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Recent advances in spirocyclization of indole derivatives

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Spiroindolines and spiroindoles are an important class of spirocyclic compounds present in a wide range of pharmaceuticals and biologically important natural alkaloids. Various spiroindolines and spiroindoles possess versatile reactivity which enables them to act as precursors for other privileged heterocycles. In view of the importance of this scaffold, many researchers focused their efforts to develop facile and mild synthetic methods for spirocyclization of indoles. However, the synthesis of spiroindolines and spiroindoles is known to be difficult due to rapid 1,2-migration to restore aromaticity. This review aims to briefly discuss the latest developments to access highly functionalized spiroindolines and spiroindoles to stimulate further research in the field to find new and efficient methodologies for accessing new spiroindolines and spiroindoles.

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Key learning points
(1) This review will provide a good introduction to the field of spirocyclization reactions of indoles and will serve as a springboard for further reading.
(2) This review highlights the recent and significant advances in the construction of spiroindolines and spiroindoles.
(3) It highlights the recently used ligands and catalysts to achieve diastereoselective and enantioselective synthesis of spiroindolenines.

1. Introduction

Spirocyclic compounds are unique because of their rigidity and three-dimensional geometries. Spiroindolines and spiroindoles are an important class of spirocyclic compounds present in a wide range of pharmaceuticals and biologically important natural alkaloids.[1] There are two classes of spiroindoles based on the position of the spirocycle: C2-spirocyclicindolines and C3-spirocyclicindoles or C3-spirocyclicindolines. These spirocyclic compounds are rich in biological activities and are widespread in nature[2] (Fig. 1 and 2). Spiroindolines and spiroindoles possess versatile reactivity which enables them to act as precursors for other privileged heterocycles including indolines, oxindoles, carbazoles, indoles and others.[3]

The spirocyclic core structure was first reported by A. Pictet and T. Spengler in 1911 as an intermediate, which rapidly underwent 1,2-migration to restore aromaticity. The first successful isolation of a spiroindoline was achieved in 2010 by the research group of S.-L. You utilizing an Ir catalyst.[4] Since then, many synthetic strategies have been successfully applied for the synthesis of spiroindolines (sometimes referred as spiroindolenines or spirocyclic 3*H*-indoles) which were reviewed by Unsworth and co-workers a few years back.[2] They have described various synthetic strategies for the synthesis of spirocyclic indolenines mainly grouped into three categories: (1) interrupted Fischer indolisations, (2) dearomatization reactions of indoles, and (3) condensation reactions.

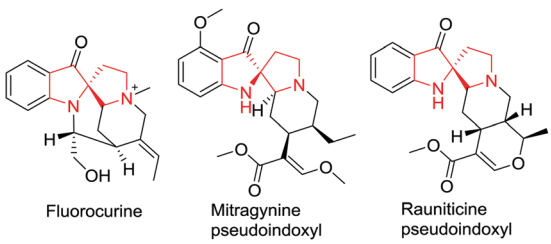

Fig. 1 Natural alkaloids containing the C2-spirocyclicindole core structure.

In recent years, spirocyclization has attracted great interest of chemists around the world, proved by hundreds of reports in

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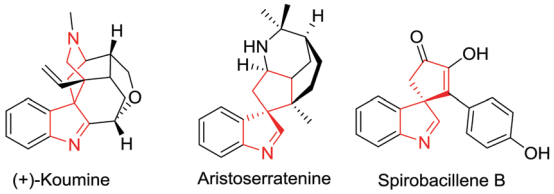

Fig. 2 Natural alkaloids containing the C3-spirocyclicindoline core structure.

this field appearing within the last two years. Looking at the biological significance and synthetic challenges for the construction of spiroindolines and spiroindoles, there is an urgent need to compile the recent developments in the field. The recently developed methodologies to access diverse spiroindolines and spiroindoles are divided into categories based on their structural complexity as detailed in Fig. 3.

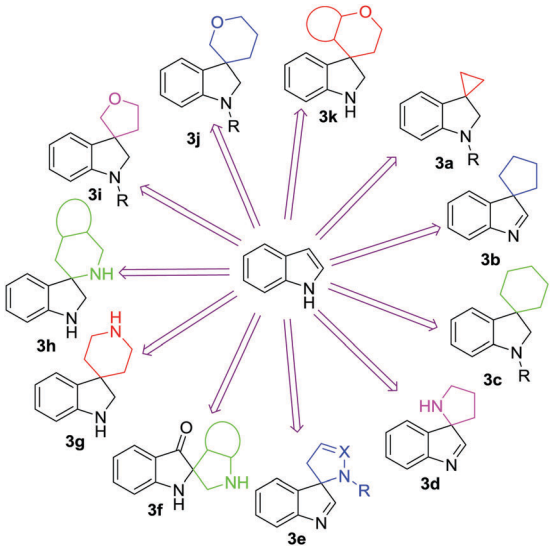

Fig. 3 Different categories of spiroindolines and spiroindoles.

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2. Spirocyclization of indoles

Indoles may be spirocyclized *via* their 2- or 3-position to give variably substituted spirocyclic indolines and spiroindoles as discussed in the following sub-sections.

a. Spirocyclization *via* the 2-position of the indole skeleton

Indoles containing a C2-spirocyclic quaternary carbon center are important structural subunits found in a variety of indole alkaloids such as fluorocurine, mitragynine pseudoindoxyl and rauniticine pseudoindoxyl (Fig. 1). Despite their important biological properties, C2-spirocyclic indolines are scarcely explored as compared to C3-spirocyclic indolines and spiroindoles. This section is devoted to the latest developments in C2-spirocyclic indoline synthesis.

Li and co-workers[5] have reported a novel copper-catalyzed oxidative dearomatization/spirocyclization of indole-2-carboxamides

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Leonid G. Voskressensky received his PhD degree in Organic Chemistry from the Peoples Friendship University of Russia in 1999. In 2001 he joined the Prof. Cosimo Altomare (Universita Degli Studi di Bari, Italy) group as a Post-Doc Fellow (Medicinal Chemistry). In 2001 he became Assistant Professor, in 2006, Associate Professor and in 2011, Full Professor of the Organic Chemistry department of the RUDN. Since 2013, he has been the Dean of the Science Faculty of the RUDN. His group scientific interests mainly focus on domino reactions methodology, new MCR reactions as well as medicinal chemistry.

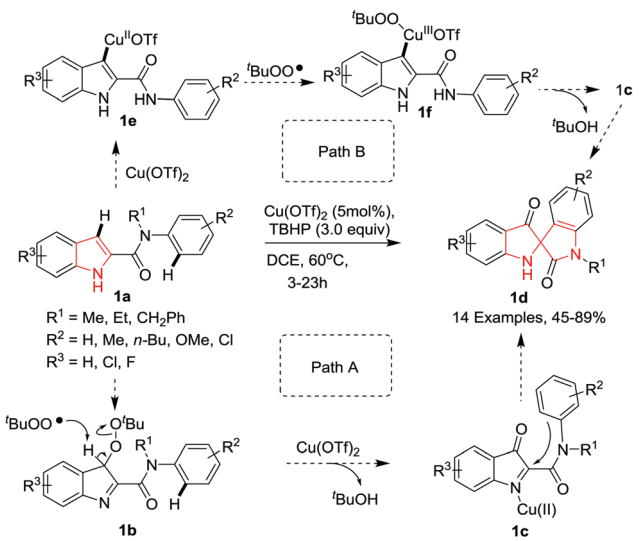
Erik V. Van der Eycken

Erik Van der Eycken received his PhD degree (1987) in organic chemistry from the University of Ghent, with Prof. Maurits Vandewalle. From 1988 to 1992, he worked as a scientific researcher at the R&D-laboratories of AGFA-Gevaert, Belgium and moved back to the University of Ghent in 1992. In 1997 he became a Doctoral-Assistant at the Katholieke Universiteit Leuven. He has been a visiting scientist at the University of Graz (C. Oliver Kappe), at The Scripps Research Institute (K. Barry Sharpless), and at Uppsala University (Mats Larhed, Anders Hallberg). He was appointed Professor at the Katholieke Universiteit Leuven in 2007.

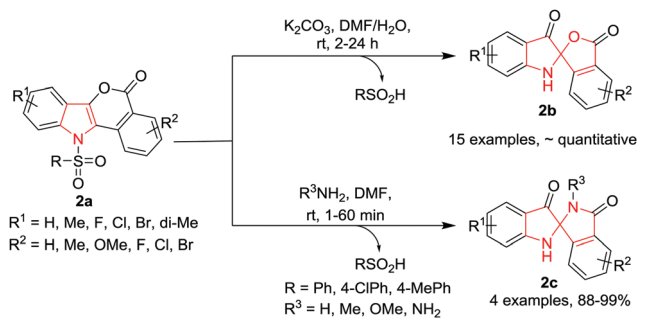
1a using *tert*-butyl hydroperoxide (TBHP) as oxidant, giving access to C2-spiro-pseudoindoxyls **1d**. The reaction proceeds smoothly under optimized conditions where $Cu(OTf)_2$ proved to be the best catalyst among other copper salts in DCE at 60 °C. It was found that a variety of *N*-alkyl substituents (R^1) on the amide group were compatible with the reaction delivering the desired spiro compounds. With various electron-donating groups (R^2) at the 4-position of the *N*-phenyl substituent good yields were obtained. However, electron-withdrawing groups led to low yields due to the decreased nucleophilicity of the *N*-phenyl ring. Interestingly, when a 2-methyl substituted *N*-phenyl ring was employed, two isomeric spirocyclized products were obtained in almost equal amount, indicating that both the *ortho* C–H bonds on the *N*-phenyl ring could be competitively functionalized. Further, indole-2-carboxamide bearing a tetrahydroquinoline on the amide moiety cyclized readily under the standard reaction conditions to afford the highly strained polycyclic spiroindole. Substitution of chlorine or fluorine on the indole was well tolerated and gave access to the corresponding products in moderate yields. The reaction proceeds probably *via* either of two pathways where path **A** involves the formation of a highly reactive 3*H*-indol-3-one intermediate **1b** followed by aromatic electrophilic substitution with the *N*-aryl ring of the amide moiety to produce the product **1d**. Alternatively, path **B** involves the formation of indolylcopper(II) intermediate **1e** followed by reaction with the *tert*-butylperoxy radical to give the Cu(III) intermediate **1f** which undergoes reductive elimination followed by elimination of *t*-BuOH to deliver the same intermediate **1c** as in path **A** (Scheme 1).

Du, Zhao and co-workers[6] have developed a new strategy for the ring contraction of isochromeno[4,3-*b*]indol-5(11*H*)-ones **2a** *via* an unusual nucleophile-induced disproportionation/spirocyclization cascade process to gain access to *N*-unsubstituted spiro[indoline-2,1′-isobenzofuran]-3,3′-diones **2b** and spiro-[indoline-2,1′-isoindoline]-3,3′-diones **2c** without using any transition-metal catalyst or oxidant. The reaction proceeds smoothly at room temperature using K_2CO_3 as the base in a mixture of DMF and H_2O (9 : 1) as the solvent. The use of strong bases such as NaOH or KOH led to a significant decrease of the yields, although the reactions were completed within short times. Diversely substituted isochromeno-[4,3-*b*]indol-5(11*H*)-ones **2a** were converted into the corresponding spiro products in almost quantitative yields. It has been observed that substitution (R^1 and R^2) on the aromatic rings of **2a** does not affect the yields of the product. However, an electron-withdrawing halogen as R^2 was found to speed up the reactions whereas electron-donating groups slow them down. Further, replacement of the tosyl group with other sulfonyl groups such as 4-$ClPhSO_2$ or $PhSO_2$ gave access to the corresponding product **2b** in quantitative yield. However, with a butanesulfonyl group a mixture of the desired product **2b** was obtained in a moderate yield, along with the deprotected starting substrate. Interestingly, the scope of other nucleophiles revealed that nitrogen nucleophiles, such as $NH_3{\cdot}H_2O$, $MeNH_2$ in aqueous solution, or $MeONH_2$, gave the corresponding *N*,*N*′-(un)substituted ketal **2c** in excellent yields within a few minutes. However, sulfur nucleophiles, such as Na_2S and $(NH_4)_2S$, failed to give the *N*,*S*-ketal product but furnished the corresponding deprotected isochromeno[4,3-*b*]indol-5(11*H*)-one as the sole product (Scheme 2).

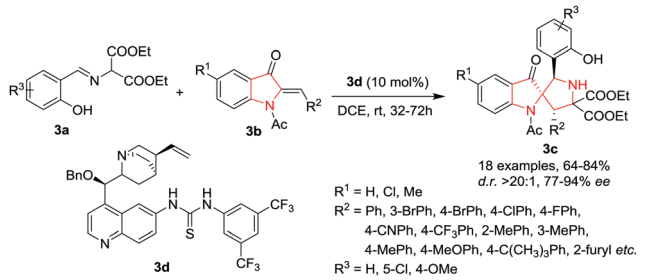
Hu, Xu and co-workers[7] have developed a novel approach for the construction of 2,2′-pyrrolidinyl-spirooxindoles **3c** by employing a hydrogen-bonding network activation strategy through a catalytic asymmetric [3+2] cycloaddition reaction. The reaction proceeds well by reacting aromatic aldimines **3a** with (*Z*)-1-acetyl-2-benzylideneindolin-3-ones (azaaruone) **3b** in the presence of cinchona-thiourea based catalyst **3d** in DCE at rt. Under the optimized reaction conditions, a variety of electron-donating and electron-withdrawing substituents on the phenyl ring of the 2-benzylideneindolin (R^2) gave access to high yields of the product with excellent diastereoselectivity and enantioselectivity (>20 : 1 d.r. and 95% e.e.). Replacement of the phenyl ring with a heterocyclic system such as furan or piperonyl aldehyde resulted in good product yields but with lower enantioselectivities. Electron-withdrawing or electron-donating groups at the 5-indolin (R^1) were also found to be well tolerated and provided similar results. Control experiments using pure (*Z*)- and (*E*)-azaaurone, respectively, revealed that under the optimal reaction conditions, the same



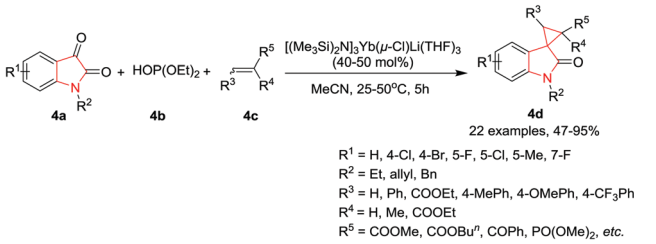
Scheme 1 Synthesis of C2-spiropseudoindoxyls **1d**.



Scheme 2 Synthesis of *N*-unsubstituted spiro[indoline-2,1′-isobenzofuran]-3,3′-diones **2b** and spiro-[indoline-2,1′-isoindoline]-3,3′-diones **2c**.



Scheme 3 Synthesis of 2,2′-pyrrolidinyl-spirooxindoles **3c**.



Scheme 4 Synthesis of spiro[cyclopropan-1,3′-oxindoles] **4d**.

product **3c** was obtained with similar yields and stereoselectivities (Scheme 3).

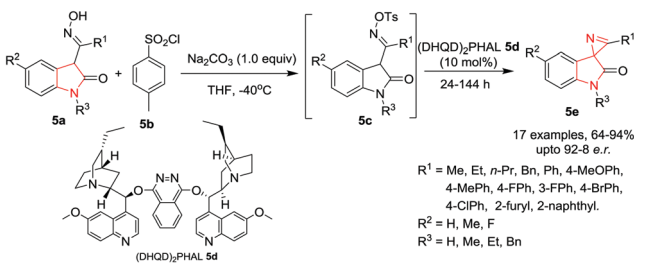
b. Spirocyclization *via* the 3-position of the indole skeleton

The interesting biological activities possessed by many C3-spirocyclic indolines and spiroindoles have attracted the interest of medicinal chemists to extensively explore this class of compounds. This section has been subdivided as per the nature of the C3-spirocyclic ring of the indole moiety for better understanding.

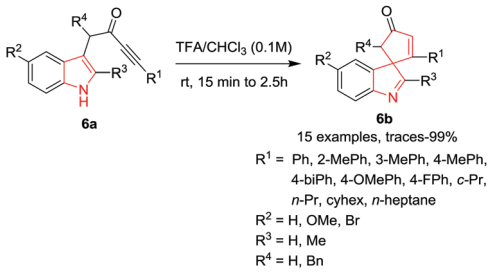
1. Three membered spiro-cyclic compounds. Xue, Xu and co-workers[8] have developed a tandem reaction of isatin **4a**, dialkyl phosphite **4b**, and an activated alkene **4c** for the synthesis of spiro[cyclopropan-1,3′-oxindoles] **4d** in the presence of a lanthanide amide based catalyst, $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$, in CH_3CN at 25 °C. The reaction proceeds *via* a four-step mechanism involving the Pudovik reaction, a Brook rearrangement, the Michael addition, and an intramolecular nucleophilic substitution. The substituents at the 2- and 3-positions of the cyclopropane unit are obtained in a *trans* configuration. Under the optimum reaction conditions, activated alkenes such as acrylates gave the corresponding 1′-allylspiro[cyclopropane-1,3′-indolin]-2′-ones in moderate to excellent yields, whereas cinnamates were found to be less reactive and required an enhanced reaction temperature (50 °C) to give high product yields. Interestingly, the reaction with diethyl maleate or diethyl fumarate gave the same main product accompanied by a small amount of its stereoisomer. Among the α,β-unsaturated ketones, 4-phenylbut-3-en-2-one gave only a moderate yield, whereas the use of chalcones resulted in high yields. Chalcones with the aryl at the 3-position, bearing electron-donating groups, afforded the corresponding products in higher yields than those bearing electron-withdrawing groups. The reaction also tolerated heteroaromatics. Further, isatins substituted at the 4-, 5-, or 7-position undergo the reaction with good to high yields, whereas *N*-ethyl and *N*-benzyl substituted isatins required an increased catalyst loading of 50 mol% to afford the corresponding spiro compound in good yields (Scheme 4).

Xu, Yuan and co-workers[9] have employed the Neber reaction process for the synthesis of chiral spirooxindole 2*H*-azirines **5e** by reacting 3-*O*-sulfonyl ketoxime **5c** which is *in situ* generated from isatin ketoxime **5a** and sulfonyl chloride **5b**. The reaction proceeds smoothly in the presence of hydroquinidine 1,4-phthalazinediyl diether $[(DHQD)_2PHAL]$ **5d** as catalyst and Na_2CO_3 as base in THF at −40 °C to give the spiro compound in high yields and high enantiomeric ratio (e.r.) under the optimized conditions. R^1 substituents like ethyl, *n*-propyl, benzyl or phenyl could be used without affecting the yields. Substitution on isatin (R^1) with both electron-donating and electron-withdrawing substituents, bulky groups such as a naphthyl group and heteromatic groups was well tolerated. Interestingly, isatin ketoximes with an R^1 alkyl substituent exhibited slightly higher reactivity than the aromatic ones. Isatin ketoximes bearing electron-withdrawing or electron-donating R^2 groups at the phenyl ring of the core skeleton were compatible and provided their respective products in high yields. R^3 substituents at the *N*1-position of isatin were well tolerated and gave access to the chiral spirooxindole 2*H*-azirines in high yields with moderate to good enantioselectivities. Further, it has been found that the electronic nature of the phenyl group of the sulfonyl chlorides had little impact on the reactivity. However, it significantly influences the enantioselectivity. The use of electron rich 4-methylbenzene-1-sulfonyl chloride gave high yields and enhanced enantioselectivity whereas electron deficient 2,4-dinitrobenzene-1-sulfonyl chloride afforded a relatively low yield and poor enantioselectivity. Alkyl sulfonyl chlorides were also tolerated and provided similar results as their aromatic counterparts (Scheme 5).

2. Five membered carbocyclic spiro-ring containing compounds. Van der Eycken and co-workers[4b] have described a high yielding Brønsted acid (TFA)-promoted protocol for the synthesis of spiroindolenines **6b** from indolyl ynones **6a** at rt within a few minutes. TFA promotes the dearomatization of the indole and results in the formation of the spiroindolenine. Interestingly, when the reaction was performed at higher temperature, a rearrangement results in the formation of a quinoline. (Un)substituted aromatic R^1-substituents gave excellent yields compared to aliphatic ones. A trimethyl silyl substituent proved to be unstable under the acidic conditions. An electron-donating



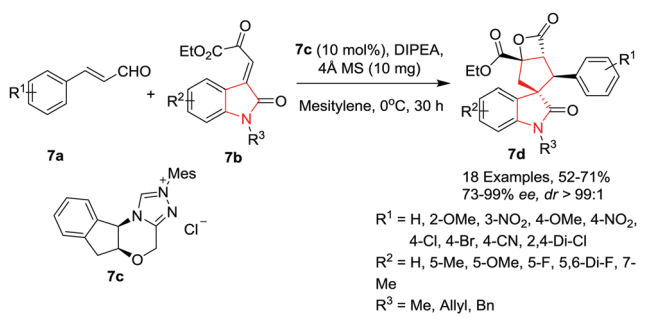
Scheme 5 Synthesis of spirooxindole 2*H*-azirines **5e**.



Scheme 6 Synthesis of spiro-indolenines **6b**.

R^2 substituent on the indole core resulted in moderate yields, while an electron-withdrawing group gave excellent yields. Interestingly, replacing the C-2 hydrogen of the indole (R^3) with methyl provided the desired product in excellent yield but required an extended reaction time. Further, the R^4-benzyl-substituted substrate resulted in the formation of an inseparable mixture of diastereomers in an excellent yield and with a d.r. = 5 : 4 (Scheme 6).

Wang and co-workers[10] have developed an asymmetric Michael-intramolecular aldol-lactonization cascade of enals **7a** with oxindolyl β,γ-unsaturated α-keto esters **7b** in the presence of N-heterocyclic carbine (NHC) generated from triazole salt **7c** as a catalyst to gain access to the β-propiolactone-fused spiro[cyclopentane-oxindoles] **7d** in moderate to high yield with excellent diastereoselectivities and enantioselectivities. The reaction gave best results when 4 Å Molecular Sieves (MS) were used as additive with 10 mol% of NHC at 0 °C. Under the optimized conditions, a variety of cinnamaldehydes bearing electron-releasing and electron-withdrawing substituents performed well to give the desired product in moderate to good yields and high to excellent enantioselectivities. Various oxindolyl β,γ-unsaturated α-keto esters bearing different *N*-substituents such as benzyl, allyl or Me on the oxindole backbone were found to be well tolerated, affording the desired products in moderate yields and with good enantioselectivities. The steric and electronic properties of the substituents on the oxindole skeleton were found to be crucial and affected the reactivity and stereoselectivity. The substrates bearing electron-donating substituents on the oxindole gave moderate yields of the products whereas electron-withdrawing or halogen substituents gave only moderate yields but with excellent enantioselectivities (Scheme 7).

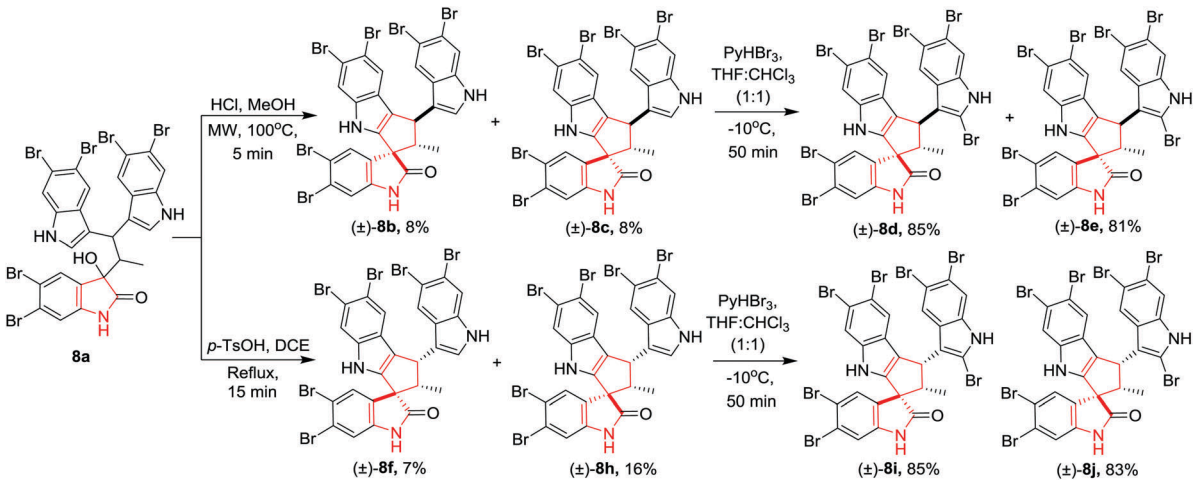


Scheme 7 Synthesis of β-propiolactone-fused spiro[cyclopentane-oxindoles] **7d**.

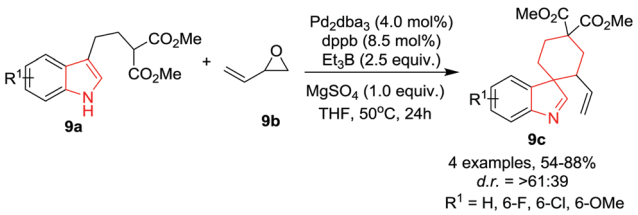
Zhang, Jia and co-workers[11] have reported the first total synthesis of polybrominated spiro-trisindole alkaloids, similisines A (+)-**8d** and B (−)-**8d** along with their stereoisomers which were first isolated from *Laurencia similis*. The important intermediate trisindole **8a** was synthesised from 5,6-dibromoindole in a few steps. The construction of key spirooxindole **8(b–c)** was achieved through acid-promoted intramolecular Friedel–Crafts cyclization. A variety of Lewis acids and Brønsted acids did not afford the desired product whereas upon treatment of trisindole **8a** with HCl in MeOH under MW irradiation (50 W, 100 °C, 5 min) provided two racemic isomers of (±)-**8b** and (±)-**8c** in very low yields along with an undesired trisindole derivative. Further, treatment of trisindole **8a** with *p*-TsOH in DCE under reflux conditions gave access to racemic isomers (±)-**8f** and (±)-**8h** in low yields. Synthesis of similisines A, B (±)-**8d** and their stereoisomers (±)-**8e**–(±)-**8j** was achieved by bromination of (±)-**8b**–(±)-**8h** with pyridinium tribromide in THF and $CHCl_3$ (1 : 1) in high yields. Compound (±)-**8d** is the racemic mixture of natural similisines A and B (Scheme 8).

3. Six membered carbocyclic spiro-ring containing compounds. You and co-workers[12] have developed a Pd-catalyzed allylic dearomatization reaction of substituted indoles **9a** with vinyl oxirane **9b** to gain access to diverse spiroindolenines **9c** in moderate yields and moderate diastereoselectivities using 1,4-bis(diphenylphosphino)butane (dppb) as ligand, $MgSO_4$ as additive and Et_3B as promoter in THF at 50 °C. Under the optimized conditions, substrates bearing an electron-donating group on the indole ring underwent the reaction smoothly, providing spiroindoles in satisfactory yields and moderate diastereoselectivities. The 6-Cl bearing substrate must be reduced from indolenine to indoline for allowing the separation of the two diastereomers (Scheme 9). Interestingly, the substrate bearing a bulky group at the C-2 position of the indole ring provided the allylic alcohol instead of the desired spiroindolenines.

Tanaka and co-workers[13] have described a diastereoselective formal (4+1) cycloaddition reaction of enones **10a** with cyclic 1,3-diketone **10b** to construct spiro[4,5]decanes **10c** bearing an oxindole moiety. A subsequent Michael–Henry cascade transformation with nitroalkenes **10d** afforded the highly functionalized polycarbocyclic compounds **10f**, bearing both the spiro[4,5]decane system and the spirooxindole system, with high diastereo- and enantioselectivities. Spiro[4,5]decanes **10c** were converted to polycarbocyclic compounds **10f** within a few hours using quinine **10e** as catalyst in the presence of 4 Å molecular sieves in benzene at rt. Under the optimized conditions, various nitrostyrenes afforded the spirooxindole polycyclic products. Irrespective of the electronic nature of the R^2 substituent on the nitrostyrene, all products were obtained in low yields but with high enantioselectivity. Spiro[4,5]decanes **10c** bearing (un)substituted phenyl or alkyl groups (R^1) underwent the reaction with low yields of the corresponding polycyclic compounds **10f**. Interestingly, the enantiopurity was found to decrease as the yield of **10f** increased with prolonged reaction times. Thus, isolation of **10f** from the reaction mixture within 5 to 10 hours is necessary for high enantioselectivity (because of the kinetic resolution) (Scheme 10).



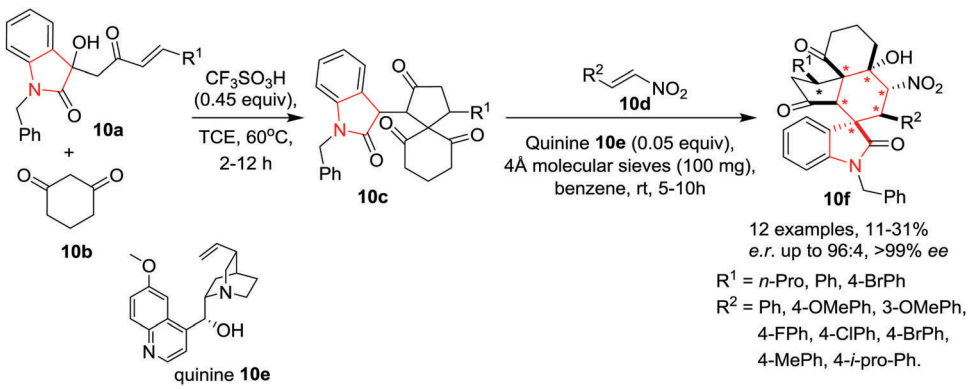
Scheme 8 Synthesis of similisines A (+)-**8d** and B (−)-**8d** along with their stereoisomers (±)-**8e**- to (±)-**8j**.



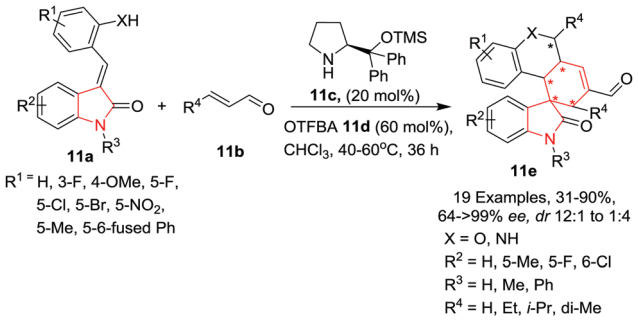
Scheme 9 Synthesis of Pd catalyzed spiroindolenines **9c**.

Liu, Zhao, Zhang and co-workers[14] have reported the synthesis of polycyclic spiro-fused carbocyclicoxindoles **11e** in moderate to high yields, excellent enantioselectivity and good control over the diastereoselectivity by reacting (*E*)-3-(2-hydroxybenzylidene) oxindole **11a** with crotonaldehyde **11b** in the presence of α,α-L-diphenylprolinol trimethylsilyl ether **11c** and 2-(trifluoromethyl)benzoic acid (OTFBA) **11d** in a quadruple-cascade manner at 40–60 °C in chloroform. The substitution pattern on the benzylic part of (*E*)-3-(2-hydroxybenzylidene) oxindole **11a** has a significant influence on the outcome of the reaction as halogens and electron donating substitutions gave high yields with excellent enantioselectivity and good diastereoselectivity, whereas electron withdrawing groups such as NO_2 drastically reduced the product yield and diastereoselectivity. Further, fused phenyl rings as R^1 resulted in complete inversion of diastereoselectivity. Hydroxyl groups as well as amines are well tolerated on the benzyl ring. Substituents such as halogens and a small alkyl group (Me) on the indole are well tolerated and gave high to excellent yields and enantioselectivities of the products and good control over the diastereoselectivities. Substitution on the indole nitrogen drastically reduced the product yield but provided excellent control over the diastereoselectivities. Substitution on the crotonaldehyde also has a significant influence on the product yields whereas unsubstituted (R^4 = H) crotonaldehyde resulted in inversion of diastereoselectivity. Some of the compounds were found to induce apoptosis in HCT116 cells through a cascade-dependent pathway by blocking the MDM2-mediated p53 degradation (Scheme 11).

4. Five membered one nitrogen containing spiro-cyclic compounds. Wang and co-workers[15] have reported a catalytic asymmetric [3+2] cycloaddition reaction of 3-amino oxindole HCl-salt **12a**, aldehyde **12b** and α,β-enone **12c** to gain access to a diverse array of spiro[pyrrolidine-2,3′-oxindoles] **12e** with high levels of regio- and enantiocontrol using 3,3′-(9-phenanthryl)-modified phosphoric acid **12d** as catalyst under basic conditions in Et_2O at 35 °C. Under the optimal conditions, a broad



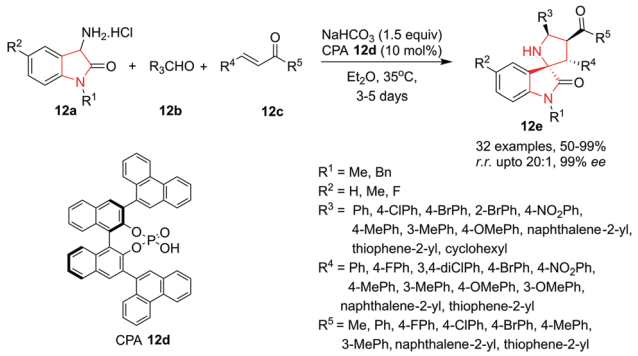
Scheme 10 Synthesis of functionalized polycarbocyclic compounds **10f**.



Scheme 11 Synthesis of polycyclic spiro-fused carbocyclicoxindoles **11e**.

range of aromatic as well as heteroaromatic aldehydes were found to be compatible with this new process, irrespective of the electronic properties of the substituents on the phenyl ring, and provided access to the cycloadducts in good to excellent yields. However, the use of aliphatic aldehydes resulted in very low regio- and enantioselectivity. Electron-donating or electron-withdrawing groups at the 5-position of the oxindole framework are well tolerated. Further, a diverse array of chalcones were found to be suitable dipolarophiles in this cycloaddition reaction. In addition, aliphatic ketones also work well in this reaction (Scheme 12).

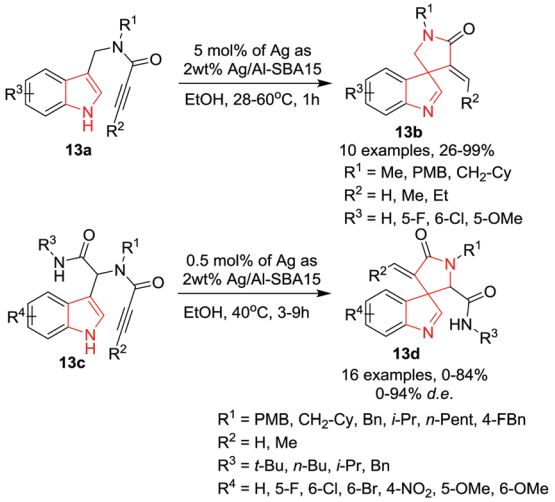
Van der Eycken and co-workers[16] have developed an efficient process for spirocyclization of 3-substituted indoles **13a** and **13c** to access 3-spiroindolenines **13b** and **13d** in moderate to high yield with high to excellent diastereoselectivity by employing novel supported Ag-nanoparticles in ethanol at 28 °C. Under the optimized conditions, the 5-*exo*-dig process for 3-substituted indoles **13a** was found to be efficient and provided high yields of 3-spiroindolenines **13b**. Substrates bearing terminal alkynes (R^2 = H) showed good to excellent reactivity resulting in high product yields. However, internal alkynes ($R^2 \neq$ H) cyclize slowly and required extended reaction times, high reaction temperature and higher loading of catalyst. Further, in some cases, small amounts of inseparable 6-*endo*-dig products were also formed. The electronic nature of the substituent at C5-(R^3) did not affect the reaction output whereas substitution of chlorine at C6-position resulted in a drastic loss of product yield. By slight alteration in reaction conditions, diversified Ugi adducts **13c** were cyclized to the desired spiroindolenines **13d**.



Scheme 12 Synthesis of spiro[pyrrolidine-2,3′-oxindoles] **12e**.

Various substrates bearing terminal alkynes provided high product yields along with very minor amounts of the undesired tetracyclic product. Substituents at the C5- or C6-position (R^4) did not affect the yields; however, a nitro-substituent at the C4-position decreased the product yield drastically and no diastereoselectivity was observed. Further, a less sterically demanding R^3-substituent, such as butyl, caused a severe drop in the yield. Furthermore, the performance of the catalyst was found to be unchanged up to 10 catalytic cycles and only a small amount of metal was leached (0.35% leaching of the original silver) during the reaction (Scheme 13).

Wang and co-workers[17] have developed a novel one-pot 1,3-dipolar cycloaddition of indolenines **14c**, 3-aminooxindoles **14a**, and aldehydes **14b** to provide access to indolenine-substituted spiro[pyrrolidin-2,3′-oxindoles] **14d** in high yields and excellent diastereoselectivities using 3 Å MS in DCM at rt. Various benzaldehydes bearing electron-donating and electron-withdrawing substituents including naphthaldehyde and heteroaromatic aldehydes were well tolerated. However, electron deficient benzaldehydes afforded moderately lowered yields and exhibited lower reactivity than the neutral or electron-rich derivatives, whereas no difference in diastereoselectivities was observed. Interestingly, *ortho* substitution on the benzaldehydes decreased diastereoselectivity compared to *meta*- and *para*-substitution. Substitutions on the benzene ring of 3-aminooxindole were well tolerated and provided good product yields with excellent diastereoselectivities. Indolenines with electron-withdrawing or electron-donating groups at the C5-position reacted smoothly and afforded desirable products with excellent yields and diastereoselectivities, while a nitro group reduced the activity. To further induce diversification at the C3 and C5 positions of the pyrrolidine ring, preformed 2-alkenylindolenines **14e** were employed in the cycloaddition reaction. However, diphenyl phosphate (DPP) must be used to enhance the efficiency and diastereoselectivity of the products. Under these modified conditions, various 2-alkenylindolenines underwent the [3+2] cycloaddition reaction smoothly and gave indolenine substituted



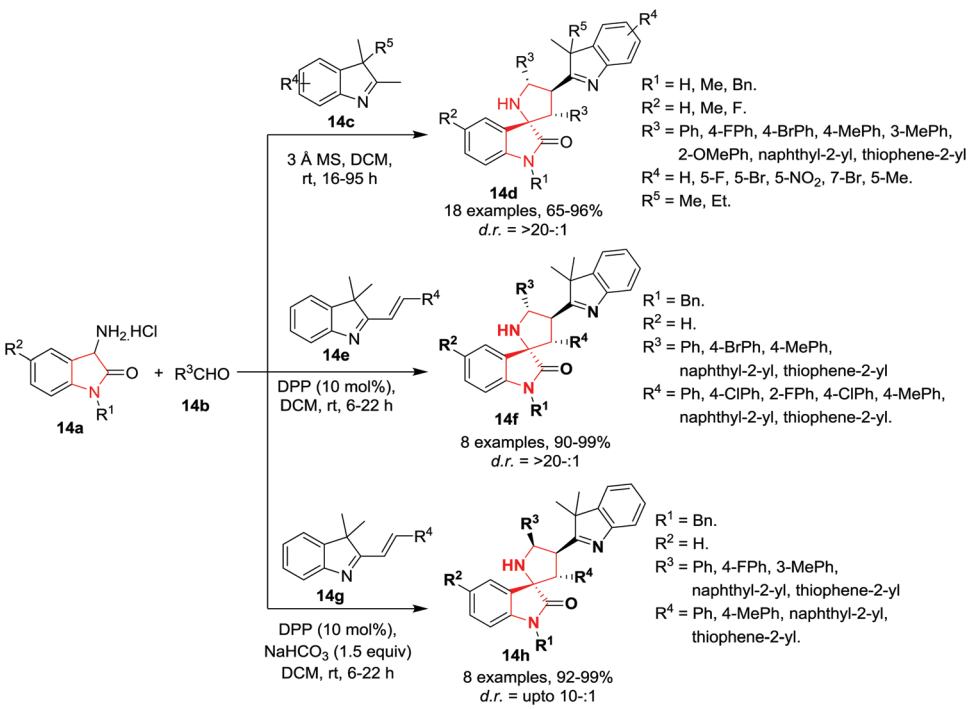
Scheme 13 Synthesis of 3-spiroindolenines **13b** and **13d**.

spiro[pyrrolidin-2,3′-oxindole] **14f** in excellent yields and diastereoselectivities. Interestingly, the use of $NaHCO_3$ as base and DPP as catalyst resulted in switching of the diastereomeric ratio. Under these new conditions, diversely substituted 2-alkenylindolenines underwent the reaction smoothly to give epimer **14h** as the major product with high reactivity in high yields and with moderate to good diastereoselectivity. The switch of diastereoselectivity of the product by using $NaHCO_3$ and DPP is still unclear (Scheme 14).

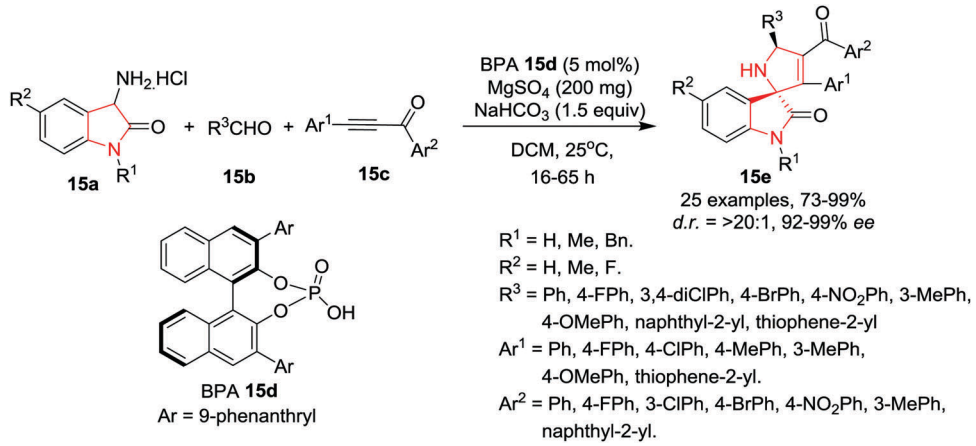
Wang and co-workers[18] have developed an organocatalytic asymmetric 1,3-dipolar [3+2] cycloaddition reaction of 3-amino oxindole-based azomethine ylides (obtained by the reaction of 3-amino oxindole **15a** and aldehydes **15b**) with α,β-ynones **15c** in the presence of chiral 3,3′-(9-phenanthryl)binaphthol-phosphoric acid (BPA) **15d** as catalyst, $MgSO_4$ as a dehydrating agent and $NaHCO_3$ as base in DCM at rt to afford spiro[dihydropyrrole-2,3′-oxindoles] **15e** in high yields and with excellent enantio- and diastereoselectivities. A diverse array of aromatic aldehydes bearing electron-neutral, electron-deficient, or electron-rich groups were found to be suitable in this reaction and afforded the corresponding products in high yields with excellent enantioselectivities and diastereoselectivities. Additionally, heteroaromatic and naphthaldehydes were also found to be suitable and afforded excellent product yields. Substitution at C-5 of the 3-amino oxindole framework is well tolerated. A diverse array of ynones were found to be suitable as dipolarophiles for this cycloaddition reaction as electronically diverse substituents on aromatic rings or heteroaromatic groups at the alkynyl terminus are well amenable to the cycloaddition reaction, delivering enantiopure cycloadducts in excellent yields. Similarly, with respect to the ketone terminus, a variety of aromatic groups are well tolerated. The scaled up reaction of cycloadducts maintained the efficiency and stereoselectivity (Scheme 15).

Zhao, Shang and co-workers[19] have developed a highly stereoselective 1,3-dipolar cycloaddition reaction of imino esters **16a** and methyleneindolinones **16b** using a chiral thiourea based quaternary ammonium salt **16c** as phase-transfer catalyst at rt in Et_2O using K_2CO_3 as base to provide facile access to chiral spiro[pyrrolin-3,3′-oxindoles] **16d** in high yields and with excellent enantio- and diastereoselectivities. Among the imino esters bearing different ester groups, the *t*-butyl imino ester provided the product with the highest enantioselectivity compared to other esters (*i.e.* Et, Bn). Further, a wide array of *t*-butyl imino esters originating from heterocyclic or aromatic aldehydes bearing electron-donating or electron-withdrawing substituents on the aromatic ring provided the spiroindoles with excellent enantioselectivities and good to excellent diastereoselectivities. Interestingly, *N*-methyl or benzyl protected indolinone provided excellent results whereas *N*-Boc-protection reduced the enantioselectivities and diastereoselectivities. Further, methyleneindolinones derived from aromatic and aliphatic aldehydes underwent the reaction smoothly and provided excellent product yields. However, reactions with propyl- and phenethyl-substituted methyleneindolinones afforded the products with comparatively lower diastereoselectivities. The indolinone moiety bearing various substituents at the C5 or C6 position were well tolerated and provided excellent results (Scheme 16).

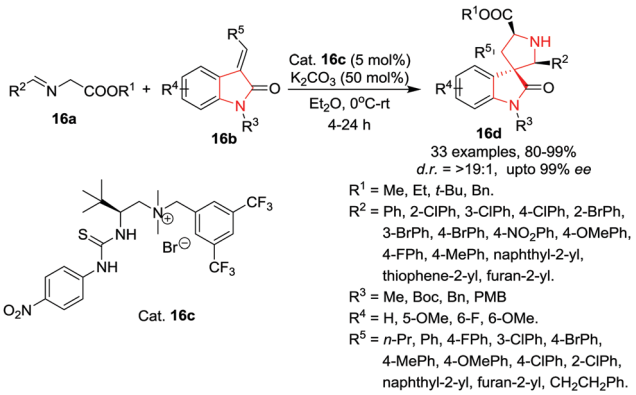
Recently, Yan, K. Wang, R. Wang and co-workers[20] have reported a facile 1,3-dipolar cycloaddition reaction of 3-alkenyloxindoles **17a** with CF_3-containing ketimines **17b** in the presence of Cinchona alkaloids-derived thiourea catalyst **17c** to access 2′-CF_3-spiro-pyrrolidine-3,3′-oxindoles **17d** with excellent yields,



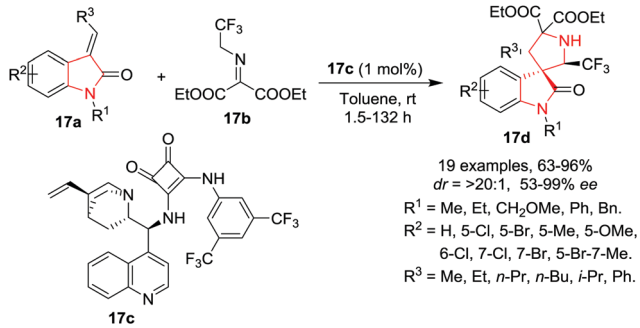
Scheme 14 Synthesis of indolenine-substituted spiro[pyrrolidin-2,3′-oxindoles] **14d**, **14f** and **14h**.



Scheme 15 Synthesis of spiro[dihydropyrrole-2,3′-oxindoles] **15e**.



Scheme 16 Synthesis of chiral spiro[pyrrolin-3,3′-oxindoles] **16d**.

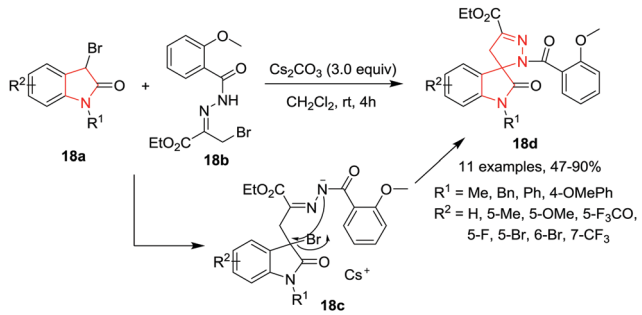


Scheme 17 Synthesis of 2′-CF_3-spiro-pyrrolidine-3,3′-oxindoles **17d**.

enantioselectivities and diastereoselectivities using toluene as reaction medium at rt. With the optimized conditions, various 3-alkenyl-oxindoles as dipolarophiles were found to be suitable in this reaction as various substituents such as ethyl, CH_2OCH_3 or benzyl groups at the *N*-1 position underwent the reaction smoothly, and gave the cycloadducts with excellent enantioselectivities and diastereoselectivities, although in lower yields and with longer reaction times. Meanwhile, a phenyl group at the *N*-1 position of the 3-alkenyloxindole resulted in high yield, excellent enantioselectivity but moderate diastereoselectivity. Further, various electron-withdrawing and electron-donating groups at the aromatic ring of the 3-alkenyloxindole were well tolerated, and provided the corresponding adducts in good yields, excellent enantioselectivities as well as diastereoselectivities. Dipolarophiles bearing an electron-withdrawing substituent at the 5-position of 3-alkenyloxindole have higher reactivity. Substituents on the alkenyl moiety played an important role in the reaction as an increase in the length of the substituent from methyl to ethyl, *n*-propyl, *n*-butyl or isopropyl resulted in a slower reaction rate, even with increased catalytic loading. Despite the slow reaction rate, the cycloadducts were obtained in high yields with excellent enantioselectivities and diastereoselectivities. Further, the phenyl substituted alkenyl substrate resulted in low product yield and poor enantioselectivity even after prolonged reaction time (Scheme 17).

5. Five/six membered spiro-ring with more than one heteroatom. Chen and co-workers[21] have developed a formal [4+1] annulation reaction of 3-bromooxindoles **18a** and 1,2-diaza-1,3-dienes **18b** to gain access to spiropyrazoline oxindoles **18d** in high yields, using Cs_2CO_3 as base in CH_2Cl_2 at rt within a few hours. A one-pot, three-component variant of the same reaction also works smoothly to give the desired products in comparable yields. In this reaction, variation of the electronic properties at the 5-position of the phenyl ring of the 3-bromoxindoles has no effect on the reaction efficiency. However, electron-withdrawing groups such as a bromo or trifluoromethyl substituent at the 6 or 7-position of the phenyl ring furnished moderate yields of the products. Further, different protecting groups on the nitrogen atom of 3-bromooxindoles, such as benzyl, phenyl, and 4-methoxylphenyl, are well tolerated in the reaction resulting in good yields. Also the scaling-up of this procedure was elaborated. This reaction is believed to progress through intermediate **18c**, which further undergoes an intramolecular nucleophilic S_N2-substitution to form the final formal [4+1] annulation product (Scheme 18).

Nath and co-workers[22] have reported an efficient methodology for the synthesis of spiro[indoline-3,2′-thiazolidinones] **19e** in good to excellent yields by the sequential reaction of primary amines **19a** with various isatins **19b** and then the resultant Schiff base **19c** was reacted with thioglycolic acid **19d** in the presence of *p*-dodecylbenzenesulfonic acid (DBSA) as

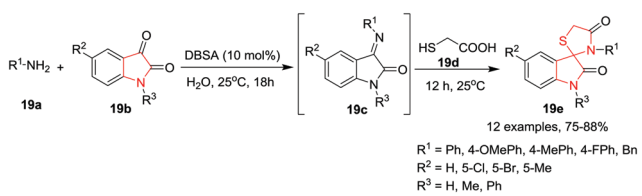


Scheme 18 Synthesis of spiropyrazoline oxindoles **18d**.

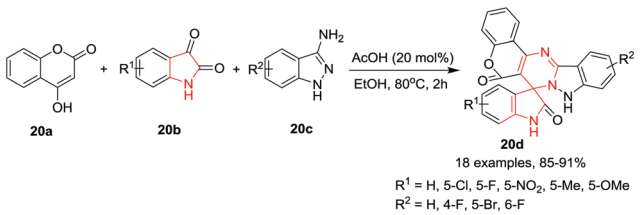
Brønsted acid catalyst in aqueous medium at 25 °C. Under the optimized conditions, various aryl amines bearing an electron-donating substituent at the 4-position of the phenyl ring underwent the reaction smoothly and produced the desired spiro-indoles in high yields, whereas substrates with electron-withdrawing substituents were found to be sluggish and afforded the desired product in slightly less yields. Interestingly, the reactions of benzylamine with various isatins and thioglycolic acid proceeded with a faster rate and afforded the desired products in higher yields. Additionally, substituents on the 5-position of isatin or the *N*-1 nitrogen have a minimal effect on the reaction output and provide high product yields. This synthetic protocol has the advantages of operational simplicity, energy-efficiency, and the use of green solvent to access the desired spiro[indoline-3,2′-thiazolidinones] in high yields (Scheme 19).

Jeong and co-workers[23] have developed a rapid synthetic procedure for spiro[chromeno[4′,3′:4,5]pyrimido[1,2-*b*]indazole-7,3′-indoline]-2′,6(9*H*)-diones **20d** by one-pot condensation reaction of 4-hydroxy-2*H*-chromen-2-one **20a**, isatin **20b** and 1*H*-indazole-3-amine **20c** in the presence of acetic acid in EtOH under refluxing conditions for 2 h. Under the optimized reaction conditions, a variety of substituents on isatin and on 1*H*-indazole-3-amine, including electron-withdrawing or electron-donating groups, were acceptable and gave high product yields. This protocol has general applicability and can accommodate a variety of substitution patterns. This method has the advantages of operational simplicity and high product yield *via* a simple work-up procedure as compared to the conventional methods (Scheme 20).

6. Six/seven membered nitrogen containing spiro-cyclic compounds. Zheng, You and co-workers[24] have developed a highly efficient desymmetrizing allylic dearomatization reaction of bis(indol-3-yl)allylic carbonates **21a** to gain access to spiroindolenines **21c** in high yields and excellent diastereo- and enantioselectivities utilizing an Ir-based catalyst and phosphoramidite



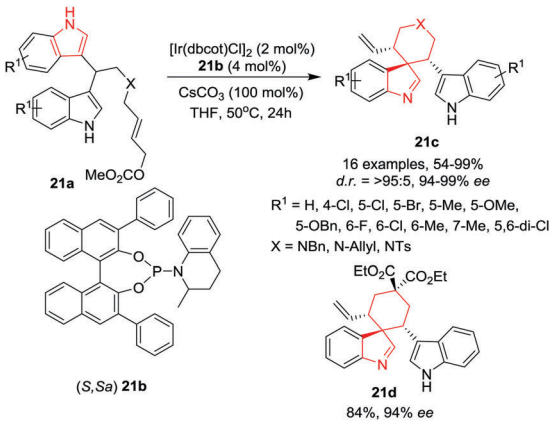
Scheme 19 Synthesis of spiro[indoline-3,2′-thiazolidinones] **19e**.



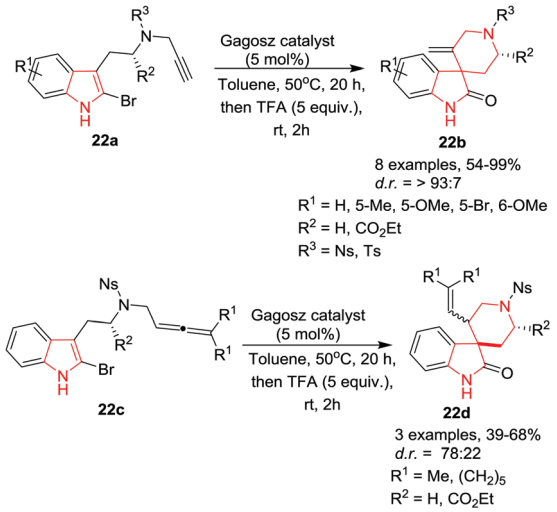
Scheme 20 Synthesis of spiro[chromeno[4′,3′:4,5]pyrimido[1,2-*b*]indazole-7,3′-indoline]-2′,6(9*H*)-diones **20d**.

ligand **21b** under basic conditions in THF at 50 °C. Under the optimal conditions, substrates bearing electron-donating or electron-withdrawing groups on the nitrogen atom of the linkage underwent the reaction smoothly providing good to excellent product yields and excellent enantioselectivities. Additionally, substrates with different linkages revealed that allylic carbonates linked with a $C(CO_2Me)_2$ group underwent the reaction smoothly and provided access to compound **21d** whereas substrates with an ester or amide tether were not reactive. A wide range of electron-donating and electron-withdrawing substituents on the indole ring were well tolerated. However, the 5,6-di-chloro bearing indole provided low yield and poor diastereoselectivity. Interestingly, the substrate bearing a one methylene elongated linkage (X = $-CH_2N(Bn)$) did not afford the seven-membered spiroindolenine. Additionally, when an unsymmetrical allylic carbonate was used, both indole rings were involved in the reaction, providing a pair of inseparable constitutional isomers ($\approx 1:1$) in a high combined yield and enantioselectivities. The reaction was found to be robust and can be performed on a gram scale, providing high yields with excellent enantioselectivities (Scheme 21).

Voituriez, Guinchard and co-workers[25] have reported a gold-catalyzed protocol to cyclize 2-bromo-*N*-propargyltryptamines **22a** to gain access to spiro[indoline-3,4′-piperidin]-2-ones **22b** in excellent yields by utilizing Gagosz catalyst ($Ph_3PAuNTf_2$) in toluene at 50 °C. 2-Bromotryptamines gave superior yields compared to their chlorinated counterparts. Similarly, the nitrobenzenesulfonyl (Ns) protected amines proved superior to tosyl-protected analogs. The reaction of indoles bearing electron-donating



Scheme 21 Ir-Catalyzed synthesis of chiral spiroindolenines **21c**.

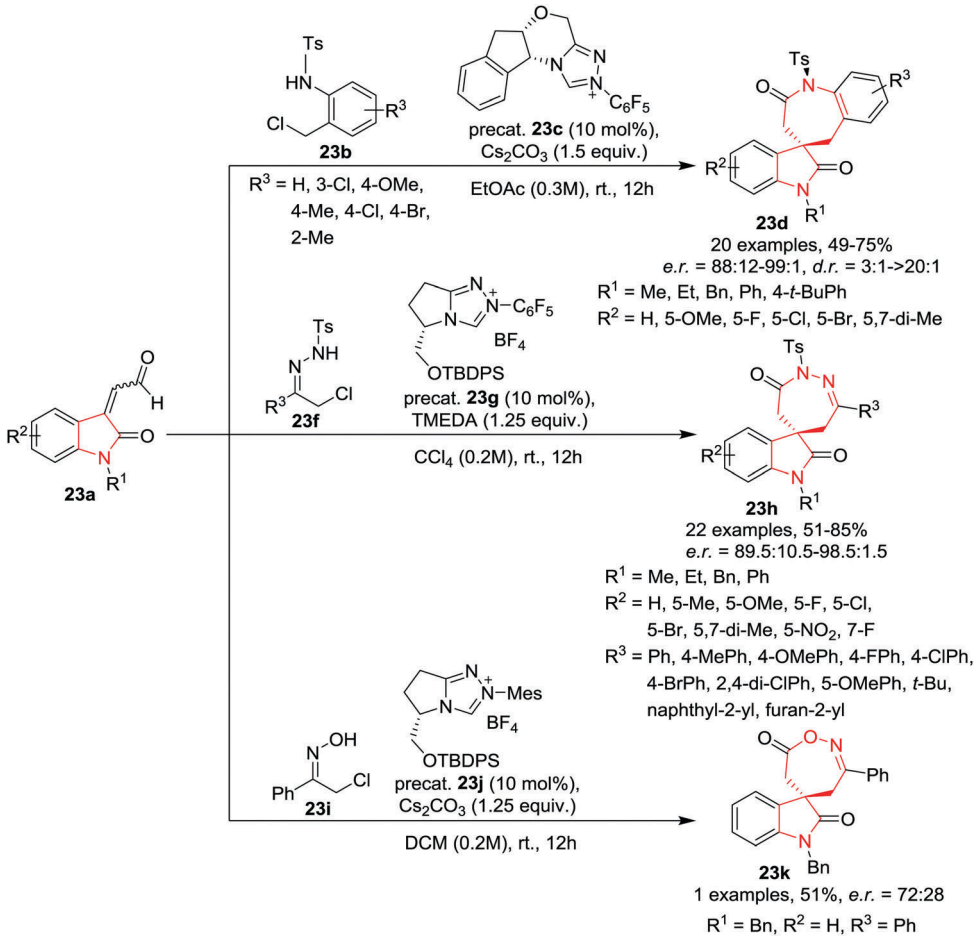


Scheme 22 Synthesis of spiro[indoline-3,4′-piperidin]-2-ones **22b** and **22d**.

or electron-withdrawing groups afforded good product yields. Further, the use of L-tryptophan esters in this cyclization afforded the corresponding spirocyclic compounds in excellent yields and diastereoselectivities. Additionally, the scope of this cyclization was extended by installing an allene function on the 2-bromotryptamine to give tryptamines **22c** which underwent smoothly a gold-catalyzed cyclization/hydrolysis sequence to furnish the spirocyclic **22d** in good yields as a mixture of diastereomers (1 : 1). Interestingly, replacement of the 2-propanediyl unit by a cyclohexanediyl unit on the allene function increased the diastereomeric ratio to 78/22 (Scheme 22).

Enders and co-workers[26] have developed an asymmetric, N-heterocyclic carbene (NHC) catalyzed formal [3+4] cycloaddition reaction of isatin-derived enals **23a** (3C component) with *in situ* formed aza-*o*-quinone methides and azoalkenes or nitrosoalkenes (4 atom components) to synthesize spirobenzazepinones **23d**, spiro-1,2-diazepinones **23h** and spiro-1,2-oxazepinones **23k** in good yield and with very good to excellent enantioselectivities by slight alteration in the reaction conditions. The *atropo*- and enantioselective synthesis of spirobenzazepinones **23d** was achieved by the reaction of isatin derived enals **23a** with *N*-(*ortho*-chloromethyl)aryl amides **23b** using a chiral triazolium salt based precatalyst **23c** and Cs_2CO_3 as base in EtOAc at rt. Various electron-withdrawing and electron-donating substituents on the benzene ring of the enal provided the corresponding spirobenzazepinones in good yields, high enantiomeric ratio and with good diastereoselectivities. Variation of the *N*-substituents of the enal resulted in good to excellent enantioselectivities of the product. A wide range of electron-rich and electron-deficient substituents on the *N*-(*ortho*-chloromethyl)aryl amides were found to be compatible to afford the respective spiroheterocycles in good yields, high enantiomeric ratios but with moderate diastereoselectivities. The use of 6-Cl-substituted amides resulted in reduced enantioselectivity. Interestingly, *N*-(*ortho*-chloromethyl)aryl amides bearing a methyl group at the *ortho*-position afforded excellent diastereoselectivities probably due to the fact that substituents at this position of the benzene ring of seven-membered benzolactams increase the conformational barrier of the corresponding atropisomers. This methodology was extended to achieve the synthesis of spiro-1,2-diazepinones **23h** by reacting α-halogenohydrazones **23f** with isatin-derived enals **23a** using chiral triazolium salt based precatalyst **23g** as precatalyst and TMEDA as base in CCl_4. A broad range of enal substrates bearing electron-neutral, -releasing, and -withdrawing substituents on the aromatic ring provided the corresponding spiro-1,2-diazepinone products with excellent enantioselectivities and moderate to very good yields. Enal substrates with varied *N*-substituents when employed in this annulation procedure provided excellent yields and high enantioselectivities. Various aromatic, aliphatic and heterocyclic α-chloro *N*-tosyl hydrazones were also found to be suitable as azoalkene precursors, yielding the desired spiro-1,2-diazepinones with excellent yields and high enantioselectivities in most cases. Additionally, polycyclic spiro-1,2-diazepinones were obtained in good yields and excellent diastereo- and enantioselectivities utilizing the standard NHC catalysis conditions by using cyclic hydrazones. Interestingly, seven-membered hydrazine under the standard catalytic conditions provided the corresponding polycyclic spiro-1,2-diazepinone with two fused seven-membered rings in good yield and with an enantiomeric ratio of 91.5 : 8.5. Further, spiro-1,2-oxazepinones **23k** were obtained with good yields and moderate enantiomeric ratio utilizing a similar NHC strategy where α-chloro oximes **23i** were used as substrates and utilizing precatalyst **23j** and Cs_2CO_3 as base in DCM (Scheme 23).

7. **Fused nitrogen-heterocycle containing spiro-cyclic compounds.** Boitsov, Stepakov and co-workers[27] have developed a highly efficient stereoselective synthesis of a novel class of substituted 3-spiro[cyclopropa[*a*]pyrrolizine] **24d**, **24e** and 3-spiro[3-azabicyclo[3.1.0]hexane]-oxindoles **24g**, **24i** and **24k** *via* a one-pot three-component 1,3-dipolar cycloaddition reaction of cyclopropenes **24a** with azomethine ylides generated from isatins **24b** and α-amino acids **24c** and with azomethine ylides generated from isatins and benzylamine **24h**, dipeptide **24f** or Gly–Gly **24j** under refluxing conditions in MeOH alone or in a mixture with water or with benzene. A variety of cyclopropenes were found to be suitable for this reaction to gain access to the corresponding spirocyclic-3,3′-oxindoles **24d**, **24e** in moderate to high yields and with moderate to excellent stereoselectivities. However, cyclopropenes bearing methyl substituents at the double bond or tetra-substituted cyclopropene did not undergo this reaction. Further, a number of primary α-amino acids **24f** or dipeptides **24j** were also found to be suitable substrates for this reaction by slightly modifying the solvent to a mixture of MeOH/EtOH and water (3 : 1) to gain access to the 3-spiro[3-azabicyclo[3.1.0]hexane]oxindoles **24g**, **24k** in good to moderate yields and with high diastereoselectivity. Surprisingly, glycine and DL-alanine were found to be unsuitable for this reaction and produced only trace amounts of the desired products along with an unidentified mixture of compounds. Additionally, the application of benzylamine **24h** as an amine component in a modified solvent mixture of MeOH and benzene (3 : 1) under reflux conditions provided the spirooxindoles **24i** in



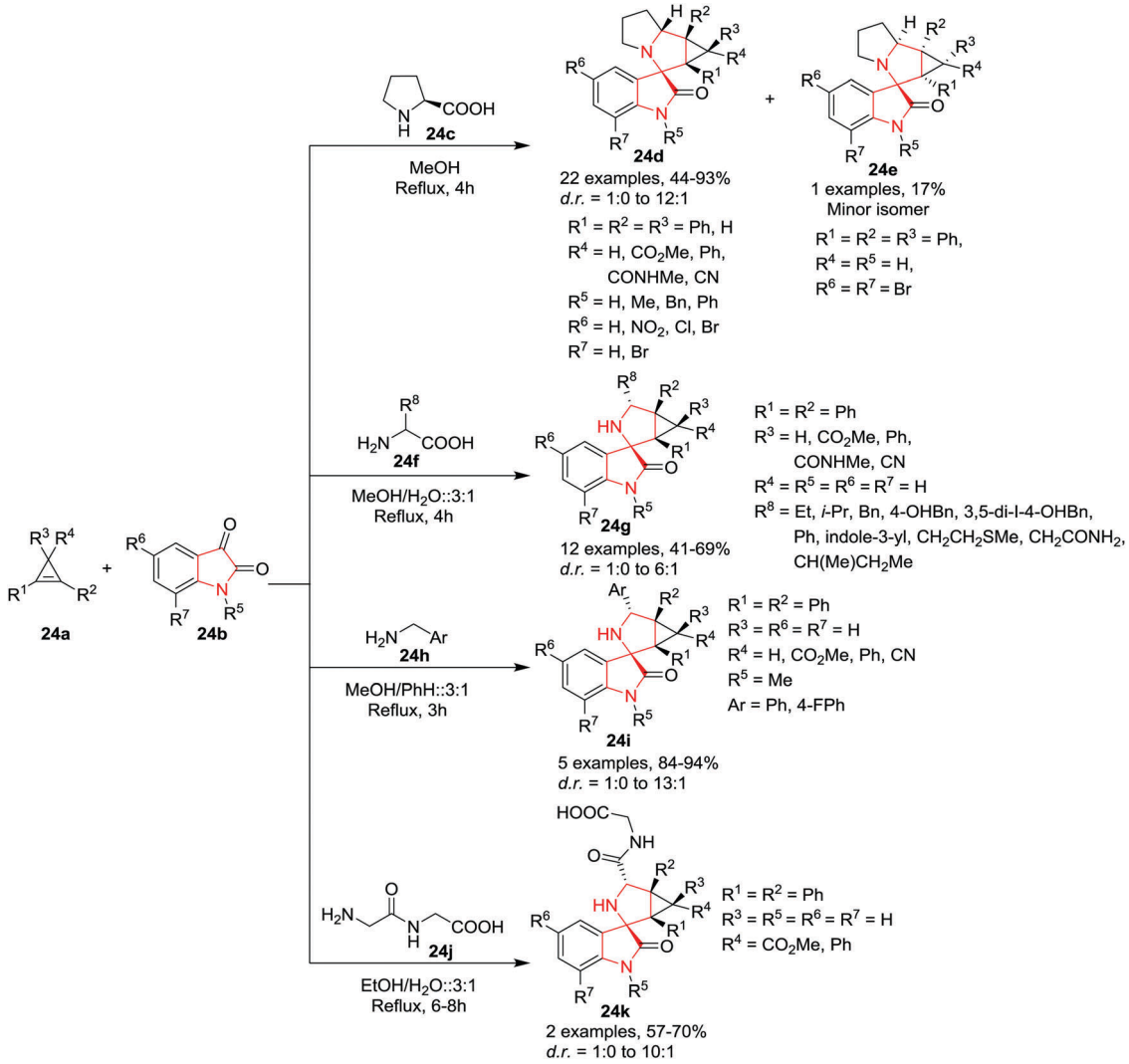
Scheme 23 Synthesis of spirobenzazepinones **23d**, spiro-1,2-diazepinones **23h** and spiro-1,2-oxazepinones **23k**.

excellent yields irrespective of the substitution pattern of the reactants (Scheme 24).

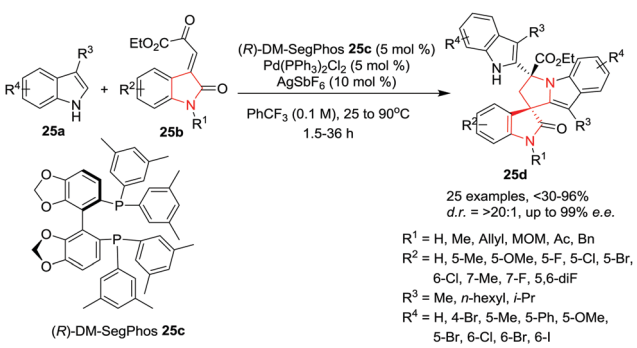
Wang and co-workers[28] have developed a cascade asymmetric Friedel–Crafts alkylation/*N*-hemiketalization/Friedel–Crafts alkylation reaction of 3-alkylindoles **25a** and oxindolyl β,γ-unsaturated α-ketoesters **25b** to give spiro-polycyclic indoles **25d** in high yields with excellent enantioselectivities and diastereoselectivities. This cascade sequence is catalyzed by a combination of $Pd(PPh_3)_2Cl_2$ and $AgSbF_6$ using (*R*)-DM-SegPhos **25c** as ligand in $PhCF_3$. Under the optimized conditions, the various *N*-(un)protected oxindolyl β,γ-unsaturated α-ketoesters **25b** underwent the reaction smoothly and provided the desired products in very good yields and with excellent enantioselectivities. The oxindolyl ring bearing either electron-donating or electron-withdrawing groups at the 5-position are well tolerated giving the desired products in excellent yields and enantioselectivities with >20 : 1 d.r. However, substrates bearing a methyl group at the 5-position of the oxindolyl ring gave the desired products in comparatively low yield and low enantioselectivity. Various substituents on the 3-substituted indoles at the 5- or 6-position are well tolerated under the reaction conditions. Interestingly, a 4-Br substituent gave a low product yield with moderate enantioselectivity. At the 3-position, small or large alkyl chains are well tolerated whereas sterically hindered groups such as isopropyl were found to be unsuitable in this reaction and provided very poor yields (Scheme 25).

Van der Eycken and co-workers[29] have reported an efficient reaction which converted the Ugi-adduct **26a** to the corresponding polycyclic spirocyclic indoles **26b** by using a catalytic system of $Au(PPh_3)SbF_6$ in $CDCl_3$ at rt in a short time. Under these conditions, various substituents on the alkyne, isonitrile, indole, and amine groups were tolerated and provided good product yields. However, bulky substituents on the alkyne yielded low product yields. Noticeably, methyl substitution at the 2-position of the indole core completely inhibited the cyclization. Further, the tosyl group on the indole nitrogen was found to be unfavorable for cyclization (Scheme 26).

Further, Van der Eycken and co-workers[30] have applied a MW-assisted protocol to the Ugi-adduct **26a** to access the corresponding polycyclic spirocyclic indoles **26c** in good to excellent yields using Au nanoparticles supported on Al-SBA15. For substrates bearing terminal alkynes, the reaction proceeds smoothly and provides good to excellent product yields within 20 min in ethanol at 110 °C. However, bulky substituents at the amide nitrogen (R^3) provided poor product yields which is attributed to the interference in the trapping of the iminium moiety by the amide in the spirointermediate. Interestingly, these reaction conditions were found to be unsuitable for substrates bearing

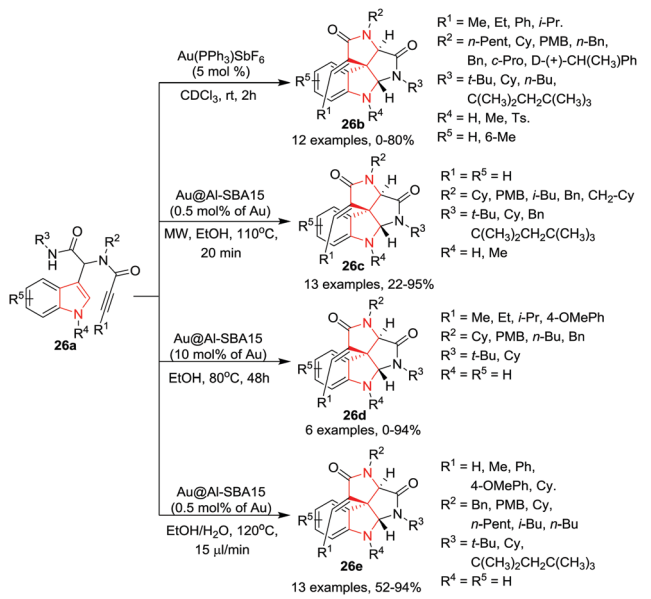


Scheme 24 Synthesis of 3-spiro[cyclopropa[α]pyrrolizine] **24d**, **24e** and 3-spiro[3-azabicyclo[3.1.0]hexane]-oxindoles **24g**, **24i** and **24k**.



Scheme 25 Synthesis of spiro-polycyclic indoles **25d**.

substituents on the alkynes, as even increased temperature and longer reaction times fail to give satisfactory product yields. However, under conventional heating these substrates were spirocyclized to give polycyclic indoles **26d**. Noticeably, with the increase of the bulkiness of the alkyne substituent, the product yield dropped sharply. For example, changing the substituent

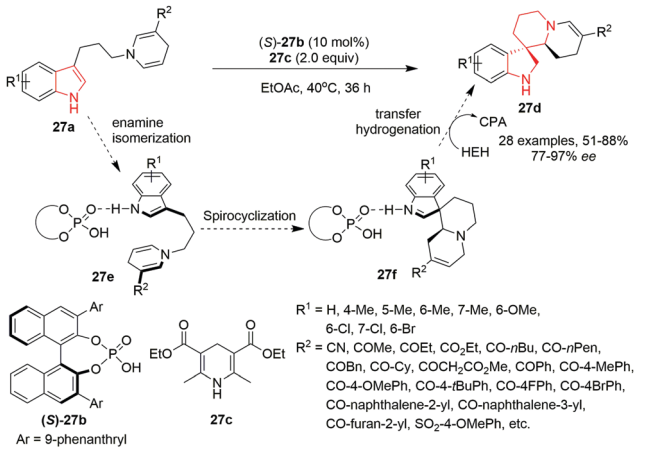


Scheme 26 Synthesis of polycyclic spirocyclic indoles **26b–26e**.

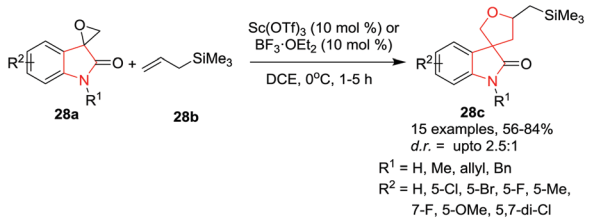
from a methyl-group to an ethyl-group resulted in a drop of yield by 76% whereas the change with a *t*-butyl group resulted in complete failure of the reaction (Scheme 26).

Further, Noël, Van der Eycken and co-workers[31] have developed an efficient protocol for the cycloisomerization of Ugi-adduct **26a** using a heterogeneous gold based catalyst Au@Al-SBA15 (0.5 mol% of Au as 2.0 wt% Au@Al-SBA15) in a mixture of EtOH and water to yield polycyclic spirocyclic indoles **26e** under microflow conditions (15 μL min^{-1}) in good to excellent yields. Under the optimized conditions (120 °C, Res. time 5.5 min), several aliphatic, aromatic or unsubstituted alkynes underwent the spiro-cyclization reaction to give good to excellent product yields. Similarly, various aliphatic substitutions at the R^2 position were tolerated and provided the product in good yields. Interestingly, bulky aliphatic groups at the R^3 position gave relatively low yields compared to other aliphatic groups. Noticeably, this reaction did not show any spiro-cyclization conversion under conventional batch conditions probably because of the very low catalyst/reactant ratio as compared to the packed bed reactor. In addition, leaching of the gold particles form the Au@Al-SBA15 catalytic bed was not observed. However, under continuous-flow conditions the activity of the catalyst usually decreased after eight injections of each 50 μmol (Scheme 26).

Zheng, You and co-workers[32] have recently reported a highly efficient synthesis of enantio-enriched spiroindolines **27d** *via* a sequential isomerization/spirocyclization/transfer hydrogenation of indolyl dihydropyridine **27a** by employing a chiral phosphoric acid **27b** as a catalyst, Hantzsch ester **27c** as a hydrogen transfer agent and 3 Å molecular sieves as an additive in EtOAc at 40 °C. Under the optimized conditions, electron-donating groups or halogens on the phenyl ring of the indole ring provided good to high yields of spiroindolines with excellent enantioselectivities. However, substrates with an electron-withdrawing group such as methoxycarbonyl did not undergo the reaction. The 1,4-dihydropyridines bearing various substituents such as aliphatic, cyclic, aryl, or heteroaryl ketone underwent the reaction smoothly to provide spiroindolines in good yields and with excellent enantioselectivities. Electron-withdrawing substituents on the C3′-position of the 1,4-dihydropyridine such as ester, cyano, and sulfonyl or a bulky group such as naphthalene underwent the reaction smoothly, although providing moderate yields but with good to excellent enantioselectivities. Notably, all the spiroindolines were obtained as single diastereoisomers, except the substrate bearing 5-chloro or 5-methyl as a substituent on the indole ring. The reaction proceeds through the enamine isomerization of indolyl dihydropyridine **27a** to generate iminium intermediate **27e** followed by cyclization at the C3 position of the indole ring, leading to intermediate **27f**, followed by transfer hydrogenation of intermediate **27f** to spiroindole **27d** (Scheme 27).



Scheme 27 Synthesis of tetrahydrospiro[indoline-3.1′-quinolizine] **27d**.



Scheme 28 Synthesis of spiro-furanoindolines **28c**.

8. Five membered oxygen containing spiro-cyclic compounds. Hajra and co-workers[33] have reported an efficient Lewis acid catalyzed formal [3+2]-annulation reaction of spiro-epoxyoxindoles **28a** and allyltrimethylsilane **28b** for the synthesis of spiro-furanoindolines **28c** in DCE at 0 °C. This reaction proceeds smoothly with differently substituted (electron-donating as well as electron-withdrawing groups) spiro-epoxyoxindoles. Interestingly, it has been observed that $Sc(OTf)_3$ (10 mol%) is optimal for all *N*-methyl and *N*-allyl spiro-epoxyoxindoles, whereas 10 mol% of $BF_3{\cdot}OEt_2$ is best for all *N*-benzyl spiro-epoxyoxindoles. These spirocyclic oxindoles were obtained as an equal diastereomeric mixture (1 : 1). Noticeably, in this reaction, a polar solvent facilitated the C–Si bond cleavage, whereas the β-silicon effect was predominant in a nonpolar solvent (Scheme 28).

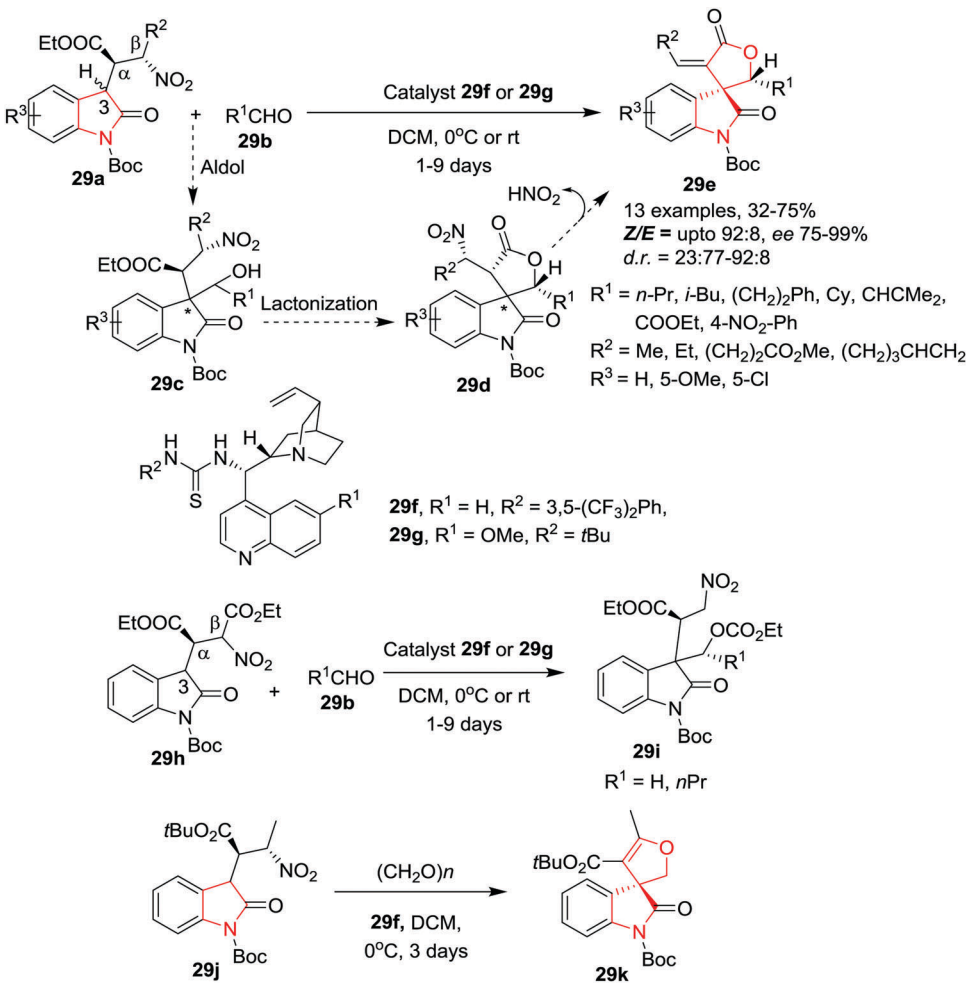
Further, Kumar and co-workers[34] have extended this methodology to get access to substituted spirocyclic oxindoles as a diastereomeric mixture in appreciable yields (60–78%) with substituted allylsilanes using a similar methodology except using DCM as reaction solvent.

Quintavalla and co-workers[35] have developed a new methodology to access pharmaceutically important 3-spiro-α-alkylidene-γ-butyrolactone oxindoles **29e** with excellent enantioselectivity and high *E*/*Z* ratio by reacting β-nitro oxindoles **29a** and aldehydes **29b**, in the presence of a bifunctional chiral thiourea based catalyst **29f** or **29g** in DCM at 0 °C or rt. Under the optimized conditions, several aliphatic aldehydes provided the corresponding spirolactone oxindoles in acceptable yields, good d.r. values, *Z*/*E* ratios and with high e.e. However, sterically hindered aldehydes required longer reaction times. Interestingly, when ethyl glyoxylate was subjected to this reaction at rt, significantly lower diastereoselectivity and decreased e.e. for the major isomer (86% e.e.) were observed, whereas the minor isomer was produced with excellent enantio-control (96% e.e.). Further, the same reaction at low temperature (0 °C) unexpectedly resulted in a reversed diastereomeric ratio and with high

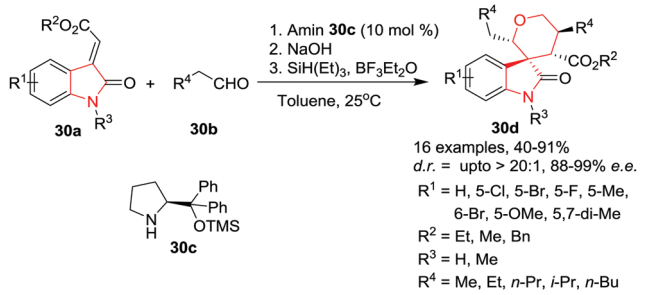
enantioselectivity of the major isomer. The use of aromatic aldehydes led to good enantiomeric excess at rt which can be improved by carrying out the reaction at 0 °C. However, this required longer reaction times and gave only low product yields. The spirolactones, variably substituted on the exocyclic double bond with alkyl groups, were obtained with good stereoselectivities and yields. Further, an electron-donating or electron-withdrawing group on the oxindole aromatic ring is well tolerated. The reaction proceeds with the proposed aldol/lactonization/elimination domino sequence. Interestingly, nitroester-derived oxindoles **29h** gave uncyclized product **29i** as a mixture of four inseparable diastereoisomers which is generated through an unexpected intramolecular 1,5 C → O migration of the ethyl ester from the Cβ to the hydroxyl group. Further, the β-nitro oxindoles **29j** bearing a *tert*-butyl ester at Cα (instead of ethyl ester) gave access to only 3-spiro dihydrofuran oxindole **29k** in low yield (15%) but with excellent enantiomeric excess (Scheme 29).

9. Six membered oxygen containing spiro-cyclic compounds. Zeng, Zhong and co-workers[36] have developed an efficient organocatalytic Michael/aldol/hemiacetalization cascade reaction of electron-deficient oxindole olefins **30a** and aliphatic aldehydes **30b** to get access to highly functionalized 5′,6′-dihydro-2′*H*,4′*H*-spiro[indoline-3,3′-pyran]-2-ones **30d** in good yields and with high stereoselectivities. This one pot protocol was catalyzed by a chiral amine **30c** under basic conditions in toluene at rt. It has been found that the reaction could accommodate a broad range of substituents (irrespective of the electronic nature) on the 3-ylideneoxindoles, and provided the products in moderate to good yields with good to excellent diastereo- and enantioselectivities. The 3-ylideneoxindoles with methyl and benzyl esters were also good substrates for the reaction and provided the desired products in moderate to good yields and diastereoselectivities with excellent enantioselectivities. Notably, changing the propionaldehyde to other aliphatic aldehydes resulted in slightly lower yields with good to excellent stereoselectivities. Furthermore, *N*-methyl protected oxindole olefin also gave the desired product in good yield and with excellent diastereoselectivity, although the e.e. was lowered to 85% (Scheme 30).

Wu and co-workers[37] have reported the first organocatalytic enantioselective Michael/cyclization cascade reaction of α-cyano ketones **31a** and isatylidene malononitriles **31b** to get access to new spiro[4*H*-pyran-oxindoles] **31d** in the presence of quinidine-derived organo-catalyst **31c** and morpholine as additive in DCM



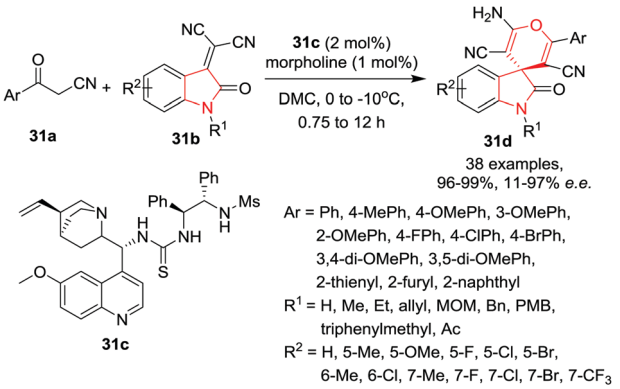
Scheme 29 Synthesis of 3-spiro-α-alkylidene-γ-butyrolactone oxindoles **29e**.



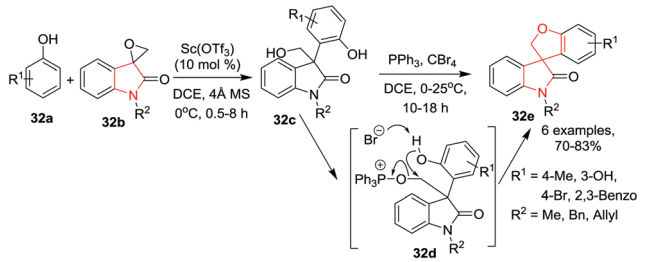
Scheme 30 Synthesis of 5′,6′-dihydro-2′*H*,4′*H*-spiro[indoline-3,3′-pyran]-2-ones **30d**.

at 0 °C in quantitative yields with good to excellent enantioselectivity within 2 h. Under optimized conditions, differently substituted isatylidene malononitriles provided excellent yields irrespective of the electronic nature of the substituents and with good to excellent enantioselectivities. Interestingly the 6-methyl substituted isatylidene malononitriles required extended reaction times to give the desired product with excellent yield and enantioselectivity. Substituents on the nitrogen atom have a significant impact on the stereoselectivity of the reaction. The low steric hindrance of an *N*-alkyl substituent increased the enantioselectivity of the product whereas *N*-acetyl-substituted substrate provided inferior enantioselectivity. Isatylidene malononitrile with an unsubstituted *N*H group underwent the reaction smoothly but gave inferior enantioselectivity. Interestingly, when performing the same reaction at −10 °C, the enantioselectivity was improved significantly. The α-cyano ketones bearing an electron-rich substituent at the 4-position of the phenyl ring provided better enantioselectivities than those with an electron-withdrawing group. Further, substituents at the 3- and 2-position of the phenyl ring provided lower enantioselectivities likely due to the different stereoelectronic effects. Heterocyclic and polycyclic α-cyano ketones also provided excellent yields and enantioselectivities (Scheme 31).

10. Fused oxygen-heterocycle containing spiro-cyclic compounds. Hajra and co-workers[38] have developed a metal triflate-catalyzed intermolecular Friedel–Crafts reaction of arenes **32a** and spiroepoxyoxindoles **32b** to achieve the regioselective synthesis of 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-ones



Scheme 31 Synthesis of spiro[4*H*-pyran-oxindoles] **31d**.

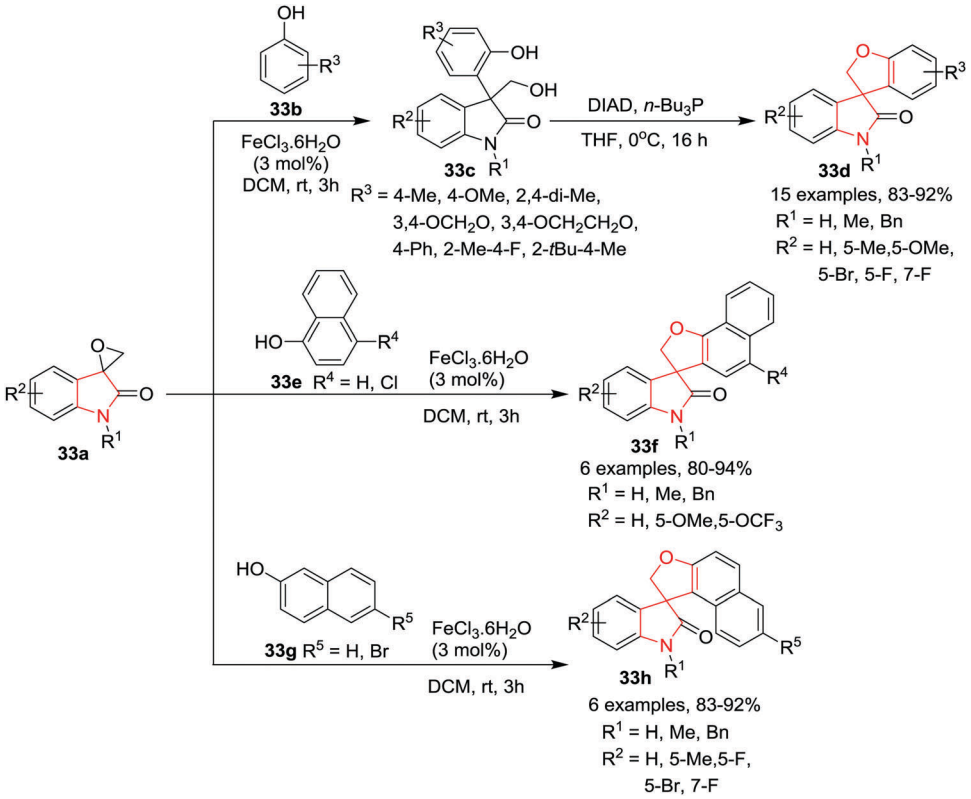


Scheme 32 Synthesis of 2*H*-spiro[benzofuran]-3,3′-oxindoles **32e**.

32c in good yields. These were subsequently utilized for the synthesis of 2*H*-spiro[benzofuran]-3,3′-oxindoles **32e**. The intermediate 3-aryl-(3-hydroxymethyl)oxindoles **32c** were subjected to Ph_3P and CBr_4 under Appel reaction conditions. This intramolecular etherification reaction was found to be general with a number of 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-ones and proceeded smoothly to provide very high yields of 2*H*-spiro[benzofuran]-3,3′-oxindoles. The reaction is believed to proceed through the intermediate alkoxyphosphonium salt **32d** which underwent intramolecular S_N2 cyclization with the phenolic OH, leading to the formation of the desired spiro[benzofuran]-3,3′-oxindoles (Scheme 32).

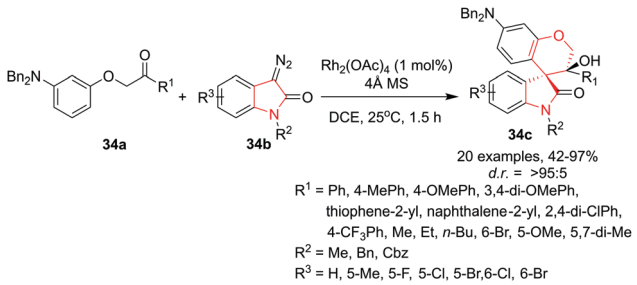
Wei and co-workers[39] have developed an efficient synthesis of 3-(3-indolyl)-oxindole-3-methanols **33c** through an Fe(III)-catalyzed, regioselective ring-opening/Friedel–Crafts-type arylation of spiro-epoxyoxindoles **33a** with phenols **33b**. Subsequently the generated 3-(3-indolyl)-oxindole-3-methanol **33c** has been utilized for the concise synthesis of novel 2*H*-spiro[benzofuran-3,3′-indolin]-2′-ones **33d**. Under the standard Mitsunobu reaction conditions, irrespective of the electronic nature of the substituents on the 3-(3-indolyl)-oxindole-3-methanols **33c**, 2*H*-spiro[benzofuran-3,3′-indolin]-2′-ones **33d** were synthesized in excellent yields. Interestingly, spiro-epoxyoxindoles underwent tandem Friedel–Crafts type arylation and *O*-cyclization with naphthols **33e** and **33g** in the presence of a catalytic amount of $FeCl_3{\cdot}6H_2O$ in DCM to yield novel naphthofuranyl-spirooxindoles **33f** and **33h** in high regioselectivity and excellent yields. The electronic nature of the substituent on the oxindole rings or on the naphthols was found to have a minimal effect on the reaction outcome and provided the addition/*O*-cyclization products in high to excellent yields. Besides *N*-methyl or benzyl-protected spiroepoxyoxindoles, *N*-unsubstituted spiro-epoxy-oxindoles also underwent this reaction smoothly, albeit with slightly lower yield (Scheme 33).

Hu and co-workers[40] have reported a simple, mild and efficient rhodium-catalyzed reaction of α-phenoxy ketones **34a** and 3-diazooxindoles **34b** for the synthesis of functionalized spiro[chroman-4,3′-oxindoles] **34c** in very high yields and stereoselectivities. The use of $Rh_2(OAc)_4$ in DCE at 25 °C in the presence of 4 Å molecular sieves was found to be optimal to achieve excellent product yields and diastereoselectivities. The optimized transformation protocol tolerates differently substituted aryl groups (electron-donating or electron-withdrawing as well as heterocyclic) on the α-phenoxyarylethanones and provides access to the desired products in very good yields and



Scheme 33 Synthesis of 2*H*-spiro[benzofuran-3,3′-indolin]-2′-ones **33d** and naphthofuranyl-spirooxindoles **33f** and **33h**.

excellent diastereoselectivities, even with bulky aryl groups such as naphthyl substituted substrates. Notably, 4-CF_3-phenyl-substitution provided the product with low diastereoselectivity probably due to partial isomerization of the *syn*-product under the standard reaction conditions. Importantly, small alkyl groups (methyl or ethyl) were also compatible whereas bulkier groups such as *n*-butyl afforded the corresponding spiro[chroman-4,3′-oxindole] with relatively low diastereoselectivity. Further, various electron-donating as well as electron-withdrawing substituents at the C-5 and C-6 positions of the 3-diazooxindoles gave access to the desired products in good yields with high diastereoselectivities. Importantly, replacement of the *N*-benzyl substituent of the 3-diazooxindole by *N*-Cbz or with *N*-Me slightly reduces the yields and diastereoselectivities. The synthetic efficiency of this process was proved by a gram-scale reaction that gave the desired product in 86% yield (1.09 g) with 95 : 5 diastereoselectivity (Scheme 34).



Scheme 34 Synthesis of functionalized spiro[chroman-4,3′-oxindoles] **34c**.

3. Outlook and conclusion

In this tutorial review, we have highlighted some recent advances in the construction of spiroindolines and spiroindoles which are the centre of attraction among medicinal chemists, due to their rigidity and unique three-dimensional geometries. Spirocyclization of indoles *via* the 2- or 3-position has been achieved successfully in high yields by utilizing various inorganic or organic catalytic systems. We have witnessed the use of various cinchona/quinidine based chiral catalysts for efficient spirocyclization in excellent yields, enantioselectivities and diastereoselectivities. The use of phosphoric acid based chiral ligands proved to be helpful for reaching a high level of regio- and enantiocontrol in spirocyclization reactions. Among these reactions, [3+2] or [3+4] cycloaddition, and [4+1] annulation reactions have proved to be a hallmark over the last few years. Further, the cascade Friedel–Crafts alkylation reaction has been applied successfully for the spirocyclization of indoles. Another interesting approach utilizes the cycloisomerization of appropriately substituted indoles. Our own contribution in this field utilized this approach where post Ugi-adducts were cycloisomerized, yielding highly functionalised polycyclic spirocyclic indoles. The application of MW-assisted and continuous-flow conditions in such processes opened a new avenue for spirocyclic reactions by employing a high catalyst/reactant ratio. It is likely that over the time, many more powerful and mild methodologies will emerge in this field.[11,21,27] Overall, we trust that this review will serve to update

the researchers focused on the synthesis of spiroindolines/spiroindoles, and will serve as an anchor to encourage further growth in this field.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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References

1 J. Reymond and M. Awale, *ACS Chem. Neurosci.*, 2012, **3**, 649–657.
2 M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem. – Eur. J.*, 2016, **22**, 2856–2881.
3 M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361.
4 (*a*) Q. F. Wu, H. He, W. B. Liu and S. L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418–11419; (*b*) P. D. Fedoseev and E. V. Van der Eycken, *Chem. Commun.*, 2017, **53**, 7732–7735.
5 L. Kong, M. Wang, F. Zhang, M. Xu and Y. Li, *Org. Lett.*, 2016, **18**, 6124–6127.
6 X. Zhang, G. Zhou, Y. Zhang, D. Zhang-Negrerie, Y. Du and K. Zhao, *J. Org. Chem.*, 2016, **81**, 11397–11403.
7 L. Zhang, Y. Wang, X. Hu and P. Xu, *Chem. – Asian J.*, 2016, **11**, 834–838.
8 C. Peng, J. Zhai, M. Xue and F. Xu, *Org. Biomol. Chem.*, 2017, **15**, 3968–3974.
9 J. Zhao, D. Yue, X. Zhang, X. Xu and W. Yuan, *Org. Biomol. Chem.*, 2016, **14**, 10946–10952.
10 J. Zhang, N. Li, S. Yin, B. Sun, W. Fan and X. Wang, *Adv. Synth. Catal.*, 2017, **359**, 1541–1551.
11 L. Shi, L. Li, J. Wang, B. Huang, K. Zeng, H. Jin, Q. Zhang and Y. Jia, *Tetrahedron Lett.*, 2017, **58**, 1934–1938.
12 R. D. Gao, Q. L. Xu, L. X. Dai and S. L. You, *Org. Biomol. Chem.*, 2016, **14**, 8044–8046.
13 J. Huang, M. Sohail, T. Taniguchi, K. Monde and F. Tanaka, *Angew. Chem.*, 2017, **56**, 5853–5857.
14 L. Zhang, W. Ren, X. Wang, J. Zhang, J. Liu, L. Zhao and X. Zhang, *Eur. J. Med. Chem.*, 2017, **126**, 1071–1082.
15 G. Zhu, Q. Wei, H. Chen, Y. Zhang, W. Shen, J. Qu and B. Wang, *Org. Lett.*, 2017, **19**, 1862–1865.
16 F. Schröder, U. K. Sharma, M. Mertens, F. Devred, D. P. Debecker, R. Luque and E. V. Van der Eycken, *ACS Catal.*, 2016, **6**, 8156–8161.
17 G. Zhu, S. Liu, S. Wu, L. Peng, J. Qu and B. Wang, *J. Org. Chem.*, 2017, **82**, 4317–4327.
18 G. Zhu, S. Wu, X. Bao, L. Cui, Y. Zhang, J. Qu, H. Chen and B. Wang, *Chem. Commun.*, 2017, **53**, 4714–4717.
19 J. Zhang, H. Wang, Q. Jin, C. Zheng, G. Zhao and Y. Shang, *Org. Lett.*, 2016, **18**, 4774–4777.
20 J. Su, Z. Ma, X. Li, L. Lin, Z. Shen, P. Yang, Y. Li, H. Wang, W. Yan, K. Wang and R. Wang, *Adv. Synth. Catal.*, 2016, **358**, 3777–3785.
21 D. Chen, W. Xiaoa and J. Chen, *Org. Chem. Front.*, 2017, **4**, 1289–1293.
22 A. Preetam and M. Nath, *Tetrahedron Lett.*, 2016, **57**, 1502–1506.
23 A. M. Jadhav, S. G. Balwe, K. T. Lim and Y. T. Jeong, *Tetrahedron*, 2017, **73**, 2806–2813.
24 Y. Wang, C. Zheng and S. L. You, *Angew. Chem., Int. Ed.*, 2017, **56**, 15093–15097.
25 V. Magne, F. Blanchard, A. Marinetti, A. Voituriez and X. Guinchard, *Adv. Synth. Catal.*, 2016, **358**, 3355–3361.
26 L. Wang, S. Li, M. Blumel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen and D. Enders, *Angew. Chem.*, 2016, **55**, 11110–11114.
27 A. S. Filatov, N. A. Knyazev, A. P. Molchanov, T. L. Panikorovsky, R. R. Kostikov, A. G. Larina, V. M. Boitsov and A. V. Stepakov, *J. Org. Chem.*, 2017, **82**, 959–975.
28 N. Li, J. Zhang, B. Sun, H. Li and X. Wang, *Org. Lett.*, 2017, **19**, 1954–1957.
29 S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. V. Meervelt and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2012, **51**, 9572–9575.
30 F. Schröder, M. Ojeda, N. Erdmann, J. Jacobs, R. Luque, T. Noël, L. V. Meervelt, J. Van der Eycken and E. V. Van der Eycken, *Green Chem.*, 2015, **17**, 3314–3318.
31 F. Schröder, N. Erdmann, T. Noël, R. Luque and E. V. Van der Eycken, *Adv. Synth. Catal.*, 2015, **357**, 3141–3147.
32 Z. L. Xia, C. Zheng, S. G. Wang and S. L. You, *Angew. Chem., Int. Ed.*, 2018, **57**, 2653–2656.
33 S. Hajra, S. Roy and S. Maity, *Org. Lett.*, 2017, **19**, 1998–2001.
34 B. M. Sharma, M. Yadav, R. G. Gonnade and P. Kumar, *Eur. J. Org. Chem.*, 2017, 2603–2609.
35 L. Cerisoli, M. Lombardo, C. Trombini and A. Quintavalla, *Chem. – Eur. J.*, 2016, **22**, 3865–3872.
36 L. Zhu, Q. Chen, D. Shen, W. Zhang, C. Shen, X. Zeng and G. Zhong, *Org. Lett.*, 2016, **18**, 2387–2390.
37 J. Xie, W. Xing, F. Sha and X. Wu, *Eur. J. Org. Chem.*, 2016, 3983–3992.
38 S. Hajra, S. Maity and S. Roy, *Adv. Synth. Catal.*, 2016, **358**, 2300–2306.
39 M. Luo, R. Yuan, X. Liu, L. Yu and W. Wei, *Chem. – Eur. J.*, 2016, **22**, 9797–9803.
40 S. Jia, Y. Lei, L. Song, A. Gopi, K. Reddy, D. Xing and W. Hu, *Adv. Synth. Catal.*, 2017, **359**, 58–63.

