

## SYNTHETIC APPROACHES TOWARDS 2-SPIROPSEUDOINDOXYLS

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**Abstract.** Spiropseudoindoxyls (or 2-spirocyclic fused 1,2-dihydroindol-3-ones) are a core structure of a number of bioactive compounds and natural products. While there have been several recent advances in their synthesis, the synthetic literature on this structure is quite scattered. In an attempt to make this chemistry more accessible to the scientific community, we review the leading approaches and recent developments for the synthesis of these C2-spiropseudoindoxyls.

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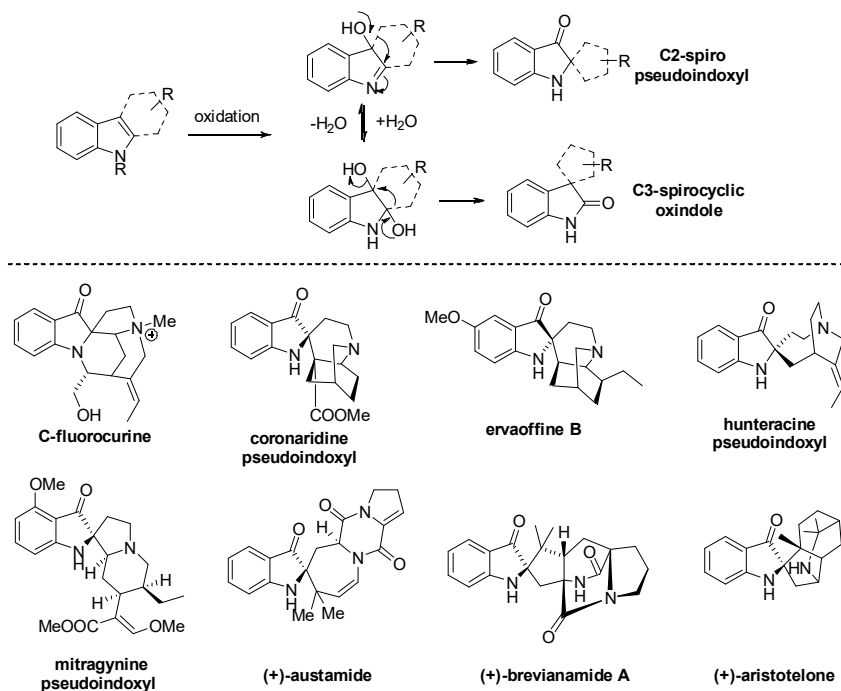
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**1. Introduction**

Many examples from the Iboga, Corynanthe and Aspidosperma family of indole alkaloids are known to undergo oxidative transformations, amongst others towards the corresponding 3-spirocyclic indol-2-ones, named oxindole analogues, or 2-spirocyclic fused 1,2-dihydroindol-3-ones.<sup>1</sup> The latter compounds are also named spiropseudoindoxyls (Figure 1). In both cases the structural rearrangement is believed to proceed *via* a pinacol-type 1,2-alkyl shift.<sup>2</sup> Whether or not these compounds are formed in the organism as secondary metabolites or formed due to air mediated autoxidation during treatment of the plant material,<sup>3</sup> several spiropseudoindoxyls have been isolated<sup>4</sup> and demonstrated pronounced biological activities.

As an example, mitragynine pseudoindoxyl is a Corynanthe type alkaloid isolated from Rubiaceae plants with analgesic activity. In fact, this compound is the oxidative derivative from mitragynine, which displays a 100 times less potent activity as  $\mu$ -opioid agonist as compared to the corresponding pseudoindoxyl.<sup>5</sup> C-Fluorocurine is the oxidative product from the parent alkaloid mavacurine,<sup>6</sup> and conopharyngine pseudoindoxyl is the rearranged product derived from jollyanine (the 3-hydroxyindolenine analogue of conopharyngine).<sup>7</sup> Other examples include e.g. ibogaine- (*syn.* iboluteine), voacangine- (*syn.* voaluteine), voacristine- and ibogamine-pseudoindoxyls.<sup>8</sup> Recently, new iboga-type pseudoindoxyl compounds, named ervaoffines were isolated from *Ervatamia officinalis*.<sup>9</sup> Remarkable is the reverse stereochemistry of the spirocenter as compared to most other isolated analogues. With respect to the spirocenter stereochemistry, it has been observed experimentally that isomerization to a mixture of both isomers can occur in case of pseudoindoxyls which are derived from tetrahydro-betacarboline type alkaloids and this *via* a retro Mannich type ring opening followed by rotation and ring closure (see paragraph 3, Scheme 5) or by a reduction/ring expansion/oxidation/ring contraction sequence.<sup>10,11</sup> Other notable examples of isolated pseudoindoxyls are austamide,<sup>12,13</sup> brevianamide<sup>14,15</sup> and aristotelone.<sup>16</sup> Spiropseudoindoxyls have also found applications in material chemistry as fluorescent dyes.<sup>17</sup>

While spirooxindoles with quaternary centers at the C3 position are very well described in the literature and show a broad range of bioactivities, the isomeric C2 pseudoindoxyl moiety currently is an underappreciated structure in the field of medicinal and organic chemistry. In this review, the various approaches made towards these spirocyclic structures are summarized.



**Figure 1.** Selected natural products bearing the spiropseudoindoxyls core.

## 2. Synthetic approaches towards pseudoindoxyls

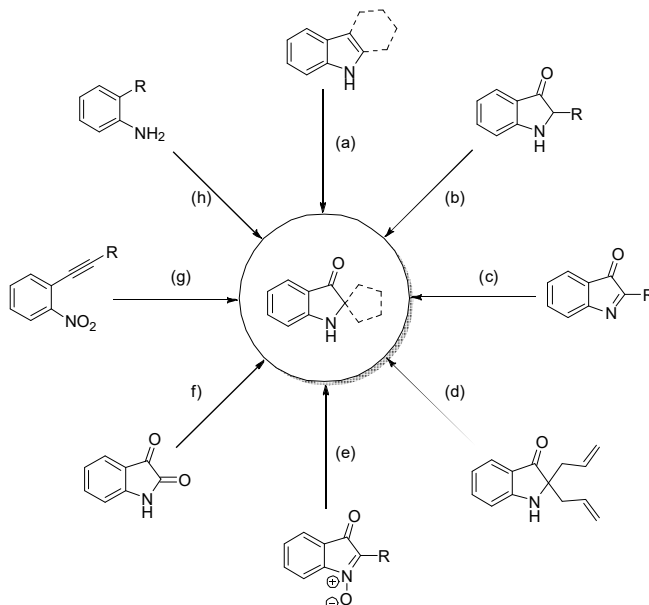
Several approaches towards the spiropseudoindoxyl core have already been reported in literature. A number of straightforward entries start from related indole(-like) structures. Oxidation of [2,3]-fused indoles at the C3 position, followed by a 1,2-shift/ring contraction affords spiropseudoindoxyls (Scheme 1 path **a**). Deprotonation of 3-indolinones and quenching with suitable electrophiles can afford 2,2-disubstituted pseudoindoxyls and the corresponding spirocycles after an intramolecular cyclization (Scheme 1 path **b**). Similarly, indoleninones are susceptible to reactions with nucleophiles at the C2-position and cyclizations of double C2 functionalized pseudoindoxyls can afford spiropseudoindoxyls (Scheme 1 path **c** and **d**). While these reactions are relatively straightforward, these are limited to starting materials derived from indoles.

Other approaches make use of isotogens which can undergo a (3+2) cycloaddition with alkenes to afford fused pseudoindoxyls which can be transformed to ‘open’ spirocycles *via* reduction of the N-O bond (Scheme 1 path **e**). Isatins typically undergo reactions at the more reactive C3-position, but various rearrangements of these adducts to the C2 position are reported (Scheme 1 path **f**). All the aforementioned methods start with a heterocyclic core already similar to the desired pseudoindoxyls. Alternatively, a ring formation from *ortho*-substituted benzenes is also described in literature: cycloisomerization of an *o*-nitro alkyne or various reactions of *o*-substituted anilines are the two best known examples (Scheme 1 path **g** and **h**).

The mentioned routes towards spiropseudoindoxyls will be discussed in more detail throughout this review.

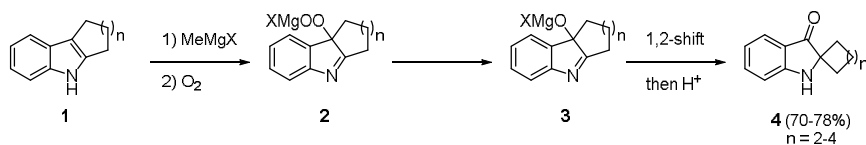
## 3. Oxidations of fused indoles

The oxidation of indoles followed by a Wagner-Meerwein type 1,2-shift has been employed successfully for the synthesis of 2,2-disubstituted pseudoindoxyls.<sup>18,19</sup> Based on previous work by the groups of Taylor<sup>20</sup> and Hootele,<sup>8</sup> a similar approach of fused indoles towards spiropseudoindoxyls is employed by Rodriguez and co-workers.<sup>21</sup>



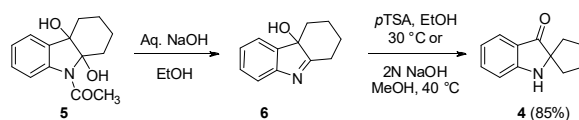
**Scheme 1.** Synthetic approaches towards spiropseudoindoxyls.

They observed the formation of **4** as a by-product while performing a C3-alkylation of an indolylmagnesium salt. Performing the reaction under oxygen atmosphere afforded spiropseudoindoxyls **4** as the only observed products. The authors proposed the initial formation of an indolylmagnesium salt in which oxygen inserts *via* a radical mechanism to form **2**. A nucleophilic attack of indolylmagnesium salt on the formed magnesium peroxide **2** results in the formation of **3** which can undergo a 1,2-shift to afford spirocycles **4** after aqueous workup. It should be noted that in the case of a 1,2-shift of a fused cyclopentyl ( $n=1$ ) to a spirocyclobutyl, no desired spirocycle **4** was observed. Larger ring systems ( $n=2-4$ ) generally resulted in the formation of **4** in good isolated yields (Scheme 2).



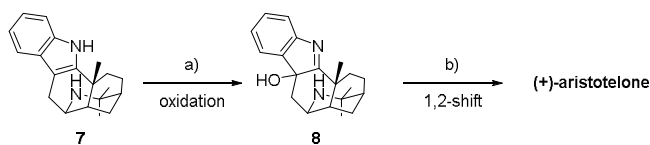
**Scheme 2.** An example of an indole oxidation/1,2-shift sequence towards **4**.

In 1950, Witkop and co-workers documented the first examples of the synthesis of spiropseudoindoxyls.<sup>22</sup> Treatment of 9-acetyl-10,11-dihydroxy carbazole **5** with base resulted in the formation of **6**, an intermediate also seen in indole oxidation (see other examples in this paragraph). A subsequent acid- or base-catalyzed rearrangement of this intermediate **6** led to the formation of the desired spirocycle **4** (Scheme 3).



**Scheme 3.** Base-catalyzed formation of **6** and **4** from carbazole **1**.

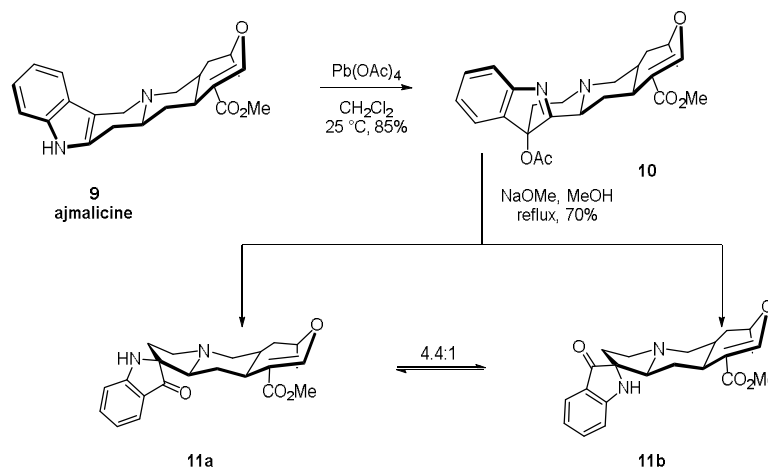
These insights were used by the groups of Borschberg and Heathcock, who independently developed a similar approach for the total synthesis of (+)-aristolone and related alkaloids.<sup>23,24</sup> Oxidation of aristoteline **7** at the C3 position affords serratoline **8**. This compound can undergo a 1,2-shift under harsh acidic or basic conditions towards the desired aristolone (Scheme 4).



**Borschberg's conditions:** a) 1) mCPBA, TFA, CH<sub>2</sub>Cl<sub>2</sub>, -40°C, 1h; 2) Me<sub>2</sub>S, 98%;  
b) (H<sub>3</sub>PO<sub>4</sub>)<sub>n</sub>, EtOH, reflux, 24h, 95% or neat, 200°C, 30min, 98%  
**Heathcock conditions:** a) 1) 1atm O<sub>2</sub>, Pt, EtOAc, rt, 24h; 2) H<sub>2</sub>, Pt, EtOAc, 0°C, 25min, 33%  
b) NaOH, H<sub>2</sub>O / MeOH, reflux, 2d, 97%

**Scheme 4.** Natural product synthesis *via* an indole oxidation/1,2-shift sequence.

In similar work on Yohimbane type alkaloids, Borschberg and co-workers reported the base-induced rearrangement of the 7-hydroxy-7*H*-indolenines derived from ajmalicine **9**, yohimbine, corynanthine, methyl reserpate, and methyl isoreserpate.<sup>10</sup> In each case, a mixture of two epimeric spiropseudoindoxyls **11a** and **11b** was obtained. Treatment of ajmalicine **9** with Pb(OAc)<sub>4</sub> furnished the 7-acetoxyindole derivative **10**. The resulting compound was treated with NaOMe in MeOH to afford a 4.4:1 epimeric mixture in a combined yield of 70% (Scheme 5).

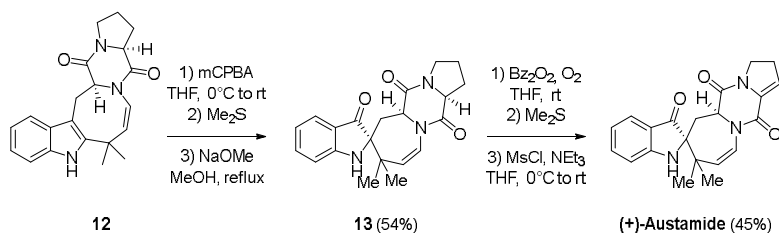


**Scheme 5.** An indole oxidation/1,2-shift sequence on ajmalicine **9**.

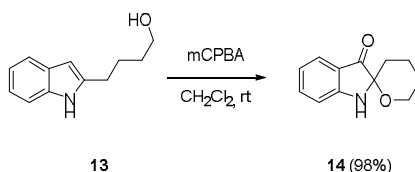
In the following years, a number of alternative oxidation methods were proposed for the oxidation (singlet oxygen using rose bengal<sup>25</sup> or Ru(bpy)<sub>3</sub> photoredox,<sup>26</sup> DMDO,<sup>27,28</sup> Pb(OAc)<sub>4</sub>,<sup>5</sup> *tert*-butyl hydroperoxide,<sup>29</sup> biocatalysis<sup>30</sup>) and 1,2-shift (Sc(OTf)<sub>3</sub><sup>27</sup>) but the general principle remained the same throughout a number of publications. One example involves the elegant synthesis of austamide by Baran and Corey.<sup>31</sup> The fused eight-membered indole **12** was oxidized using mCPBA and the formed 3-hydroxyindolenine then underwent the 1,2-shift under basic conditions in decent yields. A subsequent oxidation/elimination protocol afforded the natural product (Scheme 6).

Spiropseudoindoxyls can also be obtained in a different approach *via* the oxidation of a 2-substituted indole with an internal nucleophile present. Kobayashi and co-workers first reported this reaction in 2007, showing that treatment of **13** with mCPBA affords spiropseudoindoxyl **14** (Scheme 7).<sup>32</sup> The hemiaminal function

could be opened again *via* the addition of a Lewis acid, generating indoleninones *in situ* for further functionalization (see paragraph 5, Schemes 13 and 15).

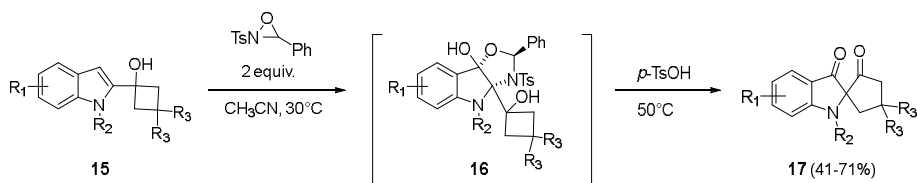


**Scheme 6.** Total synthesis of (+)-austamide.



**Scheme 7.** Synthesis of spiropseudoindoxyls **14** *via* oxidation / nucleophilic trapping sequence.

This strategy has recently been expanded by the research groups of Du<sup>33</sup> (hypervalent iodine oxidation) and Li<sup>29</sup> (anilines as internal nucleophile) for the synthesis of spiropseudoindoxyls. The research group of Zhang developed a cascade consisting of oxidative dearomatization and semipinacol rearrangement of indol-2-yl cyclobutanol **15** for the synthesis of the spiropseudoindoxyls.<sup>34</sup> The authors suggest that the treatment of cyclobutanol **15** with two equivalents of Davis reagent (*N*-sulfonyl oxaziridine) affords a dearomatized intermediate **16**. An acid-catalyzed semipinacol rearrangement of **16** then afforded spirocycles **17** in good yields (Scheme 8).



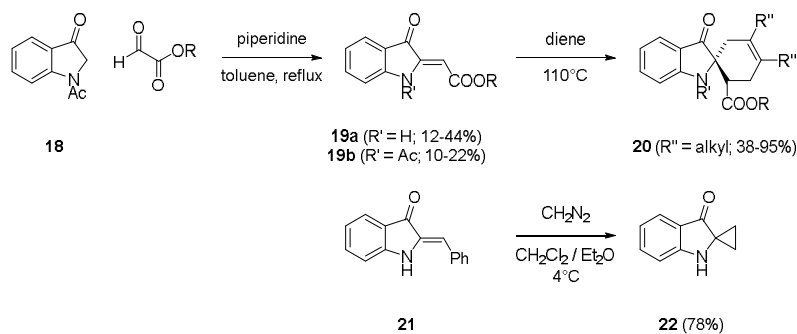
**Scheme 8.** A semi-pinacol rearrangement towards spiropseudoindoxyls **17**.

#### 4. Indol-3-ones as starting material

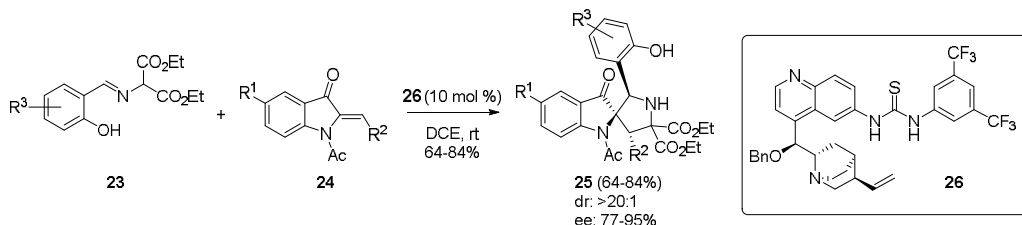
Indol-3-ones have served as suitable starting materials in the synthesis of spiropseudoindoxyls *via* initial deprotonation of the acidic  $\alpha$ -proton to install either two substituents or one double bond at the C2 position. A subsequent cyclization of the newly installed groups can then afford the desired spirocycles.

The first example of this was reported by the group of Mérour in 1996. An aldol reaction between indol-3-one **18** and glyoxylic esters resulted in the formation of a mixture of compounds **19a** and **19b** in modest yields.<sup>35</sup> Treating **19** with a suitable diene afforded spiropseudoindoxyls as single diastereomers in good yields *via* a Diels-Alder reaction. A similar approach was used by Lévai and co-workers who treated a related indolone **21** with diazomethane. This reaction led to the formation of a cyclopropyl spiropseudoindoxyl **22** in good yield (Scheme 9).<sup>36</sup>

Recently, Xu and co-workers reported an enantioselective modification of this strategy.<sup>37</sup> Employing a chiral hydrogen-bonding activation strategy, they were able to perform an asymmetric (3+2) cycloaddition on indol-3-one **24** with high *ee* and *dr*. The authors introduced an *o*-hydroxyl group at benzaaldimine **23** to improve the hydrogen-bonding network leading to higher stereoselectivity (Scheme 10).



**Scheme 9.** Cycloaddition entries to spiropseudoindoxyls **20** and **22** starting from indol-3-ones **18**.



**Scheme 10.** An enantioselective cycloaddition entry to spiropseudoindoxyls.

An alternative approach was developed by the group of Mérou, by using indol-3-ones **27** as nucleophiles in substitution reactions using 3-bromopropionitrile. The resulting nitrile **28** was then hydrogenated over platinum to the corresponding amine which underwent spontaneous intramolecular cyclization towards spirocycle **29** in excellent yield (Scheme 11).<sup>38</sup>

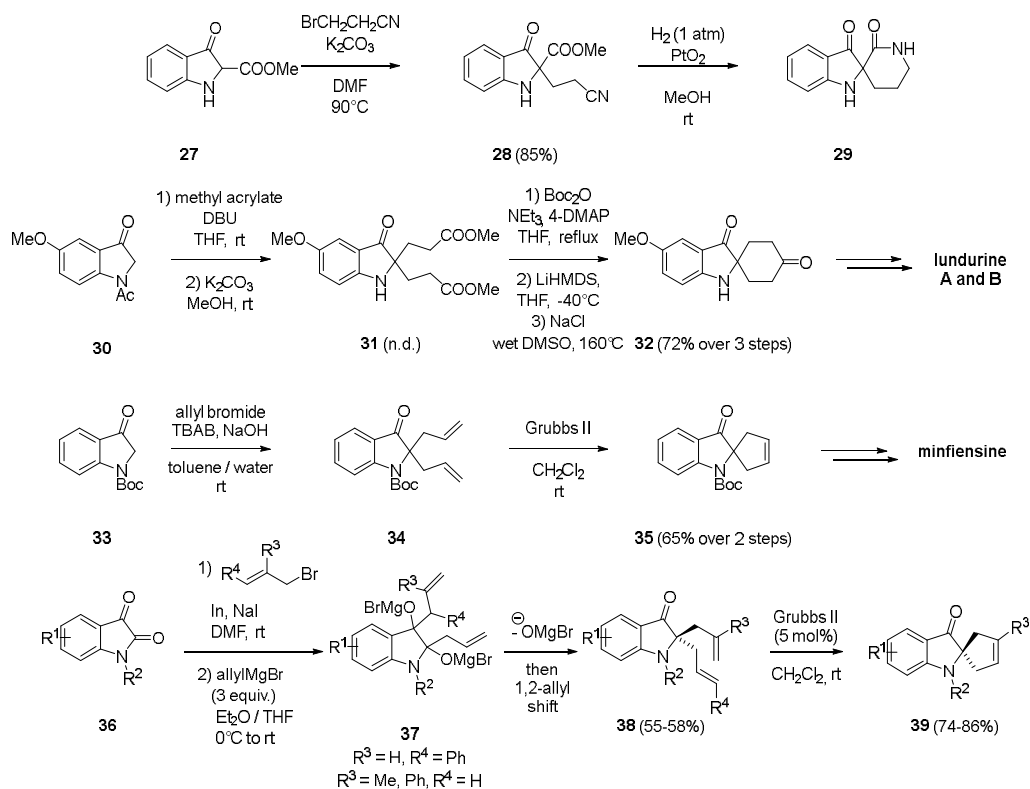
The group of Nishida started with a less functionalized starting material **30**, performing a double Michael addition of **30** on methyl acrylate, followed by deacylation to synthesize **31**. After the reintroduction of a Boc protecting group, a Dieckmann condensation and a Krapcho decarboxylation were used to afford the desired spirocycle **32**. Subsequent transformation led to the total synthesis of natural products lundurine A and B.<sup>39</sup> Similarly, Zu and co-workers performed a double allylation of protected indol-3-one **33** under biphasic conditions to afford **34**. A ring-closing metathesis then resulted in the formation of spirocycle **35**. Further functionalizations resulted in a formal total synthesis of minfiensine.<sup>40</sup> A similar approach to both spiropseudoindoxyls and carbazole alkaloids was recently developed by the Dash group.<sup>41</sup> Performing a Barbier reaction on isatin derivatives **36**, affords the expected C3 alkylated product. Treatment of this intermediate with allylmagnesiumbromide resulted in the formation of adduct **37** which underwent a rearrangement towards 2,2-dialkylated pseudoindoxyls **38**. Similarly to the cyclization of **34**, a ring-closing metathesis of **38** using Grubbs II catalyst afforded the spirocycles **39** in good yields (Scheme 11).

### 5. Indoleninones as starting material or key intermediate

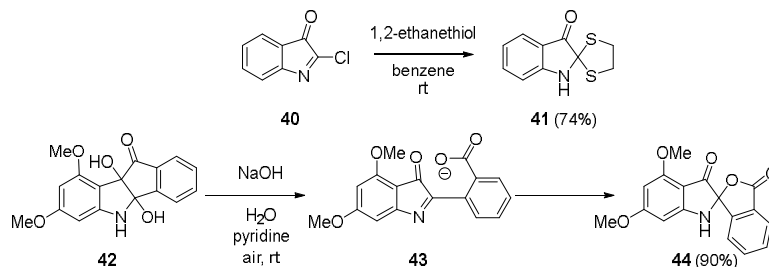
The first example of employing indoleninones in the synthesis of spiropseudoindoxyls was reported by Baker and Duke in 1972.<sup>42</sup> In this case, 2-chloroindoleninone **40** was treated with 1,2-ethanethiol to afford spirocycle **41**, probably *via* an initial addition / elimination, followed by an intramolecular cyclization of the second thiol group (Scheme 12). A later report by the group of Black treated the reaction of activated anilines and ninhydrin, affording polycycle **42**.<sup>43</sup> Treating this compound with aqueous sodium hydroxide in pyridine afforded spirocycle **44** in good yield. The authors proposed indoleninone **43** as a key intermediate, followed by intramolecular cyclization towards **44**.

Subsequent work involved was mainly based around ‘masked’ indoleninones. For example, indolic triflate **45** reacts with disubstituted ethylenediamine to afford spirocycles **47**. The authors proposed this reaction to proceed *via* an elimination of the sulfinyl group, generating indoleninone **46** *in situ*.<sup>44</sup> A

nucleophilic attack of one of the amines followed by intramolecular amide formation resulted in the formation of observed **47**. Similarly, Sakamoto and co-workers showed that C2-alkoxylated indol-3-ones **48** can act as masked indoleninones.<sup>45</sup> After reduction with NaBH<sub>4</sub>, treatment with a catalytic amount of Lewis acid (SnCl<sub>4</sub> or TMSOTf) generates **49** which undergoes intramolecular cyclization. Due to the initial reduction of the C3-carbonyl, a subsequent oxidation was needed to afford **50** in decent yield (Scheme 13).



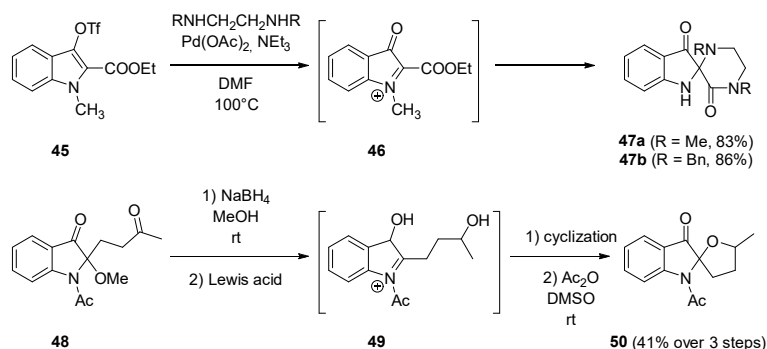
**Scheme 11.** Examples of C2 functionalization followed by cyclization.



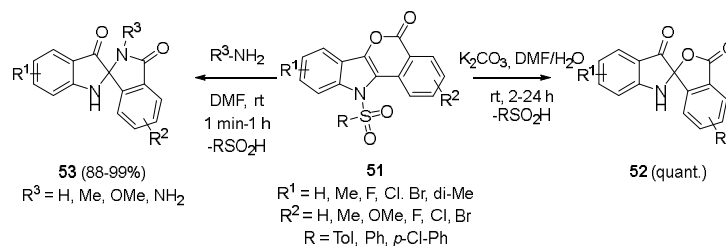
**Scheme 12.** Early examples of indoleninone transformations towards spiroseuindoxyls.

An efficient ring-contraction reaction of isochromene fused indoles **51** towards spiroseuindoxyls was reported by the group of Zhao.<sup>46</sup> Addition of a nucleophile (*e.g.* water) results in an attack at the ester and subsequent sulfonyl elimination to afford an indoleninone intermediate, similar to **43**. Subsequent

cyclization afforded the spiropseudoindoxyls in quantitative yield. When using a nitrogen-based nucleophile in aqueous solution, only formation of the *N,N*-unsubstituted aminal **53** was observed (Scheme 14).

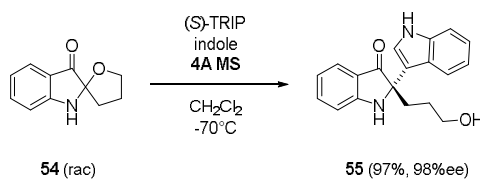


**Scheme 13.** Early examples of ‘masked’ indoleninones.



**Scheme 14.** Isochromene fused indoles as ‘masked’ indoleninones.

Spirocyclic pseudoindoxyls **54** can also act as a ‘masked’ indoleninone under acidic conditions, as shown by the group of You.<sup>47</sup> Employing a chiral phosphoric acid, they were able to transform racemic **54** into enantioenriched **55**. In these cases, the formed indoleninone was quenched with electron-rich nucleophiles, according to the same principle as described in Schemes 12-14. This methodology was employed towards the synthesis of isatisine A-like scaffolds and the scope of this reaction was later investigated further by the group of Ramana (Scheme 15).<sup>48</sup>



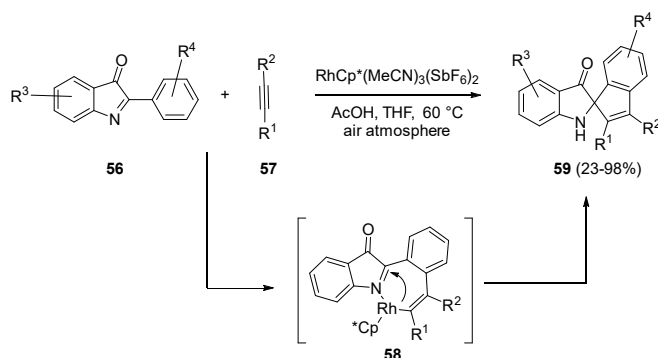
**Scheme 15.** Enantioselective transformation of ‘masked’ indoleninone **54**.

Dong described a synthesis of rigid spiropseudoindoxyls through a tandem C–H activation/alkyne insertion/addition process using rhodium catalysis.<sup>49</sup> Indoleninone **56** directs *ortho* C–H activation to form a rhodacycle intermediate which undergoes regioselective alkyne insertion to yield seven-membered ring **58** followed by intramolecular addition of the organometallic species to the imine. A final protonolysis yielded the desired spirocyclic **59** (Scheme 16).

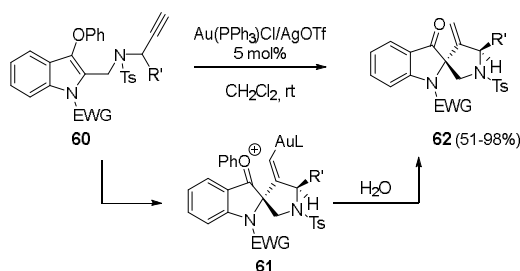
In 2011, Tu and co-workers reported a regiodivergent annulation of alkynylated 3-phenoxyindoles **60** using a gold(I) catalyst.<sup>50</sup> When the indole was protected with an electron-withdrawing group, a C2 regioselective annulation occurred towards spiropseudoindoxyls **62**. The combination of the EWG at nitrogen and the phenoxy group at C3 greatly enhanced nucleophilicity at C2 (instead of C3), allowing it to



perform a nucleophilic attack on the activated triple bond. The resulting oxonium intermediate **61** was quenched with water to afford spirocycle **62**. The participation of water in this 5-exo-dig cyclization process was confirmed by a H<sub>2</sub><sup>18</sup>O isotopic labeling experiment (Scheme 17). In contrast, protecting the indole with an alkyl group resulted in different reactivity, affording fused indoles instead.



**Scheme 16.** A Rh-catalyzed C–H activation/insertion/addition reaction on indoleninone **56**.



**Scheme 17.** Gold(I)-catalyzed annulation towards spiroseuindoxyls **62**.

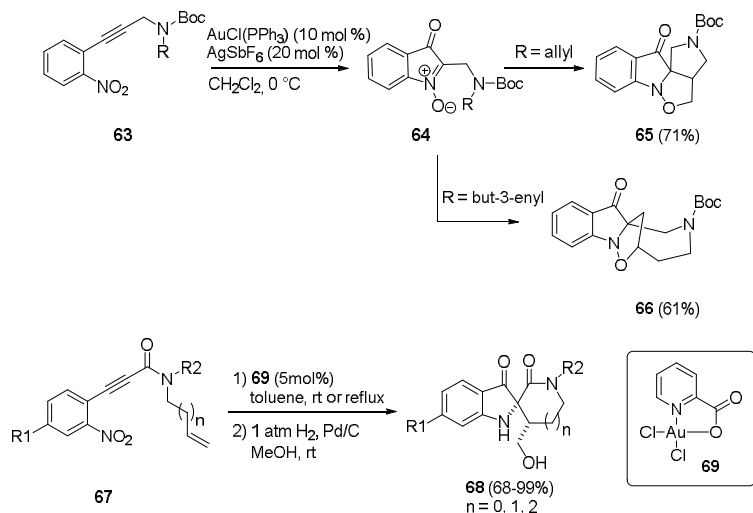
## 6. Cycloadditions with isotogens

In 2014, Ramana and co-workers reported an efficient domino process for the construction of the tricyclic core present in the spiroseuindoxyl natural products using gold(I) catalysis. An intramolecular nitro-alkyne redox transfer in **63** affords isotogens **64** which undergoes a (3+2)-cycloaddition with a suitably positioned olefin. Depending on the length of the alkyl tether, a fused **65** or bridged polycycle **66** was obtained. In some cases, anthranils were observed as a significant side product as is known in related *o*-nitro alkyne cycloisomerizations (Scheme 18).<sup>51</sup>

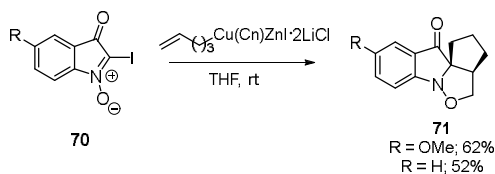
In parallel, Verniest and co-workers achieved the regioselective synthesis of spiroseuindoxyls in high isolated yields using a similar Au(III)-catalyzed cycloisomerization/cycloaddition approach of **67**. A mild hydrogenation was employed to cleave the N–O bond to afford the ‘open’ spirocycle **68** in a diastereoselective manner.<sup>52</sup> This approach was also successfully implemented by the group of Harrity in an attempt to further functionalize 2-iodoisatogens **70**. Treating these with pentenyl copper reagents resulted in a substitution towards isotogens similar to **64** and subsequent intramolecular (3 + 2) cycloaddition afforded spiroseuindoxyls **71** (Scheme 19).<sup>53</sup>

## 7. Formation of the indol-3-one five-membered ring

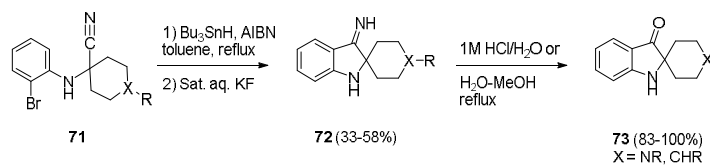
In 1999, Sulsky and co-workers designed a radical cyclization of anilinonitrile **71** towards spiroseuindoxyls **73**. Cleavage of the C–Br bond generated an aryl radical which underwent a 5-*exo*-dig cyclization to form imine **72** in moderate yield. A subsequent hydrolysis of this imine provided the desired spiroseuindoxyl skeleton **73** in (near) quantitative yields (Scheme 20).<sup>54</sup>



**Scheme 18.** Gold-catalyzed nitro-alkyne cycloisomerizations followed by (3+2) cycloaddition.

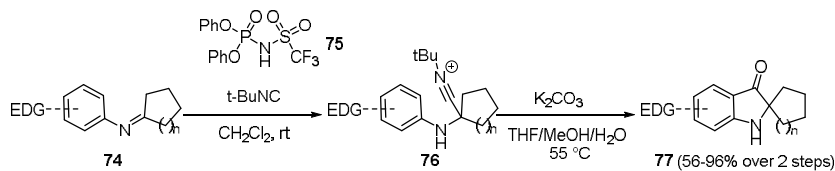


**Scheme 19.** Addition/elimination on 2-iodoisatogens **70** followed by (3+2) cycloaddition.



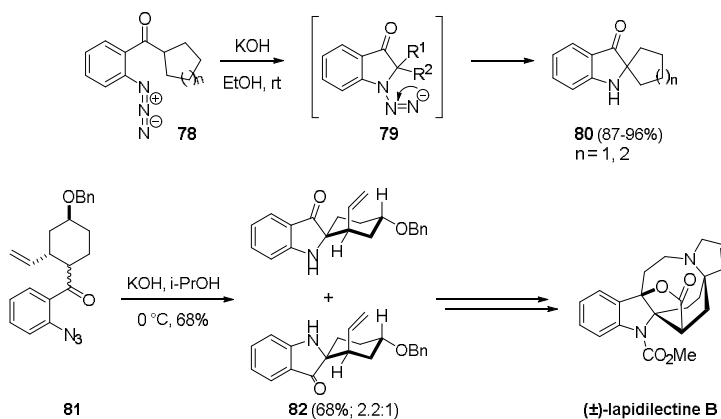
**Scheme 20.** Radical cyclization for the synthesis of spiroseuindoxyls **73**.

Sorensen and co-workers reported the synthesis of spiroseuindoxyls **77** using an interrupted Ugi reaction (*i.e.* isonitril addition to iminium species).<sup>55</sup> Replacing the carboxylic acid normally used in an Ugi reaction with a Brønsted acid bearing a non-nucleophilic counterion (here phosphoramidate **75**) allowed for the formation of an  $\alpha$ -amino nitrilium ion **76** *in situ*. The electron-rich aromatic system could then perform a Houben-Hoesch type cyclization. The resulting imine was then hydrolyzed to accomplish the synthesis of spiroseuindoxyls **77** (Scheme 21).



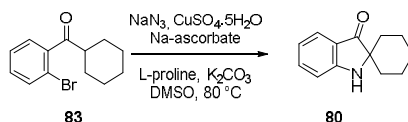
**Scheme 21.** Interrupted Ugi reaction for the synthesis of spiroseuindoxyls **77**.

In another approach developed by the group of Smalley, the anion of  $\alpha$ -azidophenyl ketones **78** underwent intramolecular cyclization towards intermediates **79**.<sup>56</sup> A loss of nitrogen and protonation then affords spiropseudoindoxyls **80** in excellent yields. This Smalley cyclization was later employed by Pearson and co-workers in their total synthesis of ( $\pm$ )-lapidilactone B (Scheme 22).<sup>57</sup>



**Scheme 22.** Smalley cyclization and representative synthesis of ( $\pm$ )-lapidilactone B.

In 2013, the Ramana research group extended this methodology by forming  $\alpha$ -azidophenyl ketones **78** *in situ*.<sup>58</sup> Using a catalytic Cu(I)-ascorbate redox system, the conversion of the  $\alpha$ -bromophenyl ketones **83** to the  $\alpha$ -azidophenyl **78** was achieved. Under these conditions, the base-induced enolate cyclization takes place to afford the spiropseudoindoxyl **80** directly in good isolated yields (Scheme 23).



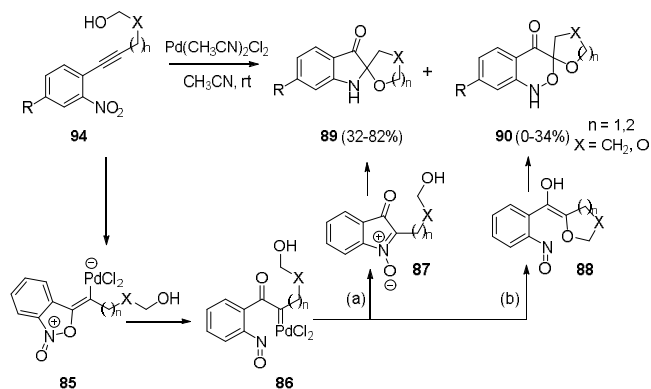
**Scheme 23.** One-pot formation of  $\alpha$ -azidophenyl ketones and subsequent Smalley cyclization.

An alternative approach from the Ramana group was based on metal-catalyzed nitro-alkyne cycloisomerizations.<sup>59</sup> Activation of the triple bond *via* a palladium catalyst resulted in a 5-*exo-dig* cyclization and ring opening towards carbenoid **86** (similar to paragraph 6, Scheme 18). Addition of the nitroso N-atom at the carbenoid leads to the isatogens **87** which subsequently undergo an intramolecular addition by the hydroxyl group followed by N-O bond reduction to afford spiropseudoindoxyl **89** (path a). In contrast, the addition of OH to the metal carbenoid followed by the proto-depalladation leads to the enol **88**, which subsequently undergoes a 6 $\pi$ -electrocyclization resulting in the formation of benzoxazinone **90** (path b). The tether length seemed to have the greatest influence on the observed product ratios: for  $n = 1$ , roughly 1:1 mixtures for **89:90** were observed whereas  $n=2$  resulted in exclusive formation of **89** (Scheme 24).

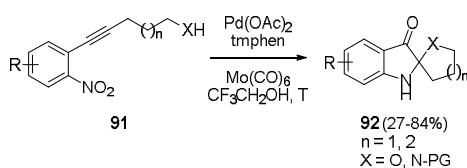
Recently, Wang and co-workers developed a similar approach starting from *o*-alkynylnitrobenzenes **91**.<sup>60</sup> The palladium catalyzed cycloisomerization is expected to occur largely similar to Scheme 24. However, the addition of Mo(CO)<sub>6</sub> as a reducing agent for the N-O bond likely enforced path a, resulting in selective formation of the desired pseudoindoxyls **92** in decent to good yield. The reactivity was also expanded by the inclusion of nitrogen-centered nucleophiles (Scheme 25).

In 1981, Kawada and co-workers documented a three step protocol for the synthesis of spiropseudoindoxyls **96** from anthranilic acids **93**.<sup>61</sup> The condensation of **93** with a bromolactone in the presence of base followed by ring closure induced by treating **94** with acetic anhydride and triethylamine

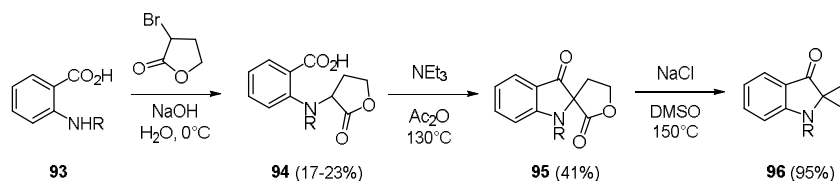
provided the spirocycle **95**. A decarboxylation of **95** with NaCl in DMSO resulted in the spirocyclopropane pseudoindoxyl **96** (Scheme 26).



**Scheme 24.** Pd(II)-catalyzed nitro-alkyne cyclization followed by nucleophilic quenching.



**Scheme 25.** Nitro-alkyne cyclization / quenching approach in presence of a reducing agent.

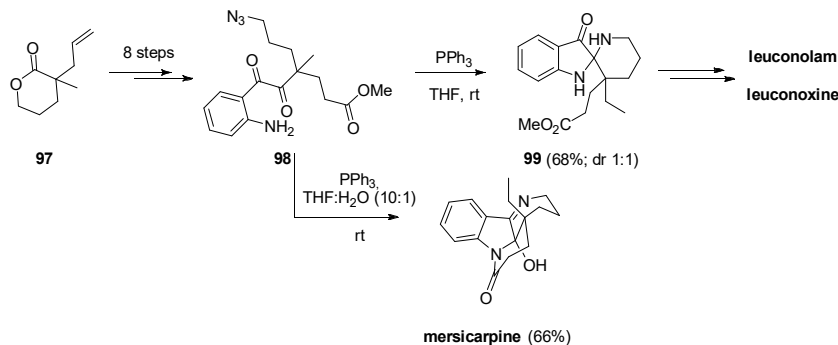


**Scheme 26.** Synthesis of a spirocyclopropane pseudoindoxyl **96**.

A recent collaboration between Stoltz and Liang resulted in a selective synthesis of leuconolam, leuconoxine, and mersicarpine alkaloids using the Staudinger reaction as a key transformation from a common acyclic intermediate.<sup>62</sup> Precursor **98** was synthesized from **97** according to literature procedures. Treatment of **98** with triphenylphosphine in a mixture of THF and water provided mersicarpine in good yield. In contrast, performing the reaction in anhydrous THF gave an inseparable diastereomeric mixture of spiropseudoindoxyl **99**. The authors suggest that the absence of water results in an *aza*-Wittig pathway, forming the 6-membered imine followed by *gem*-diamine formation towards **99**. Subsequent transformations of spiropseudoindoxyls **99** completed the total synthesis of leuconolam and leuconoxine (Scheme 27).

## 8. Conclusion

The intriguing structural architecture of spiropseudoindoxyls, combined with pronounced bioactivities of some examples, will undoubtedly continue to attract the attention of the synthetic organic community. In addition, the availability of efficient synthetic approaches can or will form the basis to prepare ‘natural product-like’ libraries of spiropseudoindoxyls using a biology or diversity oriented synthesis approach<sup>63</sup> and is hence believed to be of significant importance in medicinal chemistry.



**Scheme 27.** Divergent synthesis of mersicarpine or spiroseuodindoxyls **99**.

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