Recent Advances in Stereoselective Ring Expansion of Spirocyclopropanes: Access to the Spirocyclic Compounds

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ABSTRACT: Spirocyclopropane represents a privileged structural scaffold for accessing synthetic libraries of densely functionalized spirocarbo- and heterocyclic compounds. Due to the ubiquity of spirocyclic motifs as a potent pharmacophore in natural products and pharmaceuticals, recent years have witnessed significant advances in developing synthetic strategies that exploits carbon−carbon bond scission in spirocyclopropanes. This paper summarizes the recent developments in stereoselective ring expansion of spirocyclopropanes in diversity-oriented synthesis and highlights the synthetic as well as mechanistic rationale of those methodologies. This review also encompasses the applicability of the protocols in bioactive natural product syntheses.

1. INTRODUCTION

Over the years, catalytic ring expansions of cyclopropanes have played a predominant role in the field of strained ring systems owing to their apparently simple architectures and enormous ring strain (∼115 kJ/mol) embodied within the cyclic framework to access a diverse range of cycloadducts and natural products.1,2 In particular, the activation of kinetic rather inert carbon−carbon bonds in cyclopropanes has been attained with special allure by incorporating donor and acceptor (D−A) entities at the vicinal positions (Scheme 1A).3−5 The innate push−pull effect of the activating groups polarizes the carbon−carbon bond between donor and acceptor groups, which facilitates the ring expansion reactions with dipolarophiles. In this realm, spiro-D−A-cyclopropanes have emerged as reliable synthetic tools for the assembly of spirocarbo- and heterocyclic scaffolds as well as the key intermediates for drug developments (Scheme 1B). Spirocyclic compounds are the prevalent structural units, present in myriads of natural products and pharmaceuticals with broad bioactive spectrum.6,7 Consequently, elegant strategies that enable the construction of functionalized spirocyclic scaffolds in an atom- and step-economical fashion using these spiro-annulated strained ring systems have experienced an immense interest in modern synthetic chemistry. This mini-review takes into account the recent advances in the stereoselective ring expansion of spirocyclopropanes for the synthesis of spirocyclic compounds and their key applications in total syntheses of biorelevant natural products. The paper is organized according to the nature of donor and acceptor substituents associated with the rings and their related reactions. Pertinently, the conventional protocols for ring opening of spirocyclopropanes are not highlighted in this section.

2. SPIROCycloPROPYL OXINDOLES

The ring expansion reactions of oxindole-based spirocyclopropanes have witnessed a considerable growth in recent years owing to the profuse prominence of the oxindole moieties as a valuable and potent pharmacophore unit in naturally occurring alkaloids and bioactive compounds.6

2.1. Reaction with Imines. The seminal work on (3 + 2)-annulation of monoactivated spirocyclopro pyl oxindoles with imines was developed by Carreira and co-workers and depicts oxindole as a potential acceptor. The authors reported an elegant strategy to construct diastereoselective spiro-[pyrrolidin-3,3′-oxindoles] 3 from spiro[cyclopropane-1,3′-oxindoles] 1 and aldimines 2 under Mg(II) catalysis (Scheme 2A).8 Preliminary studies suggest that the bifunctional nature of MgI₂ assists the facile ring cleavage of spirocyclopropanes and hence facilitates the annulation reaction to afford the spiroheterocycles with excellent diastereoselectivity. Following this pioneering work, Grant and co-workers carried out a three-
component reaction for the synthesis of 3,3'-pyrrolidinyl spirooxindoles 6 in a one-pot operation under microwave irradiation (Scheme 2B).9 The reaction proceeds via (3 + 2)-annulation of the in situ formed imines with spirocyclopropyl oxindoles 1 to produce a diverse range of spiro-annulated pyrrolidines in good yields, utilizing a broad scope of both aldehydes and amines. Notably, aniline and aryl aldehyde pairings in terms of efficiency and stereoselectivity were found to be superior to their corresponding alkyl or sulfonamide counterparts.

2.2. Reaction with Nitrones. Aldonitrones and ketonitrones, due to their strong zwitterionic character, serve as versatile 1,3-dipoles in cycloaddition reactions to access privileged heterocyclic scaffolds. Recently, Zhou and coworkers employed these fascinating molecular entities in Ni(II)-catalyzed asymmetric (3 + 3)-cycloaddition of spirocyclopropyl oxindoles 7 for the synthesis of enantiomer-enriched spiro-annulated oxindole-tetrahydro-1,2-oxazines 9 with excellent diastereoselectivity using chiral bisoxazoline L1 (Scheme 3).10 The observed 3,6-trans-selectivity of the cycloadduct over the 3,6-cis-isomer is governed by a stepwise mechanism, involving an intramolecular Mannich-type cyclization accommodating a more stable transition state.

Inspired by their previous investigation, the same group later reported a Sc(III)-catalyzed one-pot strategy for the stereoselective synthesis of spiro-annulated oxindole-tetrahydro-1,2-oxazines 12 through sequential (3 + 3)-cycloaddition of spirocyclopropyl oxindoles 7 with aldehydes or ketones 10 and N-alkyl hydroxylamine hydrochlorides 11 (Scheme 4).11 The scope of the hypothesis has been extended to diversely functionalized aryl, heteroaryl, aliphatic, and α,β-unsaturated aldehydes or ketones, delivering the 3,6-trans-configured spiroheterocycles 12 in good yields. In addition, the asymmetric version of the protocol has been investigated using chiral bisoxazoline L1, providing optically active tetrahydro-1,2-oxazines. Further, the resulting cycloadducts have exhibited potential bioactivities against prostate cancer cells, which emphasizes the feasibility of this transformation in biological studies.

2.3. Reaction with Azides. In 2017, Budynina and coworkers demonstrated a concise methodology for the assembly of diastereoselective spiro[pyrrolidine-3,3'-oxindoles] 15 through sequential operations (Scheme 5A).12 The facile ring opening of spiro[cyclopropene-3,3'-oxindoles] 13 by the azide ion afforded 3-(2-azidoethyl)oxindoles 14, which then underwent subsequent transformations in a cascade sequence via Staudinger/aza-Wittig/Mannich reactions to deliver the target spiro-adducts. The diastereoselectivity of the product has developed from the intramolecular Mannich-type reaction, proceeding through a transition state TS-1 with substituents at the most favorable pseudoquartorial positions.

In contrast, the inverse chemoselectivity in the nucleophilic ring opening of spirocyclopropyl oxindoles with aromatic amines was attained by the same group, wherein the
implementation of vicinal diesters was proposed to induce unprecedented donor activity in the oxindole units (Scheme 5B). The protocol exemplified a Ni(II)-catalyzed SN2-type ring opening of spiro[cyclopropane-1,3′-oxindoles] by the N-nucleophiles at the more substituted spiro-carbon center. This inverse electron demand reactivity of spirocyclopropyl oxindole would thus lead to preferential formation of the γ-aminocarbonyl compounds in high yields. Finally, Brønsted acid-aided intramolecular cyclization of the latter afforded the spirocyclic scaffolds with good conversions and diastereoselectivities.

2.4. Reaction with Isocyanates. Isocyanates are iso-electronic to the azide ions and are classified as viable substrates for accessing functionalized aza-heterocycles in chemical space. Recently, Budynina and co-workers demonstrated the nucleophilic ring opening/cyclization of spirocyclopropanes accommodating a spiro-fused oxindole motif with potassium isocyanate to accomplish diversified spiro-[pyrrolidone-3,3′-oxindole] derivatives (Scheme 6). The
method epitomizes isocyanates as suitable N-nucleophiles for the ring expansion of spirocyclopropanes under microwave irradiation. The reaction was compatible with various N-protected spirocyclopropyl oxindoles to deliver the nitrogen-containing heterocycles, regardless of electron-rich or electron-deficient substituents in cyclopropane and oxindole moieties.

2.5. Reaction with Carbonyl Compounds. Carbonyl compounds act as suitable dipolarophiles and exhibit ring enlargement reactions with cyclopropanes under Lewis acid catalysis. In 2019, the Su group documented a convenient approach for the diastereoselective synthesis of bispirooxindoles, utilizing oxindole-fused spirovinylcyclopropanes (SVCPs) and 3-oxindoles under Pd(II) catalysis (Scheme 7). Experimental evidence divulged that the protection of N−H of both the heterocyclic components are indispensable to deliver the desired outcomes. The scope of the reaction has revealed excellent functional group tolerance for both the N-substituted spirovinylcyclopropyl oxindoles and isatins. The reaction involves the formation of zwitterion via Pd(II)-catalyzed ring opening of SVCP, which undergoes (3 + 2)-annulation with isatin to deliver the target cycloadduct (Scheme 8). The observed diastereoselectivity is attributed to the involvement of favored transition state TS-1, which leads to the preferential formation of 22, whereas the unfavorable sterically hindered, between the aryl rings, TS-2 furnishes the minor isomer 22′.

2.6. Reaction with Alkenes. Lewis acid-enabled cycloaddition of oxindole-activated spirocyclopropanes with exocyclic olefins can be executed for accessing biorelevant spirocyclic
scaffolds with multiple spirocenters. Recently, Saha and co-workers reported Mg(II)-catalyzed (3 + 2)-annulation of spirocyclopropyl oxindoles with alkylidene pyrazolones as well as N-alkylated 2,3-dioxopyrrolidines to furnish dispiropyrazolone[cyclopentane]oxindoles and dispiro-2,3-dioxopyrrolidine[cyclopentane]oxindoles (Scheme 9).

The observed stereoselectivity of the cycloadduct is realized presumably due to preferential addition to the si face of the alkene. The diastereofacial selectivity of the si adduct is also supported by the density functional theory studies.

Formal cycloaddition reactions with electron-deficient alkenes after transformations to provide a wide range of...
diversely functionalized carbo- and heterocyclic scaffolds are very limited. In 2019, the Yang group described (3 + 2)-annulation of oxindole-fused SVCPs \( \text{20} \) with nitroalkenes \( \text{27} \) in the presence of Pd(II) catalysts for the assembly of diastereoselective spiroheterocycles \( \text{28} \) in good yields (Scheme 10).\(^{17}\) The reaction involves Pd(II)-assisted ring opening of SVCP to enable the synthesis of zwitterionic \( \pi \)-allyl complex \( \text{I} \) that undergoes (3 + 2)-annulation with nitroalkene to deliver the product (Scheme 11). The observed diastereoselectivity of the cycloadduct is rationalized by a favorable \( \pi-\pi \) stacking interaction between the aryl rings in TS-1, which leads to preferential formation of \( \text{28} \) as a major product, whereas the unfavorable sterically hindered TS-2 lowers the yield of \( \text{28}' \).

2.7. Reaction with Dioxygen. Zhou and co-workers demonstrated a metal-free protocol employing oxindole-fused SVCPs \( \text{20} \) as a 1,3-dipolar synthon and air as an oxidant for the synthesis of diastereoselective spiro-1,2-dioxolanes \( \text{29} \) (Scheme 12).\(^{18}\) The protocol utilizes molecular iodine as the catalyst to construct spiro-1,2-dioxolanes \( \text{29} \) in good yields. Based on the control studies, the authors proposed a plausible mechanism wherein rapid generation of an iodine radical is initiated, which may lead to the formation of radical cation \( \text{I} \) via the single-electron transfer (Scheme 13). Subsequent addition of dioxygen can give \( \text{II} \), followed by a single-electron transfer to furnish \( \text{III} \). The latter undergoes intramolecular cyclization in either path \( a \) or \( b \) to deliver the corresponding cycloadduct diastereoselectively.

2.8. Ring Expansion of Spirocyclopropyl Oxindoles in Natural Products Syntheses. Stereoselective synthesis of spiro[pyrrolidin-3,3’-oxindole] derivatives are a fascinating area of research in chemical space because of their prominent presence in biorelevant natural products and pharmaceuticals as an active pharmacophore unit.\(^{13}\) In this direction, the pioneering (3 + 2)-annulation of spiro[cyclopropane-1,3’-oxindoles] with imines acts as a key step to deliver spiro-
annulated pyrrolidines as an inner core in total syntheses. The practicality of the hypothesis was first exemplified by Carreira and co-workers in synthesizing (±)-horsfiline, a naturally occurring oxindole-based alkaloid, extracted from the leaves of *Horsfieldia superba* (Scheme 14). The authors implemented 1,3,5-trimethyl-1,3,5-triazinan-3-one as a synthetic equivalent for *N*-methylmethanamine and MgI$_2$ as a bifunctional catalyst, wherein the synergistic operation by the Lewis acidic metal center and nucleophilic iodide led to facile ring opening of spirocyclopropane, thereby facilitating annulation with an imine to afford the cyclic adduct 32, which then furnished (±)-horsfiline by the removal of the protecting group.

Strychnofoline is an antitumor agent, which belongs to the family of *Strychnos* alkaloids. This imperative class of spiro-oxindole was isolated from the leaves of *Strychnos usambarensis* and possess significant antimitotic activity against tumor cells.

Scheme 13. Mechanism for Reaction with Dioxygen

Scheme 14. Total Synthesis of (±)-Horsfiline

Scheme 15. Synthesis of (±)-Strychnofoline

Scheme 16. Synthesis of (−)-Spirotryprostatin B
The total synthesis of (±)-strychnofoline was documented by the Carreira group (Scheme 15). They reported a MgI₂-mediated stereoselective (3 + 2)-annulation of spiro[cyclopropane-1,3'-indole] with cyclic imine to construct tetracyclic spiro[pyrrolidin-3,3'-oxindole] as the key intermediate that could deliver the target product.

The alkaloid spirotryprostatin B was isolated from Aspergillus fumigatus BM939 that exhibits promising anticancer activities against human cancer cell lines. In 2005, Marti and Carreira exploited the ring enlargement reaction of spiro[cyclopropane-1,3'-oxindole] with alkynyl imine as a key step for the total synthesis of (−)-spirotryprostatin B (Scheme 16). The
resulting spiroheterocyclic intermediate 38 underwent further transformation to access the desired alkaloid. Rhynchophylline and its spiroisomer isorhynchophylline are naturally occurring alkaloids isolated from Uncaria rhynchophylla that display antihypertensive and neuroprotective activities. Recently, Tong and co-workers reported a concise methodology, employing Mg(II)-aided ring expansion of spirocyclopropyl oxindole 39 with chiral cyclic imine 40 for the enantioselective synthesis of spiro-fused pyrrolidine 41 as a key product (Scheme 17).22 The tetracyclic intermediate 41 furnished the target (+)-isorhynchophylline after six additional steps, which underwent acid-promoted isomerization to deliver (−)-rhynchophylline.

3. SPIROCYCLOPROPYL 1,3-DICARBONYLS

Spiro-conjugated 1,3-dicarbonyls, such as 1,3-indanedione, Meldrum’s acid, and 1,3-dimethyl barbituric acid, can serve as promising acceptors by stabilizing the anion in 1,3-zwitterionic intermediates via charge distribution. Trost and co-workers reported a Pd(0)-catalyzed (3 + 2)-annulation of Meldrum’s acid-derived SVCPs 42 with a diverse range of Meldrum’s acid alkylidenes 43 to furnish spirocyclic motifs 44 with good diastereo- and enantioselectivities (Scheme 18).23 The observed stereoselectivity of the cycloadduct is attributed to preferential formation of the palladium-bonded π-allyl complex with favored spatial alignments of the substituents in order to minimize the steric interactions between the chiral ligand and alkylidene. 1,3-Indanedione-derived SVCPs 45 were employed by Liu and co-workers for the enantioselective synthesis of functionalized spirocarbocyclic scaffolds 46 in the presence of the Pd(0) complex (Scheme 19).24 Screening of various nitrogen- and phosphorus-based chiral auxiliaries suggested that the reaction using bis(tert-amine) L3 delivers the target cycloadduct in enantioselectivity. In addition, diverse functional groups on nitroalkenes such as aryl, heteroaryl, and alkyl substituents were found to be well-tolerated, delivering the spiro-compounds in good yields.
In 2016, the Vitale group demonstrated an asymmetric (3 + 2)-annulation of dicarbonyl-activated SVCPs that encompasses 1,3-indanedione, Meldrum’s acid, and \( \text{N}, \text{N}’ \)-dimethyl barbituric acid derivatives with enals for the assembly of enantioenriched spiro-annulated cyclopentanes via synergistic operations by combining Hayashi–Jørgensen organocatalyst \( \text{L}^4 \) with the Pd(0) complex (Scheme 20, condition A). A similar kind of transformation without entailing any additional ligand was later developed by Rios and Meazza (Scheme 20, condition B). The reaction was compatible with various functional groups and substituent patterns, comprising electron-deficient arenes as well as aliphatic groups to furnish the cycloadducts with excellent enantio- and diastereoselectivities.

4. OTHER ACTIVATED SPIROCYCLOPROPANES

Spirocyclopanes, stapled with oxygenated functionalities as donors or with biorelevant heterocycles other than oxindoles as acceptors are also prone to undergo ring enlargement reactions with dipolarophiles. The donor ability of cyclic ethers \( \text{51} \), followed by sequential metal-hydride reduction to deliver spirocyclopropyl alcohols \( \text{53} \). Oxidative ring expansions of the latter using hypervalent iodine resulted in \([n,5]\)-spiroketalts \( \text{54} \) via successive rearrangements. Notably, the catalytic addition of \( \text{Yb(OTf)}_3 \) led to improve the yield of the cycloadduct by coordinating to the in situ developed spirocyclopropyl aldehyde \( \text{I} \), thereby facilitating easy ring scission. Based on those results, the authors suggest that a stepwise mechanism proceeds through a zwitterionic intermediate \( \text{II} \) in the ring expansion step with prevalent formation of the thermodynamically more stable product. In contrast, configuration at the spirocenter can be preserved employing Dess-Martin periodinane as the oxidant, which may be due to the participation of a concerted reaction pathway.

N-Heterocyclic carbene (NHC)-catalyzed (3 + 2)-annulation of spirocyclopanes was described by Lupton and Candish, implementing \( \alpha, \beta \)-unsaturated acyl fluorides as a promising dipolarophile to synthesize \( \beta \)-lactone-fused spirocyclic scaffolds \( \text{57} \) with high diastereoselectivity (Scheme 22).

The scope of the hypothesis has been expanded concisely, extending from five to seven membered ring-fused spirocyclopanes to afford the spirocyclic scaffolds in good yields. The mechanism depicts the formation of acyl ethers \( \text{51} \), followed by sequential metal-hydride reduction to deliver spirocyclopropyl alcohols \( \text{53} \). Oxidative ring expansions of the latter using hypervalent iodine resulted in \([n,5]\)-spiroketalts \( \text{54} \) via successive rearrangements. Notably, the catalytic addition of \( \text{Yb(OTf)}_3 \) led to improve the yield of the cycloadduct by coordinating to the in situ developed spirocyclopropyl aldehyde \( \text{I} \), thereby facilitating easy ring scission. Based on those results, the authors suggest that a stepwise mechanism proceeds through a zwitterionic intermediate \( \text{II} \) in the ring expansion step with prevalent formation of the thermodynamically more stable product. In contrast, configuration at the spirocenter can be preserved employing Dess-Martin periodinane as the oxidant, which may be due to the participation of a concerted reaction pathway.
azolium I via the addition of NHC to the acyl fluoride and ester enolate II from cyclopropane by desilylation and retroaldol reaction (Scheme 23). Addition reaction between these two intermediates leads to the formation of hemiacetal III. Subsequent Ireland−Coates Claisen rearrangement and aldol reactions gives V, which undergoes lactonization to furnish the cycloadduct.

In 2019, the Vesely group reported asymmetric (3 + 2)-annulation of azlactone-based SVCPs 58 with α,β-unsaturated aldehydes 48 for the enantioselective synthesis of functionalized spirocyclic derivatives 59 and 59′ under cooperative catalysis (Scheme 24). After the extensive screening of various organo- and metal catalysts, high enantioselectivity with good conversion of the cycloadduct was attained by merging the chiral secondary amine L4 and the Pd(0) complex as the catalyst. The methodology was tolerated for a wide range of aryl and aliphatic substituents, delivering the desired products.

Most recently, Baranov and co-workers demonstrated the synthesis of spiro-annulated tetrahydrofuran derivatives 61 and 61′ by employing spirocyclopropyl imidazol-5-ones 60 and aldehydes in the presence of TsOH, wherein the spirocyclopropane unit is flanked by a donor aryl group and biorelevant imidazole-5-one as the acceptor (Scheme 25). The scope of the protocol was investigated with a broad range of spirocyclopropanes and aldehydes to furnish the spirocyclic heterocycles. The reaction rate and diastereoselectivity of the final outcome could be greatly affected by the electronic properties and substitution patterns of the functional groups in the course of the reaction.

5. CONCLUSION

The ring enlargement reaction of spirocyclopropanes is one of the most fascinating chemical fronts to synthesize a diverse array of polycyclic architectures with one or more embedded spirocenters. In addition, enantioselective transformations using varied chiral auxiliaries and the participation of the key methodologies in biomimetic syntheses of natural products have enriched this developing field. Moreover, countless synthetic strategies that can be envisaged by fine-tuning of donor−acceptor entities in a desirable manner will allow the scientific community to expedite this captivating research interest to a new level. Despite these indubitable advances, a majority of the efforts were focused on the assembly of spiro-annulated five- or six-membered ring systems, although there is still much room for designing and developing higher-order cycloadditions with spirocyclopropanes. We anticipate that future contributions will surmount this shortcoming and will introduce novel biorelevant fragments as activating units for further advancements.

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