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Recent advances in the synthesis and reactivity of spiro-epoxyoxindoles

Serena Monticelli[1], Laura Castoldi[1], Saad Touqeer[1], Margherita Miele[1], Ernst Urban[1], Vittorio Pace[1]*

[1] *Department of Pharmaceutical Chemistry, University of Vienna, 14 Althanstrasse, Vienna 1090, Austria; e-mail: vittorio.pace@univie.ac.at*

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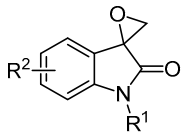


Spiro-epoxyoxindoles containing an unsubstituted methylene fragment in the oxirane ring are excellent building blocks in organic synthesis due to the high reactivity conferred by the three-membered oxygenated cycle. In this minireview, a concise survey of the methods of their synthesis and examples of reactivity with carbon and nitrogen nucleophiles is presented, with a particular focus on the stereochemical aspects. The review covers the literature for the last twenty years.

Keywords: epoxides, isatins, spiro compounds, Friedel–Crafts reaction, nucleophilic addition.

The 3,3'-disubstituted oxindole core is featured in several natural products and biologically active substances, thus representing an important target for the synthetic chemists.[1] The corresponding spiro-epoxy derivatives induce a particular interest – they are characterized by the high reactivity conferred by the oxirane ring and can be employed for the construction of complex molecular structures.[2]

Synthesis of spiro-epoxyoxindoles

Despite the availability of strategies to construct functionalized spiro-epoxyoxindoles under full stereocontrol,[3] unsubstituted analogs received much less attention and only recently reliable methods for their preparation have been disclosed. The retrosynthetic analysis indicates isatins[4] as valuable starting materials which upon a conceptually simple homologation would transform the carbonyl into the epoxide. Accordingly, three main protocols based on common homologating agents have been proposed, namely diazomethane, sulfur ylides, and halomethyllithium reagents (Fig. 1). Arndt, Eistert, and Ender[5] in the course of their seminal studies on the use of diazoalkanes in synthesis noticed the formation of rearrangement products, later confirmed by Alcaide, Almendros, and coworkers.[6] Epoxidation of isatin carbonyl group in Corey–Chaykovsky reaction, reported by Howe and coworkers[7] in the early 1970s, appeared a versatile strategy, as evidenced in more recent studies by Nair and coworkers[8] and applied further by Hajra and coworkers.[9]

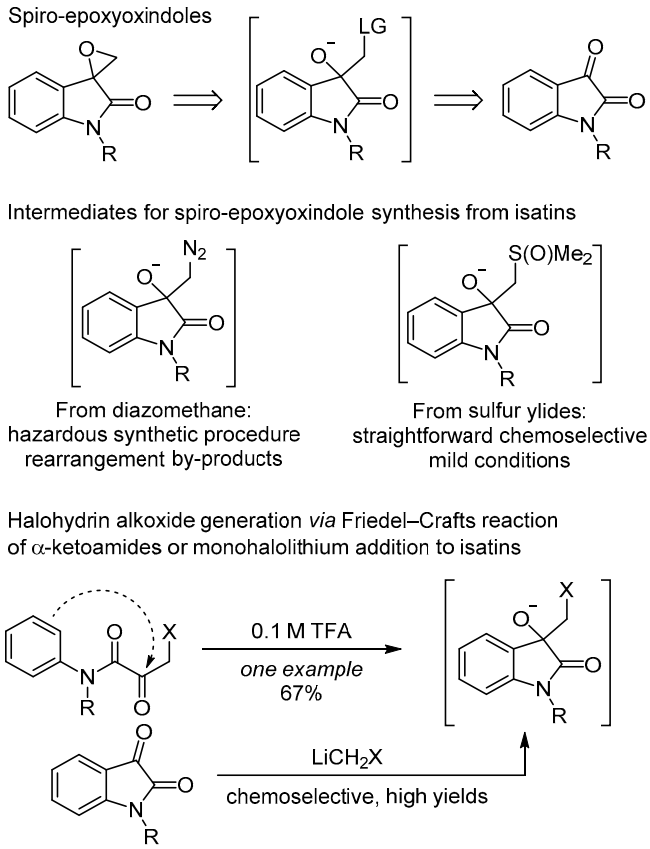


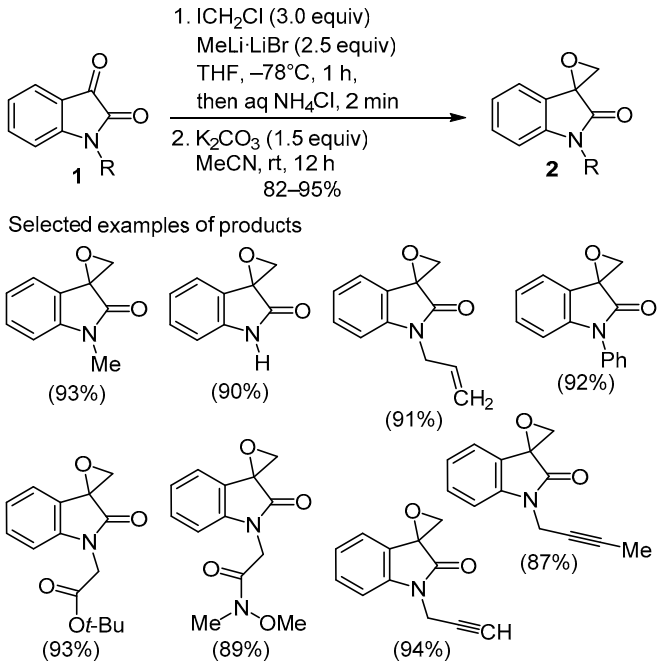
Figure 1. Spiro-epoxyoxindole synthesis strategies.

Upon reaction with a sulf(ox)onium ylide in the presence of a base, spiro-epoxyoxindoles are also smoothly obtained in good yields. The protocol is adaptable to isatins containing alkyl substituents on the nitrogen, as well as to the simplest member of the series – with unsubstituted NH. Notably, generating the ylide *in situ* from a sulfoxide and benzyne, as described by Zhang, Wang, and coworkers, could represent a useful alternative to the classical sulfoxonium deprotonation.[10] In 2011, Zhu and coworkers documented the synthesis of a spiro-epoxyoxindole *via* the intramolecular Friedel–Crafts reaction of an α-oxoanilide triggered by trifluoroacetic acid followed by basic treatment.[11] Overall, the process involves the formation of a halohydrin alkoxide which undergoes ring closure yielding a spiro compound.

A critical analysis of the strategies discussed above clearly evidences the requirement for a quaternary alkoxide featuring a β-substituent with good leaving group ability as the pivotal intermediate for the synthesis of spiro-epoxyoxindoles.

In this context, Pace and coworkers documented a robust and operationally simple tactic involving the addition of a lithium halomethylcarbenoid ($LiCH_2Cl$)[12] to isatin carbonyl,[13] thus giving the same Zhu's alkoxide intermediate through a conceptually different route. The protocol proceeds under high chemocontrol, as deducted from the selective attack of the nucleophilic $LiCH_2Cl$ to the carbonyl of isatin **1**, even in the presence of additional electrophilic functionalities (esters, Weinreb amides, amides, nitrile) or moieties which can be sensitive to organolithium reagents such as alkenes, alkynes, or bromine atoms (Scheme 1). Notably, the presence of acidic NH groups such as in secondary amides or in simple lactam (i.e., isatin) did not affect the outcome of the desired spiro-epoxyoxindoles **2**.[14]

Scheme 1. Lithium carbenoid-mediated isatin epoxidation

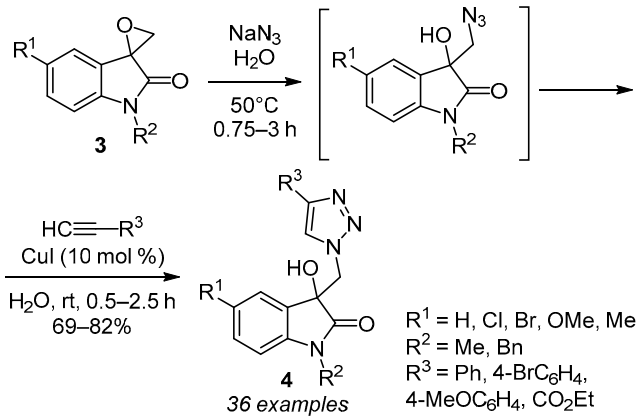


New reactivity concepts in spiro-epoxyoxindole chemistry

Reactions with nitrogen nucleophiles

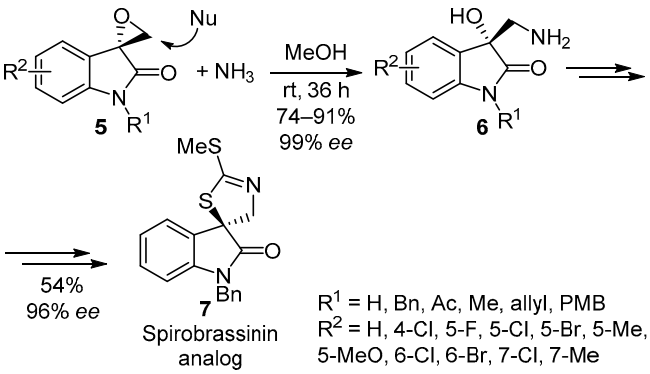
Nair and coworkers reported the regioselective aminolysis of spiro-epoxyoxindoles with both aliphatic and aromatic amines in water to give 3-aminomethyl-3-hydroxyindolin-2-ones.[8a] The same group extended the epoxide ring opening of spiro-epoxyoxindoles **3** by azidolysis followed by the Cu-catalyzed azide-alkyne cycloaddition, finally leading to diverse 1-alkyl-3-[(4-aryl(alkyl)-1*H*-1,2,3-triazol-1-yl)methyl]-3-hydroxyindolin-2-ones **4** (Scheme 2).[8b]

Scheme 2. Regiospecific azidolysis and Cu-catalyzed azide-alkyne cycloaddition on spiro-epoxyoxindoles



Sun, Hong, Wang, and coworkers demonstrated the selective, catalyst-free epoxide ring opening with a weak nucleophile such as ammonia, enabling the synthesis of the relevant 3-aminomethyl-3-hydroxyoxindoles.[15] Starting from optically active spiro-epoxyoxindoles **5**, enantiopure amino alcohols **6** with retained configuration were obtained. The reaction could be scaled up to gram quantities and be used in the synthesis of spirobrassinin derivative **7** (Scheme 3).

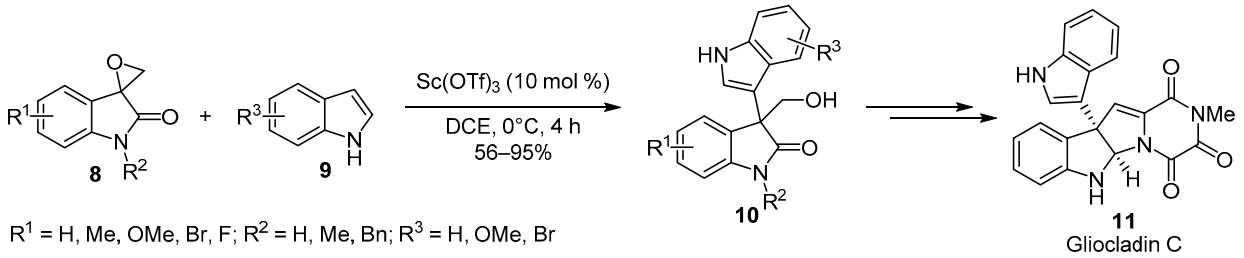
Scheme 3. Regioselective ring opening of spiro-epoxyoxindoles with ammonia



Reactions with carbon nucleophiles

Hajra and coworkers employed spiro-epoxyoxindoles **8** as convenient electrophiles in regioselective Friedel–Crafts-type reaction with indoles **9** under Lewis acid catalysis in

Scheme 4. Hajra's Lewis acid-catalyzed reaction of spiro-epoxyoxindoles and indoles

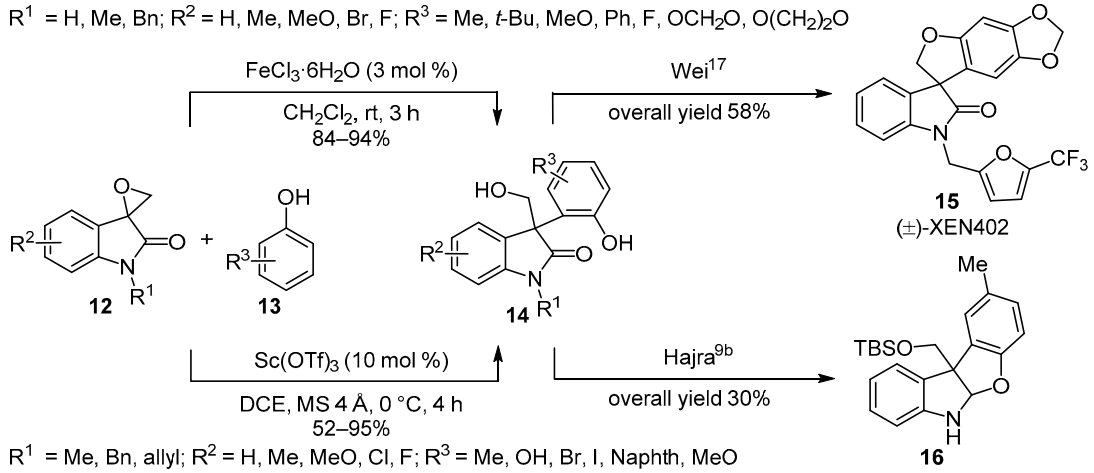


the presence of $Sc(OTf)_3$ for the synthesis of 3-(hydroxymethyl)-3-(1*H*-indol-3-yl)indolin-2-one derivatives **10**.[9a] The reaction, involving the attack of the indolic C-3 carbon atom to the sterically congested C-3 atom of the epoxyoxindole **8** has been employed in a formal synthesis of gliocladin C (**11**) (Scheme 4). The tactic is notable since the regioselective ring opening with a C-nucleophile leads to an all-carbon quaternary center. The same authors demonstrated its usefulness also in the case of related chiral spiro-aziridines in the absence of catalyst, emphasizing the key role of water as the solvent in activating the cascade.[16]

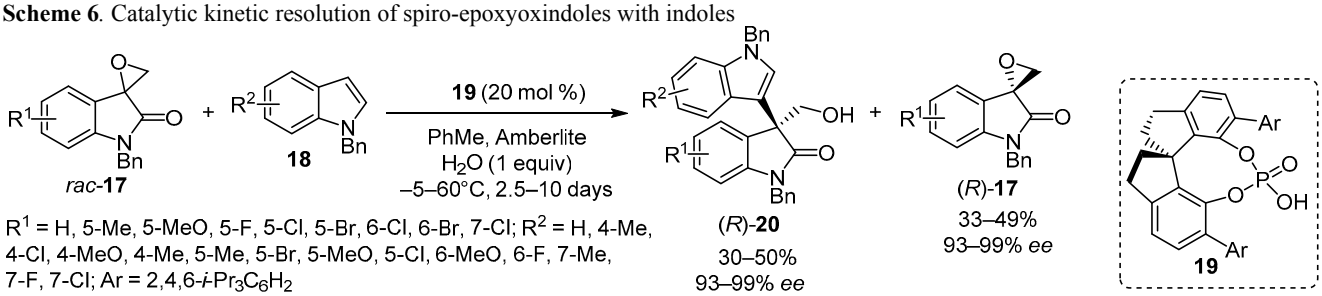
Almost contemporaneously, the same group of Hajra[9b] and the group of Wei[17] demonstrated independently the efficiency of the tactic in the case of spiro-epoxyoxindoles **12** reacting with electron-rich phenols **13** as nucleophiles leading to 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-ones **14** under Fe (Wei)[17] and Sc (Hajra)[9b] catalysis (Scheme 5). Mechanistically, the overall process constists of a tandem arylation–*O*-cyclization sequence. Notably, the method of Hajra is not limited to aromatic alcohols, but can be conveniently employed for non-hydroxy electron-rich benzenoid arenes.[9b] In both methodologies, the primary alcohol can be further activated and advantageously employed in a intramolecular nucleophilic displacement with a phenol, finally leading to a tetracyclic dihydrobenzofuro-[2,3-*b*]indoline scaffold.[9b,17] It should be mentioned that both methods are valuable tools for rapid assembly of the benzofuroindole skeleton found in biologically active substances, as demonstrated by Wei in the gram-scale total synthesis of drug candidate (±)-XEN402 (**15**) which is under IIb phase clinical trial for pain treatment and Hajra in the synthesis of benzofuroindoline **16**.

Sun, Hong, Wang, and coworkers documented the catalytic kinetic resolution (selectivity factor up to 1060) of racemic spiro-epoxyoxindoles **17** with the simultaneous regio- and enantioselective Friedel–Crafts alkylation of indoles **18** using a chiral phosphoric acid **19** as catalyst (Scheme 6).[18] The protocol provides the two highly versatile (*R*)-building blocks **17** and **20**, in excellent yields and optical purities, which can undergo subsequent transformations, as illustrated by authors in the formal total syntheses of (+)-gliocladin C or (*S*)-(–)-spirobrassinin. Interestingly,

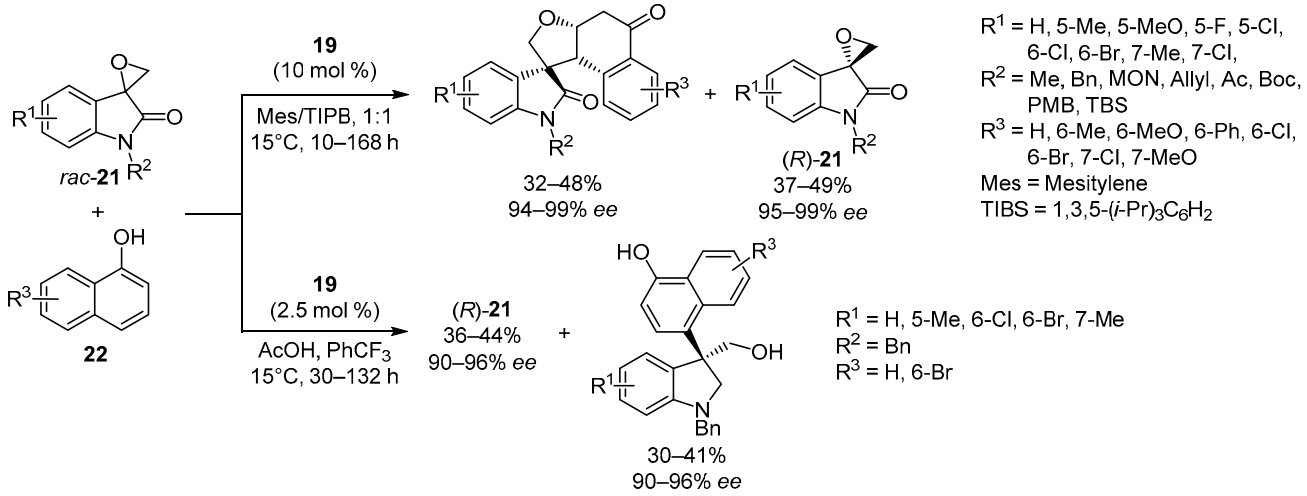
Scheme 5. Tandem Friedel–Crafts arylation – *O*-cyclization starting from spiro-epoxyoxindoles



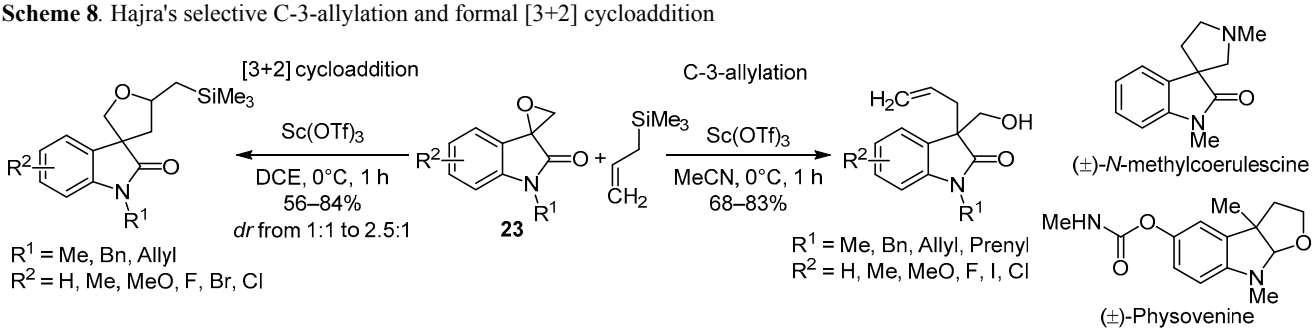
Scheme 6. Catalytic kinetic resolution of spiro-epoxyoxindoles with indoles



Scheme 7. Catalytic kinetic resolution of spiro-epoxyoxindoles with naphthols



Scheme 8. Hajra's selective C-3-allylation and formal [3+2] cycloaddition



the enantiopure alkylated (*S*)-product (*S*)-**20** can be obtained by the regioselective ring opening of (*R*)-spiro-epoxyoxindole (*R*)-**17** with the indole without the use of the catalyst.

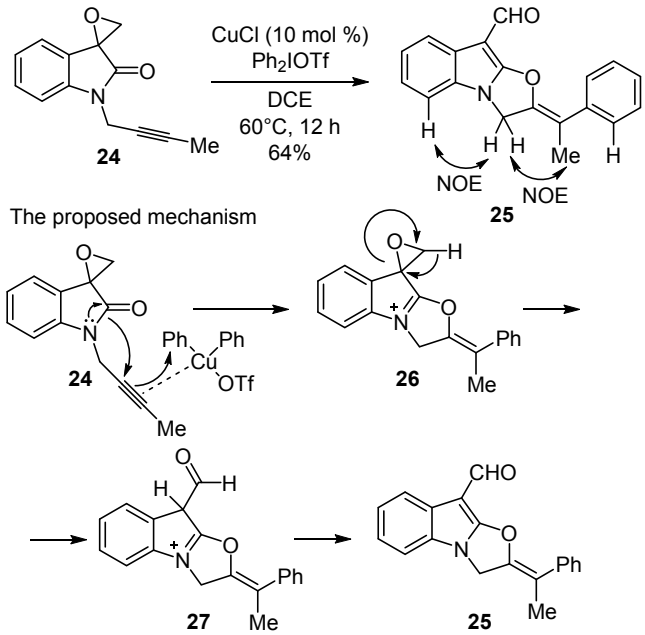
The same group succeeded in demonstrating that 1-naphtols **22** are able to act as C-4 regioselective nucleophiles in a tandem dearomatization–oxa-Michael and Friedel–Crafts alkylation with spiro-epoxyoxindoles **21**. The chemoselectivity of the process shows a significant dependence on the solvent (Scheme 7). Both chemoselective reactions were accompanied by simultaneous kinetic resolution of the racemic starting spiro-epoxyoxindoles. Notably, the protocol shows excellent diastereo- and enantioselectivity in the formation of three contigous stereocenters including a quaternary one.[19]

Hajra developed a Lewis acid-catalyzed regioselective C-3-allylation and a formal [3+2] annulation protocol of spiro-epoxyoxindoles **23** by simple change of the reaction conditions (Scheme 8). The method has been applied for the synthesis of various natural products – (±)-*N*-methylcoerulescine, (±)-physovenine, and 3a-allylhexahydropyrrolo[2,3-*b*]indole, a subunit of a large number of members of the HPI-alkaloid family.[20]

Selective rearrangements

Spiro-epoxyoxindole **24** featuring a propargylic substituent on nitrogen atom undergoes copper-catalyzed iodonium-mediated arylation – rearrangement to a tricyclic system **25** with well defined *Z*-configuration at the exocyclic C=C bond, as established by NOE experiments. This one-pot transformation is assumed to be the sequence of an intramolecular oxyarylation of spiro-epoxyoxindole **24** to give epoxy-iminium intermediate **26**, which through Lewis acid-promoted epoxide-aldehyde isomerization followed by rearomatization of intermediate **27** affords the desired product **25** (Scheme 9).[13a]

Scheme 9. Intramolecular electrophilic oxyarylation



In conclusion, in this review, the latest aspects of the methods of the synthesis and examples of reactivity of 3,3'-spiro-epoxyoxindoles were presented. The objective of the review was not to completely cover the research area but rather to introduce the reader to the recent advances in the field.

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