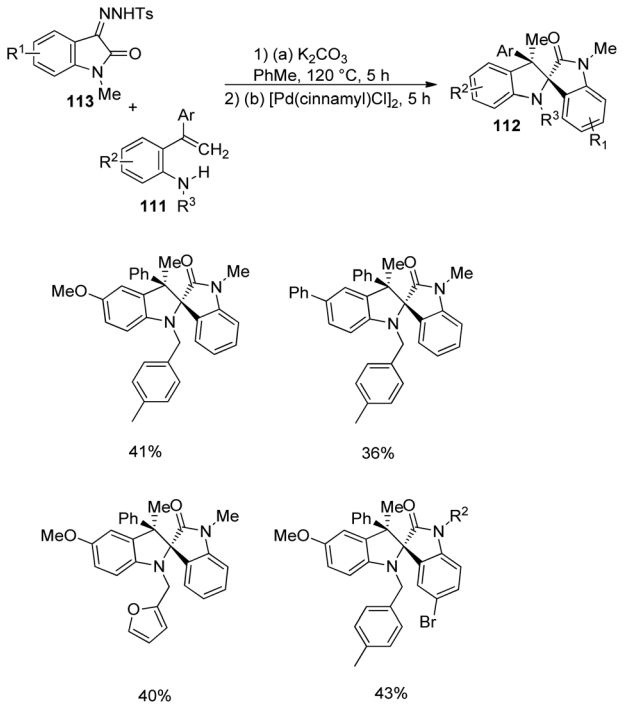
Pd-catalyzed carbenylative amination of *o*-vinylanilines **111** with diazooxindole-derivative of **91** was described by Anbarasan and co-workers.[80] A set of indoline fused spirooxindoles **112** was achieved in good yields with proficient diastereoselectivity, utilizing differently substituted substrates. The reaction conditions involved 5 mol% $[Pd(cinnamyl)Cl]_2$ in toluene at 120 °C for 5 h and the scope of *o*-vinylaniline was investigated (Scheme 55). The reaction proceeded with simple aniline, *p*-methoxy, *p*-phenyl, halo-, acetal-, acyloxy- and tosyloxy-substituted *o*-vinylanilines. Due to steric reasons, naphthyl-substituted *o*-vinylaniline was unable to perform the reaction. *o*-Vinylaniline with varied substituents on nitrogen also underwent the reaction. Different groups such as Ph, *p*-^{t}butylphenyl, *p*-tolyl, *p*-fluorophenyl and *p*-ethyl on the alkene fragment were tolerated (67–82%). Substrates with thiophenyl and cyclohexenyl substituents were also suitable for this reaction. The desired product was not obtained with simple styrene, but Me substituted one afforded the product.



Scheme 55 Diversification of *o*-vinylanilines in Pd-catalyzed carbenylative amination.



Scheme 56 Diversification of diazo compounds in Pd-catalyzed carbenylative amination.



Scheme 57 Synthesis of spirooxindoles *via* one-pot conversion of *p*-tosylhydrazone.

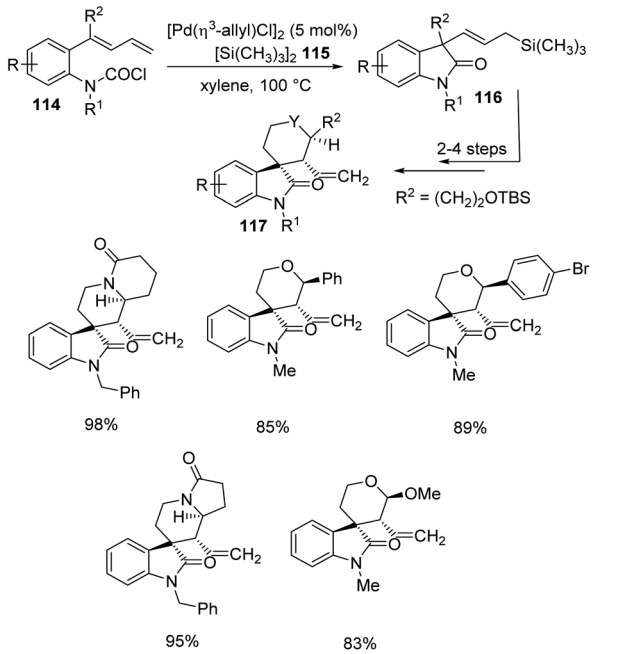
Next, the reaction was performed using differently substituted diazo compounds **91** (Scheme 56). *N*-Alkyl, *N*-propargyl, *N*-allyl and *N*-benzyl substituted diazo compounds underwent the reaction. Good yields were given by those with electron-withdrawing substituents on the fifth position. Further, spirooxindoles **112** were produced by one-pot reaction between tosyl hydrazones **113** and *o*-vinylanilines- derivative of **111** under the conditions given in Scheme 57.

Most of the reactions with oxindole derivatives employing Fe and Pd catalysts were atom economical and contributed products with excellent diastereoselectivities.

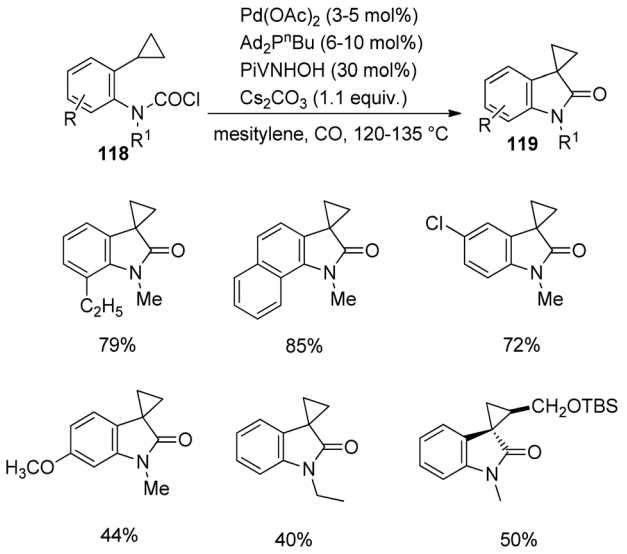
8.4 Reactions involving carbamoyl chloride derivatives

Takemoto and co-workers established a design for the preparation of spirooxindoles **117** catalyzed by palladium, in 2011.[81] It involves a carbosilylation accompanied by a Sakurai-type cyclization, in which 1,3-dienes having carbamoyl chloride **114** were used as substrates. In the first step, carbamoyl chlorides **114** were reacted with hexamethyldisilane **115** and $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol%) in xylene at 100 °C to deliver the corresponding oxindoles **116**. Then Sakurai-type cyclization was performed to produce 5-membered carbocycle-, tetrahydropyran- and piperidine-fused spirooxindoles **117** (Scheme 58).

In 2013, Takemoto *et al.* proposed a methodology which involves a $C(sp^3)$–H activation for the synthesis of cyclopropane-fused spirooxindoles **119** catalyzed by palladium.[82] It entails the $C(sp^3)$–H activation of carbamoyl chlorides having cyclopropyl group, **118.** The reaction was optimized using 6–10 mol% di(1-adamantyl)-*n*-butylphosphine, 3–5 mol% palladium(II)acetate, 30 mol% *N*-hydroxypivalamide and 1.1 equiv. caesium carbonate under CO atmosphere in mesitylene at 120–135 °C (Scheme 59). Good yields were brought by *ortho*-ethyl and *ortho*-isopropyl substituted carbamoyl chlorides. In both the cases, activation happened only to the cyclopropyl methine $C(sp^3)$–H bond. In the case of carbamoyl chloride having a naphthyl group, the activation was better for cyclopropyl methine $C(sp^3)$–H bond. The yield granted by substrates with *ortho*-substituents was superior to that



Scheme 58 Pd-catalyzed carbosilylation and Sakurai-type cyclization to synthesise spirooxindoles.



Scheme 59 Cyclopropane-fused spirooxindole synthesis catalyzed by Pd.

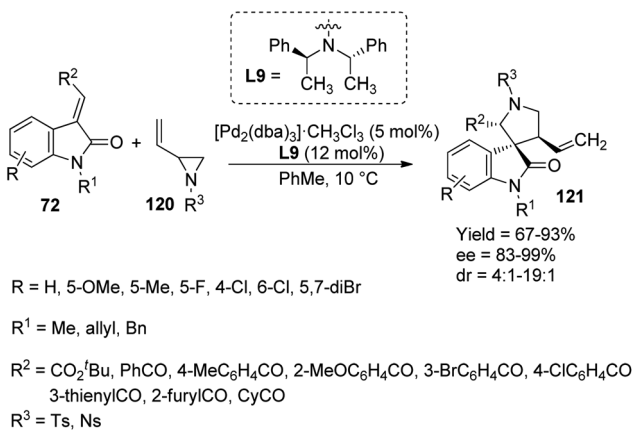
without *o*-substitution. Products were also afforded by carbamoyl chlorides holding siloxymethyl on the cyclopropane ring.

Studies related to regioselectivity was also done by the group. Heck reaction took place when N atom of carbamoyl chloride carried an alkyl group. Heck reaction > cyclopropyl methine $C(sp^3)$–H activation > methyl $C(sp^3)$–H activation > $C(sp^2)$–H activation was the order of selectivity of the reaction.

$[Pd(\eta^3\text{-allyl})Cl]_2$ and $Pd(OAc)_2$ were used as catalysts for the syntheses of spirooxindoles starting with carbamoyl chloride derivatives. The temperature applied was 100 °C for the former and 120–135 °C for the latter.

8.5 Reactions involving methyeleneindolinones derivatives

A proposal for the generation of enantioenriched 3,3′-pyrrolinyl spirooxindoles **121** catalyzed by a palladium complex was presented by Lu and co-workers.[83] Here, methyleneindolinones **72** underwent [3 + 2] cycloaddition with vinyl aziridines **120**. The optimized reaction conditions include 12 mol% of ligand **L9**, 5 mol% of $[Pd_2(dba)_3]\cdot CHCl_3$ in toluene at 10 °C (Scheme 60). They first investigated the effects of alkene substituents on methyleneindolinones. Good yields were afforded by substrates with arylacyl and ester groups. Diastereo- and enantioselectivities were not affected by electronic nature of the substituents. Methyleneindolinones carrying cyclohexylacyl, 3-thienylacyl and 2-furylacyl groups also underwent the reaction. The influence of substituents on oxindole moiety was surveyed. Methyleneindolinones with mono- and disubstitutions on aromatic ring rendered 69–90% yield, 4:1–19 : 1 dr values and 82–99% ee values. High yield and stereoselectivities were also obtained from various substituents on nitrogen of vinyl aziridine and oxindole. Gram scale reaction and diversity-directed spirooxindole synthesis were also performed by the group.



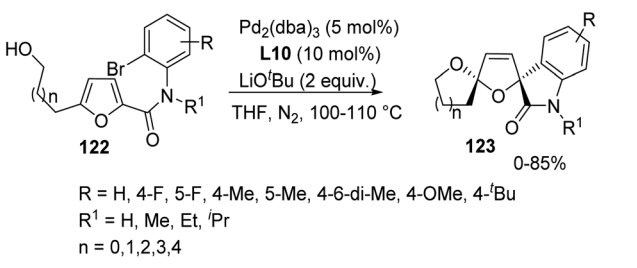
Scheme 60 Synthesis of spirooxindoles *via* [3 + 2] cycloaddition catalyzed by palladium-complex.

8.6 Reactions involving furan derivatives

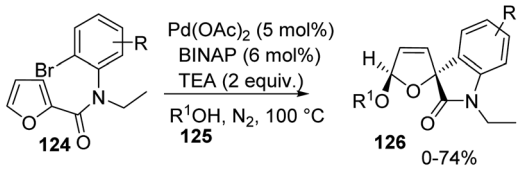
Furans are conjugated dienes having low aromatic nature and they can function as analogues of 1,3-dienes in organic reactions.

Yin and co-workers described 2,5-alkoxyarylation of furan rings for the synthesis of dispirooxindoles **123** by employing a Pd catalyst.[84] Variously substituted furans **122** underwent intramolecular cyclization under the optimized conditions of 5 mol% of $[Pd_2(dba)_3]$, 10 mol% of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (**L10**) and 2 equivalent of LiO^tBu in an atmosphere of nitrogen in tetrahydrofuran at 100–110 °C (Scheme 61). The yields were good with electron-withdrawing groups on the aromatic ring of furan substrate compared to electron-releasing ones. The products were obtained only in traces when hydrogen or ^{i}Pr was present on N atom of the substrate instead of methyl and ethyl substituents. The yield was 65–80% and 50% with substrates bearing side chain of four-carbon and five-carbon atoms respectively. It was zero in case of six-carbon and two-carbon chains.

Further the intermolecular cyclization was examined by using variously substituted *N*-2-bromophenyl-2-furamides **124** with 5 mol% of $Pd(OAc)_2$, 6 mol% of BINAP and 2 equivalent of TEA in excess alcohol **125** under N_2 atmosphere at 100 °C and the corresponding spirooxindole **126** was obtained (Scheme 62). When ^{t}butanol was employed as the solvent, spirooxindoles were not yielded. There was no significant effect for the electronic nature of the substituents on the aromatic ring of the substrate.



Scheme 61 Dispirooxindole synthesis *via* intramolecular cyclization of furan.

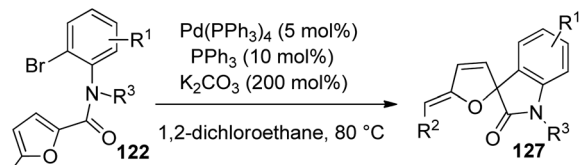


R = H, 4-Me, 5-Me, 4-6-diMe, 4-OMe, 4-*t*Bu, 4-F, 5-F
R^1 = Me, Et, *i*Pr, *t*-Bu, *n*-Pr

Scheme 62 Spirooxindole synthesis *via* intermolecular cyclization of furan rings.

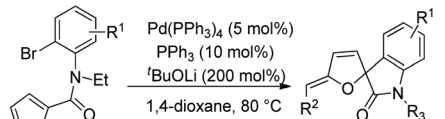
In the same year, a method for the synthesis of spirooxindoles **127** catalyzed by Pd was put forward by the same group.[85] Here also derivatives of furan-derivative of **122** were utilized which underwent intramolecular arylation and transformed into spirooxindoles **127** with high stereo- and regioselectivity. The *Z*-isomer was formed in higher amount when the reaction of *N*-(2-bromophenyl)-2-furancarboxamides proceeded with 5 mol% $Pd(PPh_3)_4$, 10 mol% PPh_3 and 200 mol% K_2CO_3 in DCE at 80–90 °C (Scheme 63). A combination of 10 mol% of PPh_3, 5 mol% of $Pd(PPh_3)_4$ and 200 mol% of ^{t}BuOLi in 1,4-dioxane as the solvent at 80 °C afforded the *E*-isomer in higher amounts (Scheme 64).

First the reaction scope for the preparation of Z-isomer was studied by employing substrates with different substituents on aryl and furan rings and also on nitrogen. Both electron-deficient and electron-rich groups on Ph ring was tolerated. When naphthyl, thiophenyl, phenyl or alkyl group other than Me was present as R^2 the selectivity was higher. The desired product was not acquired when H was present on N of the substrate. Then the effect of substituents on formation of E-isomer was examined. Substrates with *p*-Tolyl and Ph as R^2 gave the E-isomer preferentially. But in case of substrate with Me as R^2, the selectivity towards *Z*-isomer was higher even with ^{t}BuOLi as the base.



R^1	R^2	R^3	Yield (%)	Z/E
4-Me	Ph	Et	80	13/1
4-F	Ph	Et	91	12/1
4-OMe	4-MeC_6H_4	Et	80	14/1
4-Me	4-ClC_6H_4	Et	80	13/1
H	2-MeC_6H_4	Et	87	10/1
H	2-ClC_6H_4	Et	85	11/1
H	Me	Me	85	4/1

Scheme 63 Preferential synthesis of *Z*-isomer of spirooxindole from *N*-(2-bromophenyl)-2-furancarboxamides.



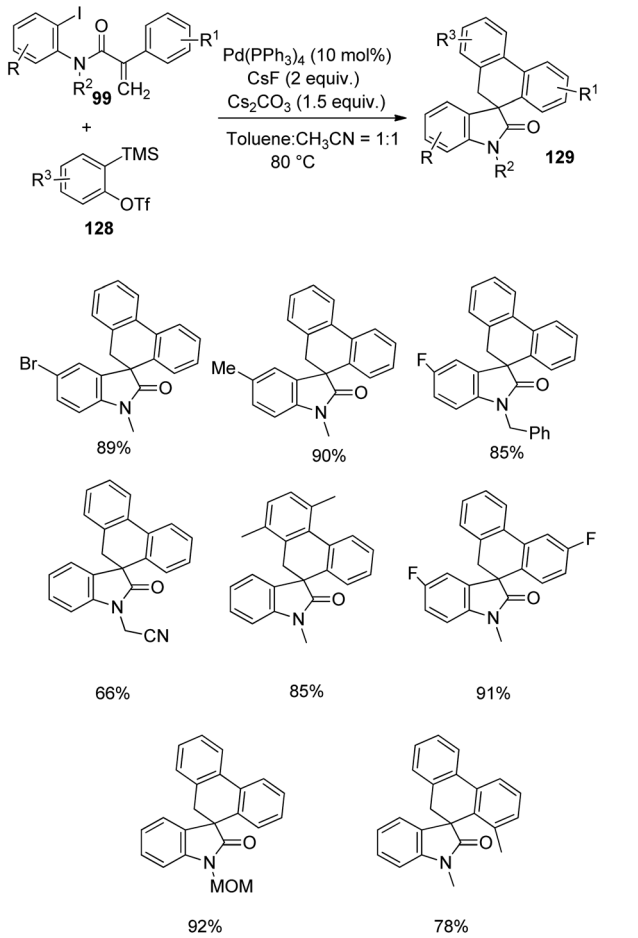
R^1	R^2	Yield (%)	Z/E
4-Me	Ph	50	1/2.7
4-Me	4-MeC_6H_4	65	1/2.1
4-OMe	4-MeC_6H_4	50	1/1.5
5-Me	4-MeC_6H_4	68	1/2

Scheme 64 Preferential synthesis of *E*-isomer of spirooxindoles from *N*-(2-bromophenyl)-2-furancarboxamides.

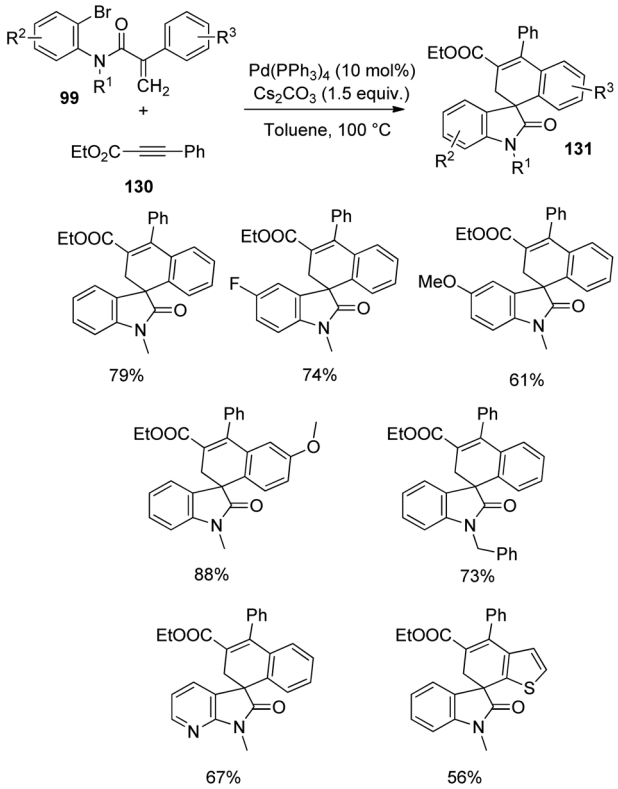
$Pd_2(dba)_3$, $Pd(OAc)_2$ and $Pd(PPh_3)_4$ were used as catalysts for spirooxindole synthesis starting from furan derivatives and they afforded the yield of up to 85%, 74% and 91% respectively.

8.7 Reactions involving acrylamide derivatives

A strategy for the formation of spirooxindoles **129** through C–H activation and subsequent benzyne insertion catalyzed by



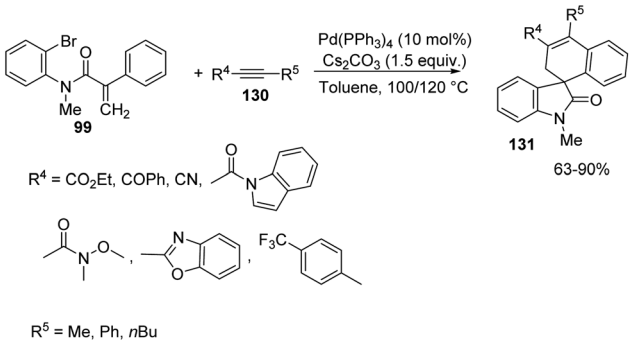
Scheme 65 Spirooxindole synthesis *via* Heck spirocyclization catalyzed by palladium.



Scheme 66 Spirocyclization with ethyl phenylpropiolate and different acrylamides catalyzed by palladium.

palladium was designed by Lautens and co-workers in 2016.[86] The reaction between acrylamides **99** and benzyne precursors **128** was optimized with 10 mol% $Pd(PPh_3)_4$, 2 equiv. of CsF, 1.5 equiv. of Cs_2CO_3 in a mixture of toluene and acetonitrile (1 : 1) at 80 °C (Scheme 65). Small amount of triphenylene was also formed along with the desired spirooxindole product. Acrylamides with electron-releasing and -deficient substituents underwent the cyclization. High yields were obtained from acrylamide bearing a fluorine atom on the attached aryl group. The presence of $CH_2CO_2C_2H_5$ and MOM on the nitrogen atom was also tolerated, but the yield was lower with electron-deficient groups. Acrylamide with attached aryl group having *ortho*-substitution afforded 78% of the product. The yield was lower with electron-withdrawing benzyne precursors compared to the electron-releasing ones. The group could produce 85% of the spirooxindoles by performing the reaction on gram scale. Further ring expansion and aromatization of the spirooxindoles were also carried out.

In the next year, the same author reported the synthesis of spirooxindoles **131** through C–H activation and alkyne insertion, with palladium catalyst.[87] The starting materials employed were acrylamides-bromo derivative of **99** and internal alkynes **130** and the optimized reaction conditions were 10 mol% $Pd(PPh_3)_4$ and 1.5 equiv. caesium carbonate in toluene as solvent at 100 or 120 °C which afforded regioselectivity >20 : 1. First ethyl phenylpropiolate-derivative of **130**, was reacted with differently substituted acrylamides **99** (Scheme 66). Electron-releasing substituents on aromatic ring next to nitrogen atom

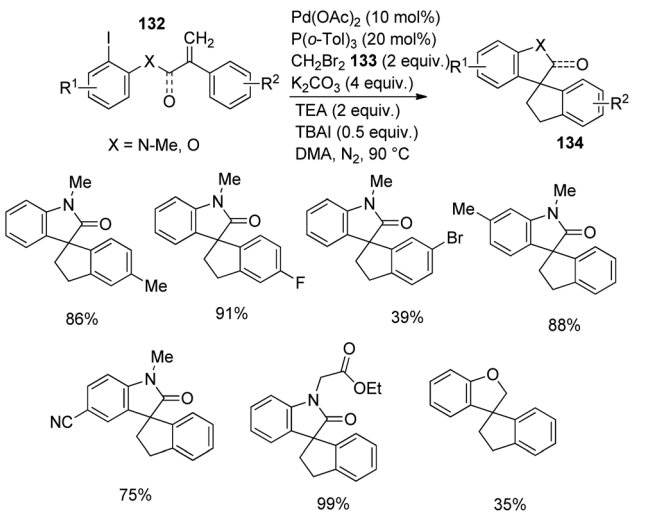


Scheme 67 Spirocyclization with acrylamide and different internal alkynes catalyzed by Pd.

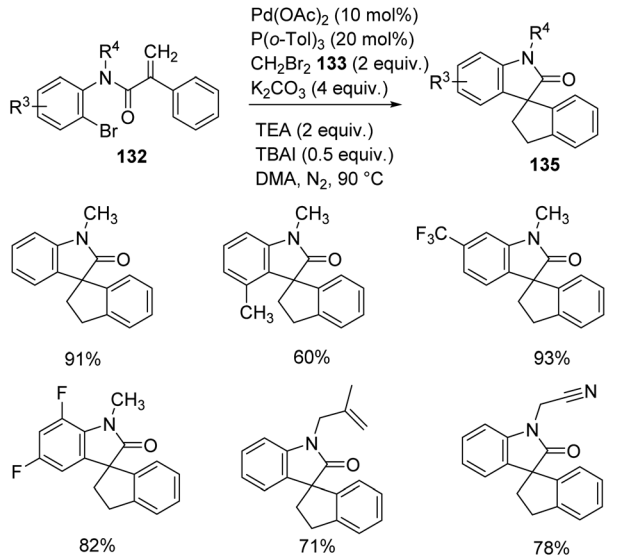
and on the other aromatic ring gave 61–88% of the desired spirooxindole products. Fluorinated acrylamides and those with *N*-Bn and *N*-MOM protection also underwent the reaction. Acrylamide bearing a tethered thiophene and that with a pyridinylbromide substituent were also tolerated. The corresponding product was not provided by the substrate with electron-poor groups on the hanging aromatic ring.

Next the reaction was performed with different internal alkynes **130** under the same conditions (Scheme 67). Indole derived and ethyl 2-butynoate inserted alkynes underwent the reaction. Alkyne with a non enolizable ketone in place of the ester group afforded 79% spirooxindole. Weinreb amide, diaryl alkyne and alkyne containing 4-triflurometyl-2-pyridine required higher temperature (120 °C). Regioselectivity was inferior (9 : 1) with phenylpropionitrile.

Zhang and co-workers described the growth of spirooxindoles **134**, **135** *via* functionalization of remote C–H, utilizing a Pd catalyst.[88] They put forward a path in which dibromomethane **133** reacted with the palladacycle achieved through C–H activation of the acrylamide substrate. The substrate scope was then investigated by reacting acrylamides at optimized



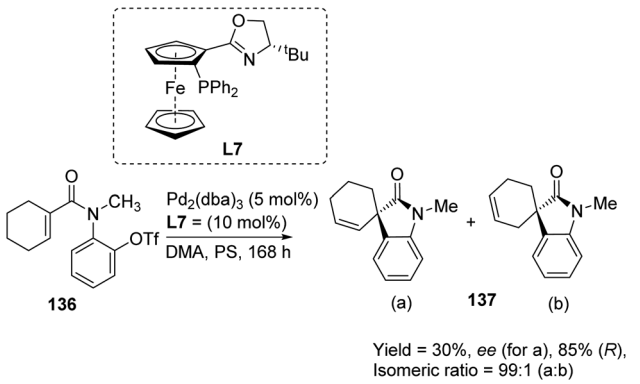
Scheme 68 Spirooxindole synthesis through remote C–H activation of acrylamide containing aryl iodides.



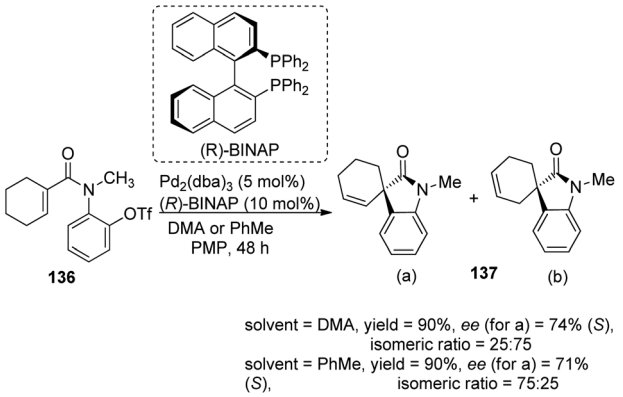
Scheme 69 Spirooxindole synthesis through remote C–H activation of acrylamides containing aryl bromides.

conditions using 20 mol% P(*o*-tol)$_3$, 10 mol% Pd(OAc)$_2$, 4 equiv. potassium carbonate, 2 equiv. dibromomethane, 2 equiv. triethylamine and 0.5 equiv. tetrabutylammonium iodide in DMA at 90 °C under N_2 atmosphere. Ph, OMe, Me or halo substitutions on the aryl ring attached to double bond were tolerated. The yield with Br was less compared to Cl and F substitutions.

Acrylamides **132** having aryl iodides were reacted under the optimized conditions (Scheme 68). Phenyl ring containing halo, other electron-deficient as well as electron-rich groups underwent the reaction. Excellent yields were provided by 2-ethoxy-2-oxoethyl, benzyl, *n*-butyl or ethyl groups on nitrogen atom. *N*-Substituted acrylamides and the one bearing an ester linkage gave no yield but 35% product was obtained from the ether analogue. Acrylamide bearing aryl bromides-bromo derivative of **99**, were examined under same conditions (Scheme 69). Due to steric hindrance, the yield was only 60% with *ortho*-methyl substituent. Trifluoromethyl and di-fluoro substituted acrylamides were tolerated in the reaction. Moderate yields were offered by substrates with *N*-cyanomethyl and *N*-2-methylallyl substituents.



Scheme 70 Heck cyclization of aryl triflates using palladium complex with ^{t}Bu-derived ferrocenyloxazoline as the ligand.

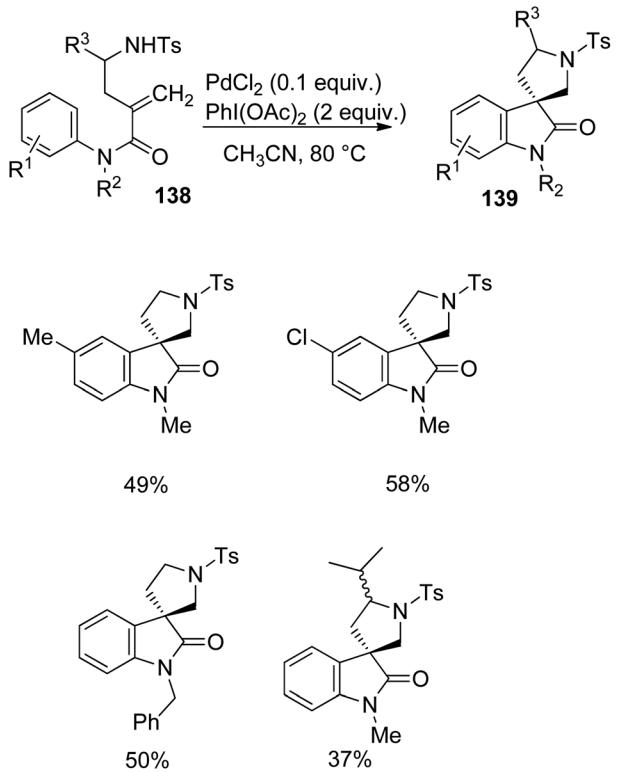


Scheme 71 Heck cyclization of aryl triflates using Pd complex with (*R*)-BINAP as the ligand.

The reactions involving acrylamide derivatives were catalyzed by Pd(PPh$_3$)$_4$ and Pd(OAc)$_2$, in which the reactions involving Pd(PPh$_3$)$_4$ were easily scalable.

8.8 Reactions involving other substrates

A comparison of the efficiency of palladium complexes with phosphinamine and (*R*)-BINAP as ligands in the intramolecular Heck cyclization of aryl triflates **136** to form spirooxindole derivatives **137** was put forth by Kiely and Guiry.[89] The group screened different ligands including (*R*)-BINAP, ^{t}Bu-substituted and ^{i}Pr-substituted ferroceneoxazoline, ^{t}Bu-derived and ^{i}Pr-derived diphenylphosphinoaryloxazoline. The product yield,



Scheme 72 Spirooxindole synthesis through alkene carboheterofunctionalization.

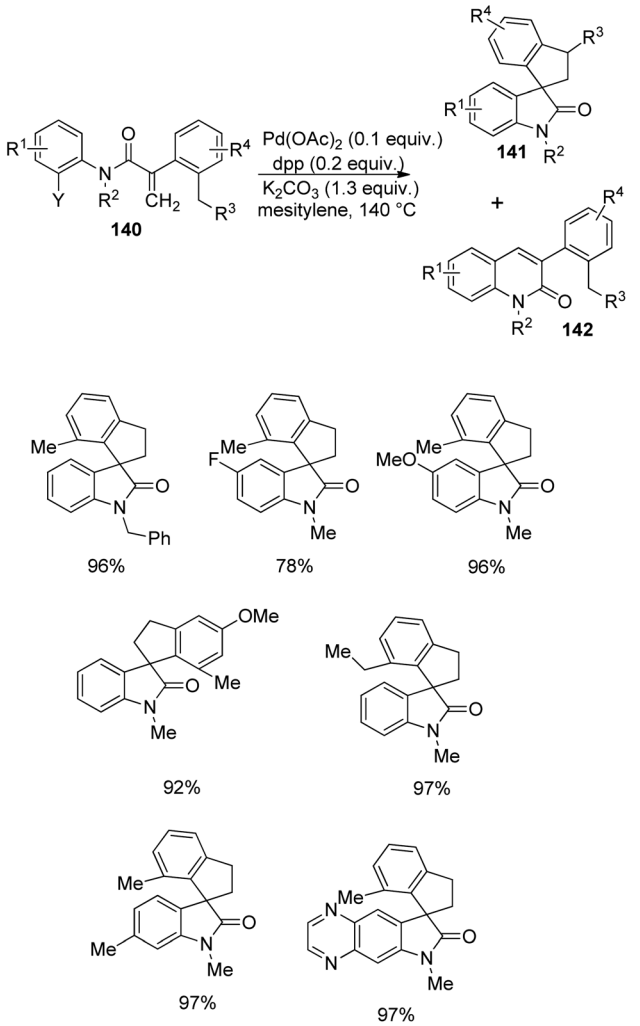
regioselectivity and enantioselectivity were investigated by employing solvents including benzene, toluene, dimethylacetamide and bases including proton sponge (PS) and 1,2,2,6,6-pentamethylpiperidine (PMP). The best enantioselectivity was gained from complex of palladium with ^{t}Bu-derived ferrocenyloxazoline ligand (**L7**) in DMA as the solvent and proton sponge as base (Scheme 70). The regioselectivity was also better with phosphinamine ligands. The reactivity was higher and the reaction time was lower when BINAP was used as the ligand with pentamethylpiperidine as base. Solvents DMA and toluene gave isomeric ratios 25 : 75 and 75 : 25 respectively (Scheme 71).

Zhu *et al.* implemented a protocol for the development of spiropyrrolidinyl oxindoles **139** catalyzed by palladium from derivatives of anilides **138** *via* carbo-heterofunctionalization.[90] The reaction was optimized with 0.1 equiv. of $PdCl_2$ and 2 equiv. of $PhI(OAc)_2$ as the oxidant in CH_3CN at 80 °C (Scheme 72). Differently substituted anilide derivatives **138** underwent the reaction and afforded spirooxindoles **139** with 37–58% yield.

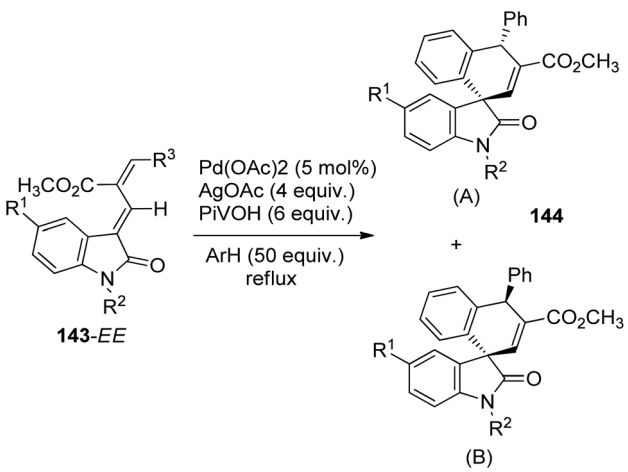
A plan for the synthesis of spirooxindoles **141** by making use of a sigma-alkyl palladium(II) complex, starting from an acrylamide derivative **140** was provided by Zhu *et al.*[91] The preparation involves a carbopalladation followed by a $C(sp^3)$–$C(sp^3)$ bond formation, *via* $C(sp^3)$–H bond activation. The reaction was optimized with 0.1 equiv. of $Pd(OAc)_2$, 0.2 equiv. of 1,3-bis(diphenylphosphino)propane as the ligand and 1.3 equiv. of K_2CO_3 in mesitylene at 140 °C (Scheme 73). In some cases, notable quantity of quinolinone **142** was also formed.

Substrate bearing chloranilide was unable to perform the reaction, but that with iodoanilide and bromoanilide provided excellent yields. Secondary amide was also unsuccessful in the reaction. Substrate with various substituents on N underwent the reaction. Substrates having substituents *o*- to the halide gave quinolinone as the major product but 78–97% yields were obtained from *m*- and *p*-substituents. Substrates containing heterocycles were also tolerated in this reaction. In the case of acrylate α-aryl substituents excellent yields were contributed by OMe, Me and ^{t}Bu groups whereas 2-(*o*-tolyl)acrylamide was fruitless in this reaction. Two diastereoisomers in 2 : 1 ratio was given by anilide with 2,5-diethyl substituted phenyl ring. The activation of methyl $C(sp^3)$–H bond was lower compared to that of naphthyl $C(sp^2)$–H bond when naphthalene was placed instead of benzene.

An approach for the synthesis of spirooxindoles **144** by using a Pd catalyst was developed by Kim *et al.*[92] The substrates used were 3-(γ,δ-disubstituted)allylidene-2-oxindoles(a) **143** which undergoes an oxidative Heck (Fujiwara–Moritani) arylation and functionalisation of the C–H bond of aryl/arylation reaction. The products **144** were formed by utilizing 4 equiv. of AgOAc, 5 mol% of $Pd(OAc)_2$ and 6 mol% of PivOH with benzene under reflux (Scheme 74). Both the isomers of the substrate **143**, **143**-*ZE* and **143**-*EE*, gave similar results due to isomerisation of C_α=C_β double bond.



Scheme 73 Substrate scope for the carbopalladation/$C(sp^3)$–$C(sp^3)$ bond formation.



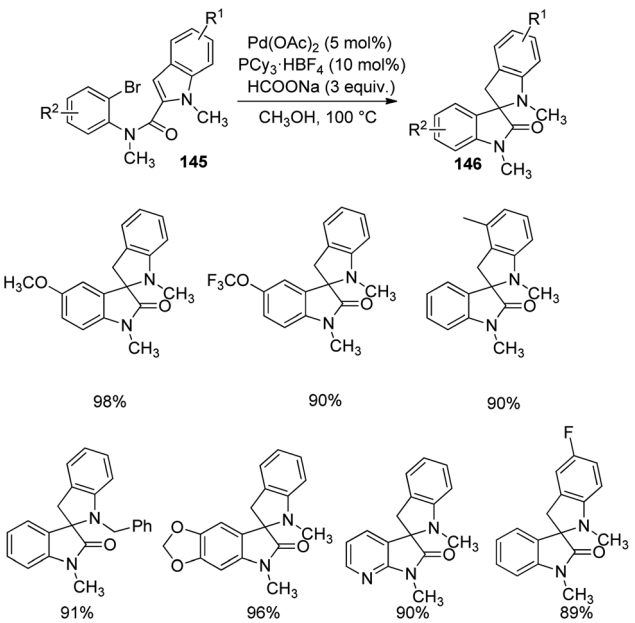
R^1	R^2	Yield %(A)	Yield %(B)
Cl	Me	62	17
OMe	Me	67	14
H	Ac	71	4
H	Me	64	10

Scheme 74 Substrate scope for spirooxindole synthesis from 3-(γ,δ-disubstituted)alkylidene-2-oxindoles.

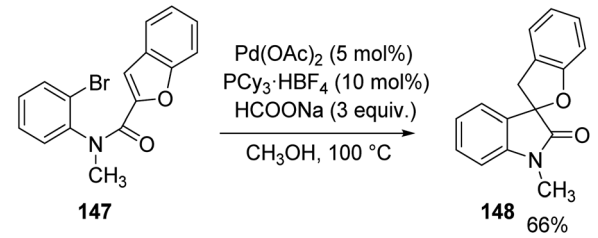
The substrate scope investigations were performed by employing **143**-*EE* isomer. The results were alike in the case of substrates with electron-withdrawing or electron-releasing group on aromatic ring. Substrates with Ac and Me groups on nitrogen were tolerated but that without any protection was unable to perform the reaction. The major product was the one formed *via* naphthalene C–H bond activation in the case of **143**-*EE* isomer with 1-naphthyl substituent. When the δ-position of the substrate carried 2,4-dichlorophenyl or 3,4-dichlorophenyl moiety, phenyl C–H activation occurred preferentially.

Jia *et al.* established a protocol for the formation of spirooxindoles **146** from indoles with C_2-substitution **145**, *via* reductive-Heck reaction with Pd catalyst.[93] Optimization was carried out using 5 mol% Pd(OAc)2, 3 equiv. HCO_2Na and 10 mol% $PCy_3 \cdot HBF_4$ in methanol at 100 °C (Scheme 75). Indoles with various substituents reacted easily without significant steric and electronic effects. 71–99% yield was accomplished with substituents at *ortho*-, *meta*- and *para*- to amino group of the 2-bromoaniline component. 90% of 7-azaspirooxindole was synthesised from indole having pyridine moiety. Product corresponding to β-H elimination was major for indole substrate with methyl at the third position. The spirooxindole product was not obtained with C2-substituted benzothiophene as the substrate but C2-substituted benzofuran **147** gave 66% yield for the corresponding product **148** (Scheme 76).

A procedure for the development of spirooxindoles **151** by employing a palladium catalyst was introduced by Yang *et al.* which involves a ring opening [3 + 2]-annualation.[94] The reaction was implemented using α,β-unsaturated nitroalkenes **149** and spirovinylcyclopropyl oxindole **150** in presence of 10 mmol% Xantphos and 5 mmol% $Pd(OAc)_2$ in toluene at rt for 12 h (Scheme 77). Both *N*-protected and *N*-unprotected spirovinylcyclopropyl oxindoles underwent the reaction but the dr



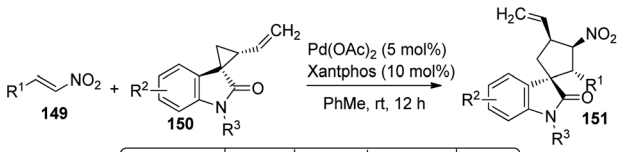
Scheme 75 Substrate scope for synthesis of spirooxindoles from indoles with C_2-substitution.



Scheme 76 Extension of reductive Heck reaction to benzofuran derived substrate.

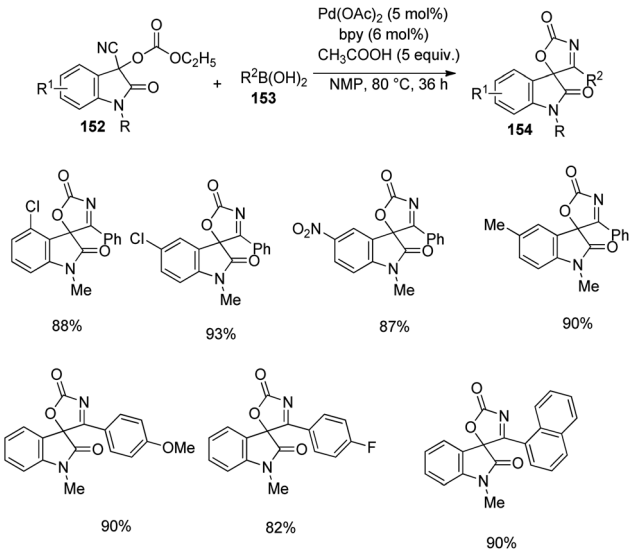
was lower with the unprotected ones. C5-, C6- or C7-substituted spirocyclopropane were tolerated. Efficient dr and good yield were obtained when C7-position of the substrate was having a Cl group. The yield dropped with nitroalkenes having *ortho*-substitution and the diastereoselectivity dropped with strong electron-releasing groups at *meta*- or *para*-position. (1*E*)-2-Phenylethenyl nitroalkene gave dr value of only 70 : 30.

Liao and co-workers studied arylboronic acid **153** addition to nitriles **152**, catalyzed by palladium, for the construction of spirooxindolyl oxazole-2(5*H*)-ones[95] **154**. The optimized reaction conditions were 5 mol% palladium(II)acetate, 6 mol% 2,2′-bipyridine and 5 equiv. acetic acid in NMP as the solvent at 80 °C (Scheme 78). The substrate scope exploration was carried out by taking different nitriles and boronic acids. *O*-Ethoxycarbonyl cyanohydrins derived from isatins were used as the nitriles and high yields were obtained from those with different groups on the nitrogen and 80–95% yields of the products were contributed by substrates with different groups on Ph ring. In the case of arylboronic acids those having electron-releasing and electron-deficient groups, excluding nitro, underwent the reaction. 9-Phenanthrene, β-naphthyl and α-naphthyl boronic acids were tolerated, but alkyl and hetero-aromatic ones were not tolerated. The group extended the reaction for the creation of other spirocycles also.



R^1	R^2	R^3	Yield (%)	*dr*
Ph	H	Boc	56	88:12
Ph	H	H	67	51:49
Ph	5-Me	Bn	64	95:5
Ph	6-Cl	Bn	69	76:24
Ph	7-Cl	Bn	67	91:9
3-OMeC_6H_4	H	Bn	77	76:24
2-ClC_6H_4	H	Bn	43	91:9
Thienyl	H	Bn	67	80:20
2-phenyl ethenyl	H	Bn	87	70:30

Scheme 77 Spirooxindole synthesis *via* ring-opening [3 + 2]-annulation catalyzed by Pd.



Scheme 78 Synthesis spirooxindolyl oxazol-2(5*H*)-one catalyzed by Pd.

Other substrates employed for Pd-catalyzed spirooxindole synthesis include derivatives of aryl triflates, anilides, indoles, nitroalkenes *etc.* and catalysts such as $Pd_2(dba)_3$, $PdCl_2$, $Pd(OAc)_2$ and so on. The respective yields of up to 58%, 98% and 87% were furnished by anilides, indoles and nitroalkenes.

9 Cu-catalyzed spirooxindole synthesis

Copper is highly sustainable, cheap and innocuous. Copper has high significance in the biological world. It is widely accepted by the synthetic community also. Through a two- and one-electron mechanism, copper can catalyze reactions and the coordination of Cu to π bonds and heteroatoms can be achieved easily.[96]

Various investigations on the Cu-catalyzed spirooxindole synthesis was reported from 2014 to 2020. These were majorly carried out using copper triflate, copper sulphate and copper ferrite nanoparticles compared to other copper catalysts. The nuleophilicity of alkenes can be greatly increased by copper triflate which is a soft Lewis acid. The advantage of nano copper ferrite catalyst is its easy recoverability and recyclability.

9.1 Reactions involving isatin derivatives

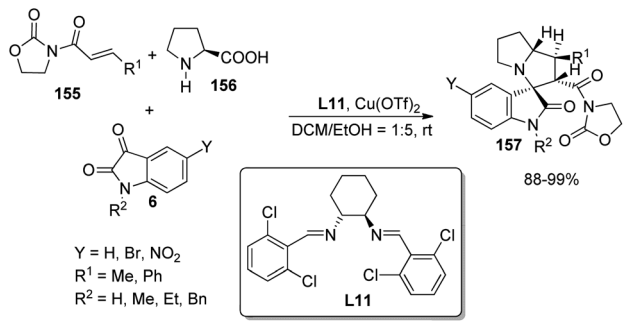
A 1,3-dipolar cycloaddition catalyzed by copper for the synthesis of spirooxindolopyrrolizidines **157** was reported in 2014.[97] The reaction between 3-(2-alkenoyl)-1,3-oxazolidin-2-ones **155**, (*S*)-proline **156** and isatin **6** was effected by $Cu(OTf)_2$ as the source of copper, cyclohexane-1,2-bis(arylmethyleneamine) carrying chloro-substituent as the ligand (**L11**) [$Cu(OTf)_2$: **L11** = 1 : 1.1] in a mixture of EtOH and DCM as the solvent at room temperature (Scheme 79). The desired spirooxindole product was obtained by the [3 + 2] cycloaddition between the dipolarophile and azomethine ylide formed *in situ* from (*S*)-proline and isatin. They could attain the yield of 88–99% and ee of 87–95%.

In the next year, the synthesis of spirooxindolopyrrolizidines using the same method by changing the ligand and solvent was reported.[98] Here they used cyclohexane-1,2-bis(arylmethyleneamine) having ^{t}Bu substituent as the ligand (**L12**) and ethanol as the solvent which afforded 85–98% yield and 82–92% ee (Scheme 80).

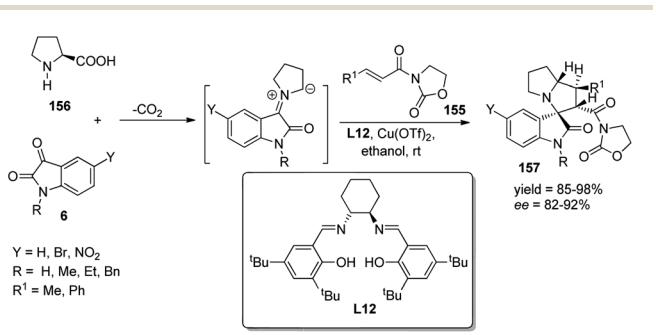
A green method for the production of indan-1,3-dione grafted spirooxindolopyrrolizidines linked 1,2,3-triazoles **161** with Cu(II) catalyst was narrated by Khurana *et al.* in 2015.[99] Here, azides **158**, *N*-propargylated isatins-derivative of **6**, sarcosine **159**, aldehydes **69** and indan-1,3-diones **160** undergo a one-pot reaction which was proceeded with 10 mol% of aq. $CuSO_4 \cdot 5H_2O$ and 20 mol% of aq. sodium ascorbate in PEG-400 at 80 °C (Scheme 81). Here sodium ascorbate will convert Cu(II) into Cu(I) and the reaction proceeds through Knoevenagel condensation/two consecutive 1,3-dipolar cycloaddition pathway. The scope of the reaction was investigated by using different azides and aldehydes.

In 2016, they described a four-component reaction of aryl azides-derivative of **158**, sarcosine **159** or L-proline **156**, *N*-propargylated isatin-derivative of **6** and coumarin-3-carboxylic acid derivatives **162** through copper-catalyzed [3 + 2] cycloaddition for the building up of spirooxindole pyrrolizidine linked 1,2,3-triazoles **163**.[100] The reaction is found to have increased regio- and stereoselectivity when catalyzed by $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in presence of acetic acid (glacial) at 60 °C (Scheme 82). Differently substituted aryl azides were utilized to investigate the generality of the procedure. Electron-withdrawing as well as electron-releasing groups afforded the spirooxindole products in 71–90% yield.

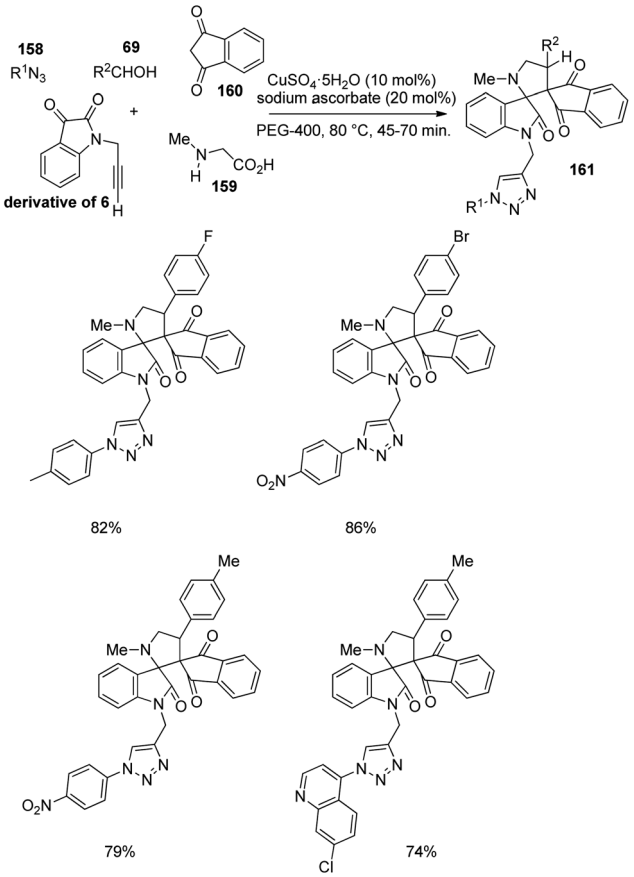
An eco-friendly magnetic copper ferrite NPs catalyzed one-pot reaction for the synthesis of spirooxindoles derivative of



Scheme 79 Synthesis of spirooxindolopyrrolizidine through 1,3-dipolar cycloaddition catalyzed by $Cu(OTf)_2$ and cyclohexane-1,2-bis(arylmethyleneamine) ligand carrying chloro substitution.



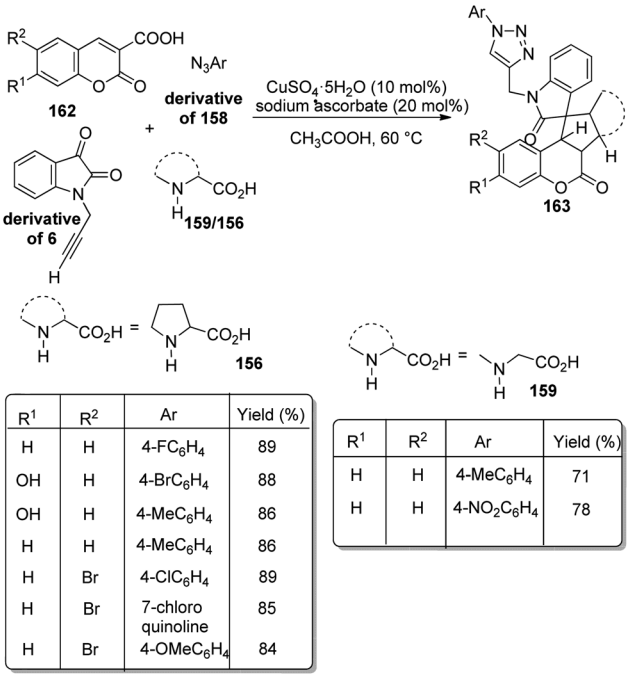
Scheme 80 Spirooxindolopyrrolizidine synthesis through 1,3-dipolar cycloaddition catalyzed by $Cu(OTf)_2$ salen complex.



Scheme 81 Substrate scope for Cu(I)-catalyzed indan-1,3-dione grafted spirooxindolopyrrolizidine linked 1,2,3-triazoles synthesis.

63, **64**, **164**, **165** was reported.[101] The three-component reaction of dicyanomethane **28**, Michael-donors and isatin **6** involved 7 mol% of $CuFe_2O_4$ NPs as the catalyst and water–ethanol mixture as solvent under reflux temperature (Scheme 83). 80–92% yields were obtained by using 4-hydroxycoumarin **50**, 1,3-cyclohexanedione-derivative of **29**, barbituric acid-derivative of **30** and thiobarbituric acid-derivative of **30** as Michael-donors. Mechanistically the reaction follows a Knoevenagel condensation/Michael addition/enolization sequence. Simple separation and reusability of the catalyst are the advantages of this green protocol.

Mo and co-workers developed a method for the synthesis of spirooxindoles *via* Cu-catalyzed reaction between alkenyl boronic acids **166** and 3-(hydroxyimino)indolin-2-ones **167**.[102] In this method isatin oximes were *N*-vinylated selectively and the *N*-vinyl nitrones **168**, **169** thus obtained were rearranged to the corresponding spirooxindoles **170**, **171** by heating (Scheme 84). The reaction conditions of 10 mmol% $Cu(OAc)_2$, 3 equiv. pyridine and 6 equiv. sodium sulphate in methanol at room temperature offered mono *N*-vinylated product **168**. When the catalyst amount and the solvent were changed to 2 equiv. and 1,2-dichloroethane respectively, the corresponding double *N*-vinylated products **169** were obtained. These *N*-vinyl nitrones offered 32–80% of the spirooxindole products by heating in toluene at 120–140 °C. Decomposition happened to mono *N*-



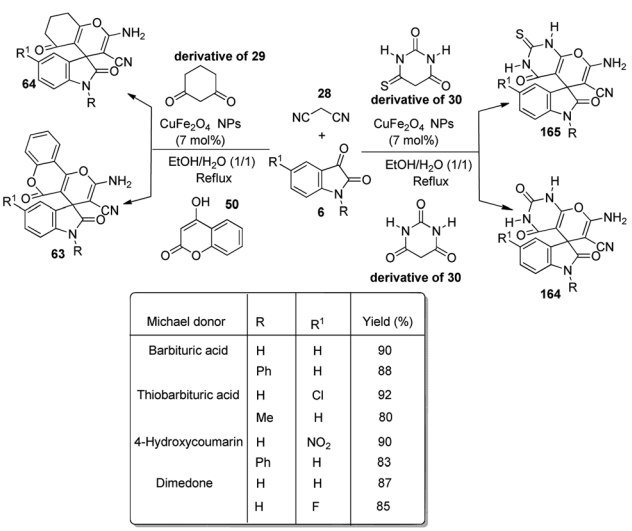
R^1	R^2	Ar	Yield (%)
H	H	4-FC_6H_4	89
OH	H	4-BrC_6H_4	88
OH	H	4-MeC_6H_4	86
H	H	4-MeC_6H_4	86
H	Br	4-ClC_6H_4	89
H	Br	7-chloro quinoline	85
H	Br	4-$OMeC_6H_4$	84

R^1	R^2	Ar	Yield (%)
H	H	4-MeC_6H_4	71
H	H	4-$NO_2C_6H_4$	78

Scheme 82 Spirooxindole pyrrolizine linked 1,2,3-triazole synthesis through copper-catalyzed four-component reaction.

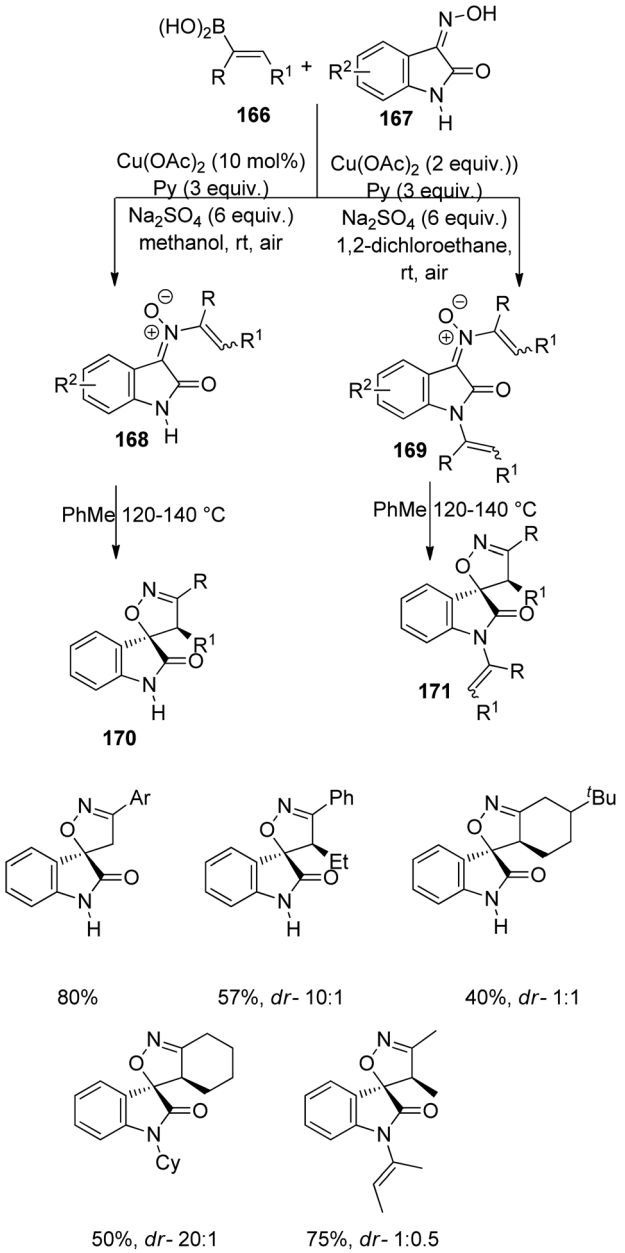
vinylated products when R^1 = *n*-Pr, *n*-Bu, $(CH_2)_4Cl$, $(CH_2)_3$-CO_2Me, *p*-FC_6H_4, *p*-$MeOC_6H_4$ and Ph.

A powerful protocol for the construction of pyrrolo[1,2-*a*] indole spirooxindoles **174** using a Cu catalyst *via* Friedel–Crafts alkylation/cyclization path was demonstrated by Bu *et al.*[103] The reaction between oxodienes derived from isatin **172** and 3-substituted indoles **173** was optimized in presence of catalyst $Cu(OTf)_2$ (20 mol%) at 35 °C with acetonitrile solvent (Scheme 85). The scope of the reaction was examined by using isatin-derived oxodienes and different 3-alkyl/aryl indoles. The yield



Michael donor	R	R^1	Yield (%)
Barbituric acid	H	H	90
	Ph	H	88
Thiobarbituric acid	H	Cl	92
	Me	H	80
4-Hydroxycoumarin	H	NO_2	90
	Ph	H	83
Dimedone	H	H	87
	H	F	85

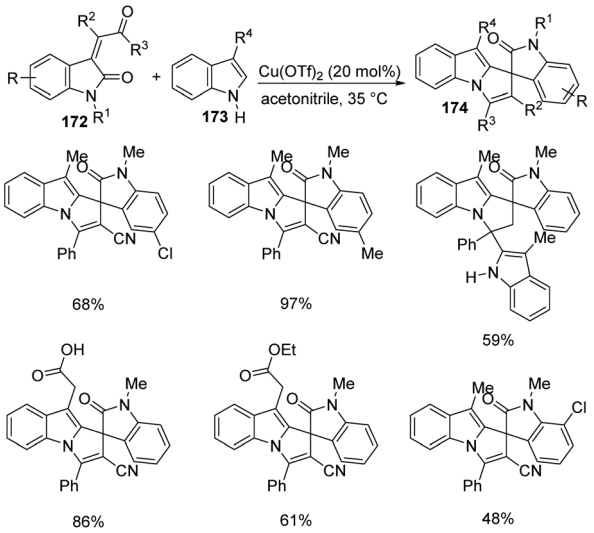
Scheme 83 Synthesis of spirooxindoles using magnetic copper ferrite NPs as the catalyst.



Scheme 84 Copper-catalyzed *N*-vinyl nitrone synthesis and subsequent conversion to spirooxindoles.

was lower with electron-deficient groups on the oxodiene aromatic ring. The substituent position also affected the yield but the nature of the substituents on N did not. Indoles with various aryl and alkyl substituents on the C3-position underwent the reaction and those with amino, hydroxyl, ester and carboxylic acid groups were well tolerated. Upto 99% spirooxindole product was obtained by executing the reaction in gram scale.

A possible mechanism for the reaction is interpreted in Scheme 86. Here, $Cu(OTf)_2$ which is a Lewis acid, caused activation of oxodiene derived from N-methyl isatin **172.** An intermediate **175** was formed through Friedel–Crafts alkylation in which 3-methyl indole-derivative of **173,** attacked the activated

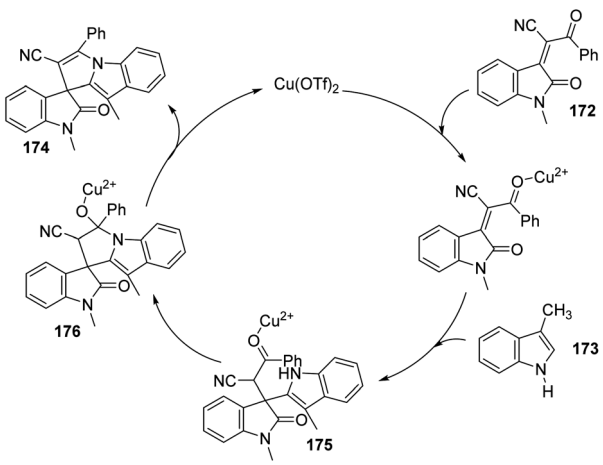


Scheme 85 Synthesis of pyrrolo[1,2-*a*]indole spirooxindole employing $Cu(OTf)_2$ as the catalyst.

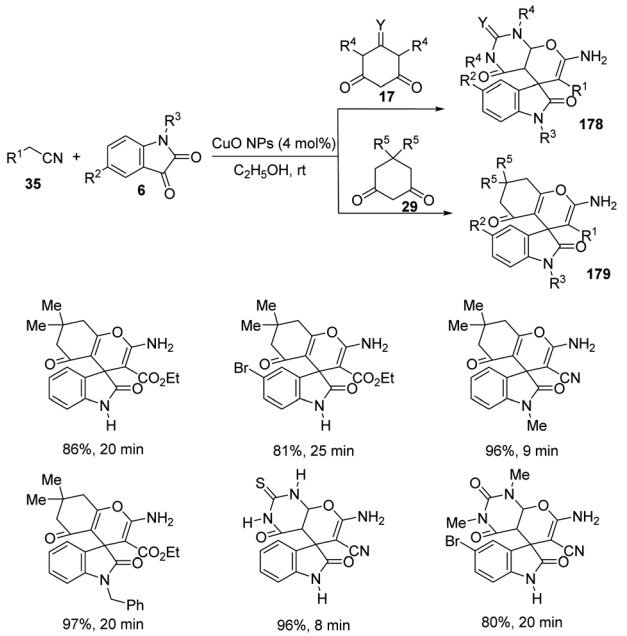
oxodiene. Another intermediate **176** was obtained by the attack of electrophilic N of indole on the carbonyl adjacent to the aryl ring. The pyrrolo[1,2-*a*]indole spirooxindole **174** was acquired from this intermediate by the elimination of a water molecule. The catalyst was regenerated in the last step.

An efficient method for spirooxindole **178, 179** synthesis from derivatives of isatin **6,** cyclic 1,3-diketone **177, 29** and activated methylene compound **35,** using CuO NPs as catalyst was reported by Moradi and Ataei.[104] The reaction was effected by CuO NPs (4 mol%) in ethanol solvent at rt (Scheme 87). Dicyanomethane gave higher yields than ethylcyanoacetate. 5-Bromoisatin gave the lowest yield compared to other isatin derivatives. In the case of various 1,3-diketones used, the yield was lowest with *N*,*N*-dimethyl barbituric acid.

An efficient and novel approach for the formation of derivatives of spirooxindole **183, 184** through environmentally



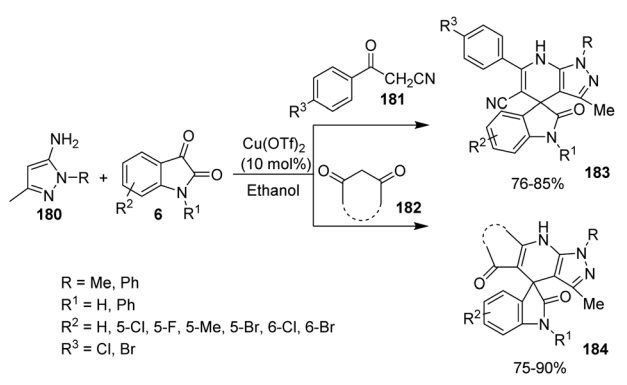
Scheme 86 The possible mechanism for the reaction [reproduced with permission from ref. 103].



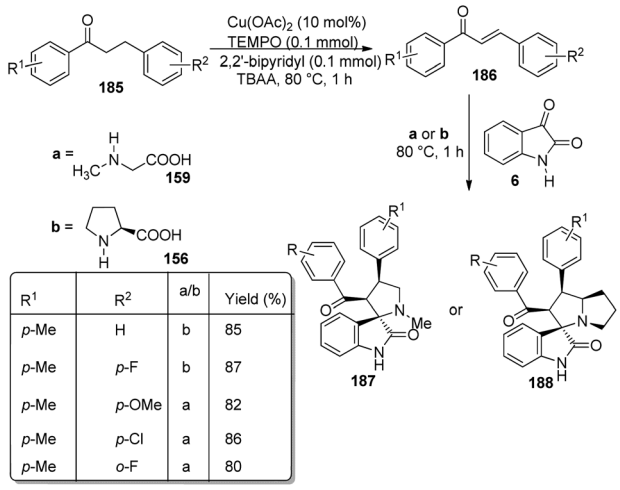
Scheme 87 Substrate scope for CuO nanoparticle-catalyzed spirooxindole synthesis.

benign copper triflate catalyzed multi-component reaction of 1,3-dicarbonyl compounds **182** or β-oxo-benzenepropanenitrile **181**, 5-aminopyrazole **180** and isatin **6** has been put forward.[105] The reaction in the presence of $Cu(OTf)_2$ as the catalyst and ethanol as solvent ensued in different spirooxindole derivatives in 75–90% yield (Scheme 88).

Khan and co-workers introduced a Cu/TEMPO catalyzed generation of spirooxindoles **187**, **188** through a dehydrogenative cycloaddition.[106] First alkylated ketones **185** were used as the substrates which undergo dehydrogenation in presence of 10 mol% of $Cu(OAc)_2$ as the catalyst, 0.1 mmol of TEMPO and 0.1 mmol of 2,2′-bipyridyl as the additives in TBAA (tetrabutylammonium acetate) as the solvent at 80 °C, to give an alkene **186**. After dehydrogenation isatin-derivative of **6** and sarcosine **159** or L-proline **156** were added which resulted in desired products **187**, **188** through 1,3-dipolar cycloaddition reaction (Scheme 89). Both electron-deficient and electron-releasing



Scheme 88 Synthesis of spirooxindoles through $Cu(OTf)_2$-catalyzed three-component reaction.



R^1	R^2	a/b	Yield (%)
p-Me	H	b	85
p-Me	*p*-F	b	87
p-Me	*p*-OMe	a	82
p-Me	*p*-Cl	a	86
p-Me	*o*-F	a	80

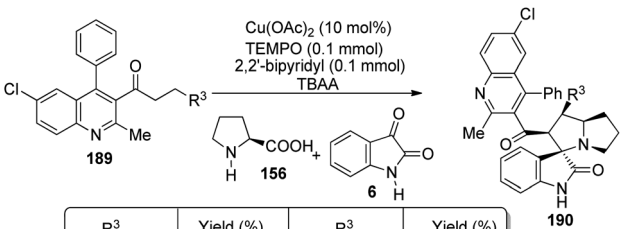
Scheme 89 Spirooxindole synthesis through dehydrogenative cycloaddition of alkylated ketones using Cu/TEMPO catalyst.

groups in the substrate afforded 80–87% of the spirooxindole products. Then quinolinyl-alkylated ketones of type 1, **189** and 2, **191** were used as substrates under the same reaction conditions and the desired products **190**, **192** were obtained in 65–84% yields (Schemes 90 and 91). Anti-diabetic and anti-oxidant properties were exhibited by almost all of the compounds produced.

Isatins were availed as the starting materials in all of the metal classes mentioned above. Majority of the approaches were eco-friendly and provided excellent enantio- and diastereoselectivities and yields.

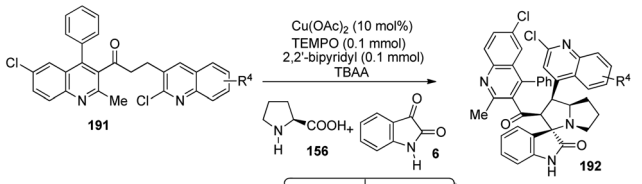
9.2 Reaction involving benzoic acid derivatives

Zhang *et al.* established an atom-economical procedure which involves Cu-catalyzed oxidative annulation for the fabrication of 3-spirooxindole benzofuranones[107] **194**. The reaction of derivatives of benzoic acid **193** under the optimized conditions of 20 mol% $CuBr_2$, 2 equiv. sodium methoxide in DMF at 150 °C under O_2 atmosphere afforded the required product **194** in 55–86% yield (Scheme 92). The yield was lower for substrates with strong electron-withdrawing substituents on aniline ring



R^3	Yield (%)	R^3	Yield (%)
Ph	81	*o*-ClC_6H_4	72
p-MeC_6H_4	84	*m*-BrC_6H_4	70
p-ClC_6H_4	75	*p*-BrC_6H_4	75

Scheme 90 Spirooxindole synthesis through dehydrogenative cycloaddition of quinolinyl alkylated ketones of type 1 using Cu/TEMPO catalyst.



R^4	Yield (%)
H	70
o-Me	68
m-Me	65
p-Me	72
o,p-diMe	70

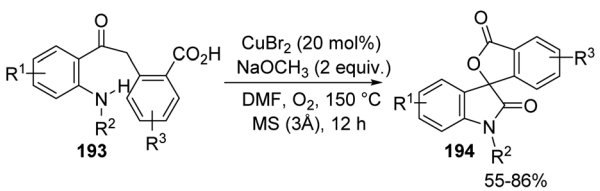
Scheme 91 Spirooxindole synthesis through dehydrogenative cycloaddition of quinolinyl alkylated ketones of type 2 using Cu/TEMPO catalyst.

compared to strong electron-releasing ones. Various *N*-substituents like Me, Bn and ^{i}Pr used to give the anticipated product in good yields. Substituted benzoic acid ring with electron-deficient and -rich groups was explored and was found fruitful under the reaction.

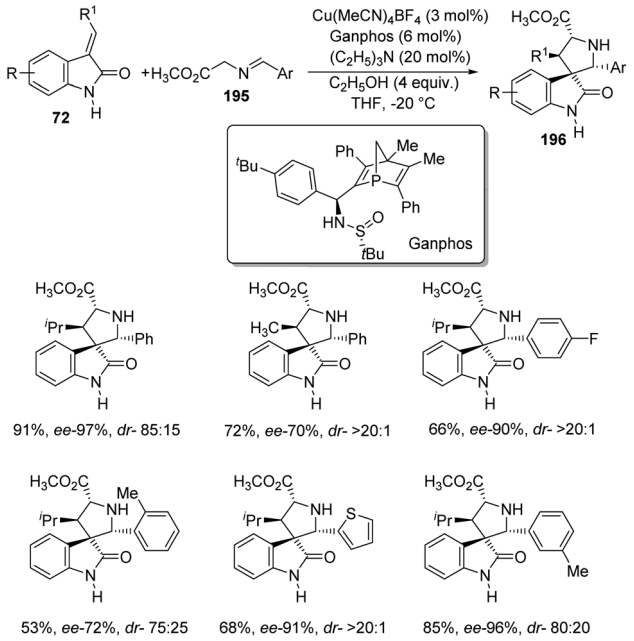
While considering copper-catalyzed spirooxindole synthesis, the yields given by benzoic acid derivatives were slightly less compared to other derivatives-isatins and methyleneindolinones.

9.3 Reaction involving methyleneindolinone derivatives

A method for the production of spirooxindoles **196** catalyzed by Cu(I)/Ganphos was established by Duan *et al.*[108] Diverse spirooxindoles **196** were produced by the reaction between 3-methylene-2-oxindoles- derivatives of **72** which are alkyl substituted and glycine imino esters **195** under the conditions of 3 mol% $Cu(MeCN)_4BF_4$, 6 mol% Ganphos which is a chiral phosphine ligand, 20 mol% triethylamine and 4 equiv. ethanol in THF at −20 °C (Scheme 93). In the case of 3-methylene-2-oxindoles, the enantioselectivities were affected by the alkyl substituents, and the methyl substituents gave only 70% ee. The yield, diastereo- and enantioselectivities were good with substrates emanated from aliphatic ketones. In the case of imino esters, decreased enantioselectivities and yields were obtained from those bearing Ph ring with *o*-substitution, but the electronic nature of the substituents had no significant



Scheme 92 Synthesis of 3-spirooxindole benzofuranone *via* copper-catalyzed oxidative annulation.

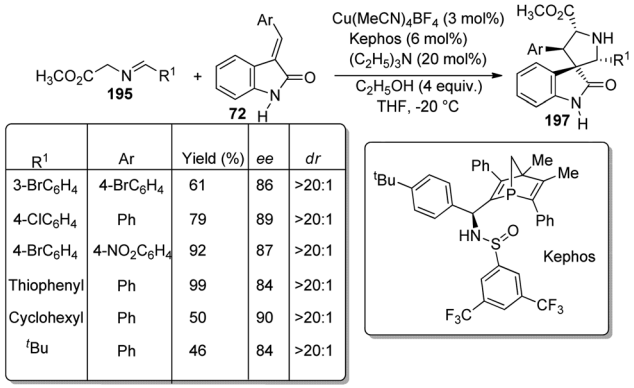


Scheme 93 Synthesis of spirooxindoles using [Cu(I)/Ganphos] catalytic system.

effect. 91% ee was given by methyleneindolinone with thienyl group as substituent.

Next the reaction of iminoesters was performed with 3-methylene-2-oxindoles- derivative of **72** which are substituted with aryl groups. Here they changed the ligand from Ganphos to Kephos, and kept the other conditions as such (Scheme 94). Diversely substituted iminoesters **197** and benzylidene indolinones underwent the reaction even those including aliphatic iminoesters. The group further examined the amount of catalyst and found that the reaction proceeded even with 0.1 mol% of the catalyst. Excellent yield and good enantioselectivities were acquired by doing the reaction in gram scale.

In the case of methyleneindolinone derivatives, Ni, Fe, Pd and Cu were used as the catalysts and could achieve the yield up to 99% with Ni- and Cu based catalysts. A diastereoselectivity of up to 99 : 1 and enantioselectivity of >99% were provided by



R^1	Ar	Yield (%)	*ee*	*dr*
3-BrC_6H_4	4-BrC_6H_4	61	86	>20:1
4-ClC_6H_4	Ph	79	89	>20:1
4-BrC_6H_4	4-$NO_2C_6H_4$	92	87	>20:1
Thiophenyl	Ph	99	84	>20:1
Cyclohexyl	Ph	50	90	>20:1
^{t}Bu	Ph	46	84	>20:1

Scheme 94 Synthesis of spirooxindoles using [Cu(I)/Kephos] catalytic system.

$FeCl_3$ and $Pd_2(dba)_3 \cdot CH_3Cl_3$ respectively. The catalyst loading of 3 mol% was enough for the copper(I)/Ganphos catalyst system and it could be reduced to even 0.1 mol%.

10 Conclusion

Spirooxindoles form an extensive class of alkaloids and other artificial compounds. They have appreciable biological and pharmaceutical applications. In organic chemistry, the evolution of synthetic procedures for spirooxindole derivatives is having soaring importance. Transition metal-catalyzed synthesis is the highest probed one among numerous described synthetic approaches. Here we have given an account of transition metal-catalyzed synthesis of spirooxindoles. There is copper, palladium, iron, nickel *etc.* catalyzed approaches through which nitrile-, pyrrolidine-, benzofuranone-, *etc.* containing spirooxindoles were synthesized efficiently. Different tactics such as oxidative annulation, 1,3-dipolar cycloaddition, Heck/cyanation, hetero-Pictet–Spengler approach and so on were applied, most of them involving wide functional group tolerability and one-pot multi-component pathways. Several green and nano catalysts were employed and diverse spirooxindole derivatives, with up to eight-membered rings, were produced with high diastereo- and enantioselectivities. The advantage of catalyst recoverability with the aid of magnet was utilized in case of catalysts like $MnFe_2O_4$, $CoFe_2O_4$@SiO_2 *etc.* In the case of catalysts like $Cu(OTf)_2$, $MnFe_2O_4$ and $Fe(OTf)_2$, the Lewis acidic sites in them triggered the reaction. In greater number of the reactions, the catalyst employed was nanoparticles which possess individual characteristics compared to the bulk, because of their large surface area to volume ratio and nano size. Derivatives of isatins, isothiocyanatooxindoles, methyleneindolinones *etc.* were generally used as the starting materials in contrast to derivatives of benzoic acids, aryl triflates, anilides and so on. It is anticipated that in the close future, transition metal-catalyzed spirooxindole synthesis would undergo huge investigations to fine tune the reaction for better regio-, diastereo- and enantioselectivities.

Conflicts of interest

There are no conflicts to declare.

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