Chemical Synthesis

Review

Recent advances in organocatalytic cascade reactions for enantioselective synthesis of chiral spirolactone skeletons

Jun Yang[1,3], Bo-Wen Pan[2], Lin Chen[1,*], Ying Zhou[2], Xiong-Li Liu[1,*]

[1]National & Local Joint Engineering Research Center for the Exploitation of Homology Resources of Southwest Medicine and Food, Guizhou University, Guiyang 550025, Guizhou, China.
[2]College of Pharmaceutical Sciences, Guizhou University of Traditional Chinese Medicine, Guiyang 550025, Guizhou, China.
[3]Department of Pharmacy, Zunyi Medical And Pharmaceutical College, Zunyi 563006, Guizhou, China.

*****Correspondence to:** Prof. Lin Chen, National & Local Joint Engineering Research Center for the Exploitation of Homology Resources of Southwest Medicine and Food, Guizhou University, Jiaxiu South Road, Guiyang 550025, Guizhou, China. E-mail: lchen5@gzu.edu.cn; Prof. Xiong-Li Liu, National & Local Joint Engineering Research Center for the Exploitation of Homology Resources of Southwest Medicine and Food, Guizhou University, Jiaxiu South Road, Guiyang 550025, Guizhou, China. E-mail: xlliu1@gzu.edu.cn

Abstract

Chiral spirolactones, including spiropropyllactones, spirobutyrolactones, and spirovalerolactones, are important heterocyclic frameworks that attracted the attention of organic and medicinal chemists because these motifs constitute the core structure of several natural products and bioactive molecules. The absolute configuration and the substituents on the fully substituted spirocyclic stereocenter of the lactone can potentially enhance specificity for ligand-protein binding and enhance bioavailability, potency, and metabolic stability. So, intensive attention from chemists has been paid to the synthetic methods leading to such prominent structural motifs. The synthetic methods can be divided into two main classes. The first approach takes advantage of the presence of the existing lactone structure and focuses on its functionalization. The second approach is the lactone framework constructed from various precursors in a direct spirolactonization reaction. In this review, for convenience in reading, the recent advances in the synthesis of spirolactones are summarized and discussed according to the two major organocatalytic asymmetric synthetic routes: (i) using the lactone-related frameworks as building blocks; and (ii) direct spirolactonization reaction using various reagents. This review also describes both the mechanisms and related transformations, and gives some insights into challenging issues in this research field, which will enlighten the future development of this field.

INTRODUCTION

The biological activities of privileged natural products are usually linked with their characteristic moiety and well-defined stereo-structure[1,2]. This observation has provided the impetus to develop highly stereoselective synthetic strategies for the privileged target structure. Spirolactones, including spiropropyllactones, spirobutyrolactones and spirovalerolactones, are the structural motifs frequently found in many natural products and biologically active molecules [Figure 1][3-5]. The essential moiety of these compounds is the spiro-lactone core with various degrees of substitution. Due to their biological activities, these compounds have drawn much attention from chemists and biologists. However, many challenges need to be addressed, e.g., (a) control of stereogenic spirocenter; (b) incorporation of suitable functional groups into the newly formed ring system for the possible late-stage chemical modification and derivatization. Although several reports have been published in the past few years, the developing efficient methods to access chiral spirolactones with high structural diversity from readily available starting materials remain a challenging but highly desirable goal.

The environmentally friendly, metal-free organocatalysis, usually under simple and mild reaction conditions, has been the frontier topic due to the described advantages[6-15]. In particular, organocatalytic asymmetric synthesis was awarded the 2021 Nobel Prize in Chemistry, which has been demonstrated as one of the most efficient methods for synthesizing chiral compounds. Thus, novel strategies for the organocatalytic asymmetric synthesis of chiral spirolactones are urgently needed. To address the aforementioned challenges, numerous elegant transformations have been developed for the organocatalytic asymmetric construction of this prominent structural motif, which usually employs the two major organocatalytic asymmetric synthetic approaches: the first approach takes advantage of the presence of the existing lactone structure and focuses on its functionalization; the second approach is the lactone framework constructed from various precursors in a direct spirolactonization reaction.

Despite ongoing progress, to the best of our knowledge, a comprehensive review article is lacking to summarize the recent advances in catalytic asymmetric synthesis of chiral spirolactones. Herein, we review for the first time the recent advances in organocatalytic asymmetric cascade reactions for synthesis of chiral spirolactone skeletons, including spirobutyrolactones and spirovalerolactones. This review is summarized and classified according to the two major organocatalytic asymmetric synthetic routes: (i) using the lactone-related frameworks as building blocks; and (ii) direct spirolactonization reaction using various reagents. Discussions of the asymmetric catalytic mechanisms and related transformations are also described. Finally, the remaining challenges in organocatalytic asymmetric synthesis of chiral spirolactones are also touched on, which will enlighten the future development of this research area.

USING THE LACTONE-RELATED FRAMEWORKS AS BUILDING BLOCKS IN ORGANOCATALYTIC ASYMMETRIC CASCADE REACTIONS

The novel skeleton could be obtained by the chemical recombination[16-20] of stereo-chemically rich scaffolds from different sources *via* complexity-generating transformations, which might exhibit unexpected or new bioactivities. Thus, the construction of these three-dimensional chiral spirolactone skeletons is highly desired in the pharmaceutical and organic synthetic community. The use of readily available lactone-related frameworks as building blocks in organocatalytic asymmetric cascade reactions is promising, which enables the construction of this type of potentially bioactive compound in one step [Scheme 1].
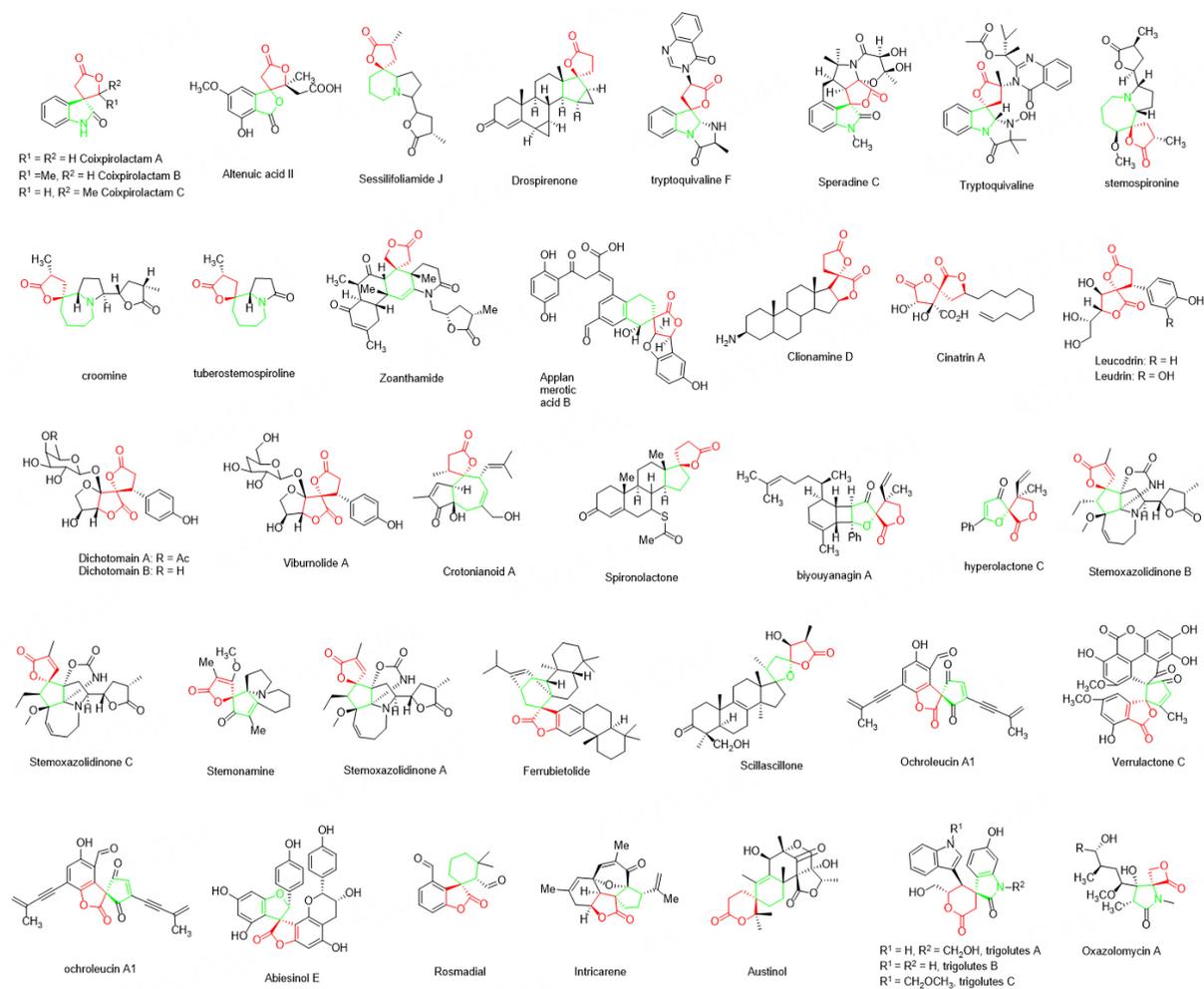
Figure 1. Typical biologically active spirolactones containing spiropropyllactones, spirobutyrolactones and spirovalerolactones.
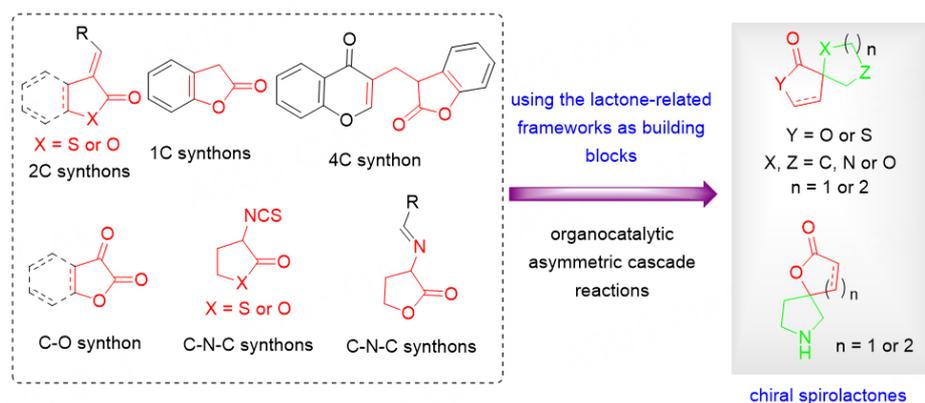
Scheme 1. Lactone-related frameworks as building blocks for the construction of chiral spirolactones.

Benzolactone-derived olefins as 2C synthons

The spiro benzolactone motif is a privileged synthetic moiety that can be found in many natural products with a wide range of biological activities [Figure 1]. For example, Rosmadial[21-23], isolated from aerial parts

of Salvia pachyphylla, inhibits the growth of human cancer cells. Bis-diterpene ferrubietolide, which was isolated from one type of mahogany-dysoxylum lenticellare, was used as the pesticide. Abiesinol E, a member of the spiro-biflavonoid family, has antitumor-initiating effects[21-23]. It is a challenging task to perform asymmetric synthesis on a highly substituted spirocyclic ring, especially the quaternary chiral carbon.

Due to the well-known β-electrophilicity of benzolactone-derived olefins, they have become elegant spirobenzolactone scaffolds for organocatalytic asymmetric cascade annulation strategies. Nucleophilic addition of β-electrophilicity of benzolactone-derived olefins with electron-rich Michael acceptor *via* an intramolecular cycloaddition gave the spirolactone annulation product in one shot [Scheme 2]. Many different electron-rich substrates have been explored over the past few years.

In the past few years, several chiral phosphines catalyzed transformations have been noted[24-31], including the asymmetric synthesis of complicated chiral spirocyclic complex structures. In this context, in 2013, Albertshofer *et al.*[32] reported an efficient organocatalytic asymmetric [3 + 2] cycloaddition reaction between benzolactone-derived olefins 1 and a phosphonium ylide, derived from diverse Morita-Baylis-Hillman carbonates 2 under chiral phosphine catalysis to provide highly complex chiral spirocyclopentenebenzolactone scaffolds 3 with excellent enantioselectivity [Scheme 3]. Three continuous stereocenters, including one all-carbon spiro carbon center, were built in a single step. It is believed that the C_2-symmetric phospholane C1 plays a critical role as an efficient nucleophilic catalyst for the described transformation.

Later on, Wang *et al.*[33] applied another organocatalytic asymmetric roadmap to diverse spirocyclopentenebenzolactones 5 and 7 catalyzed by a chiral phosphine C2 by employing benzolactone-derived olefins 1 and two types of allenic esters 4 and 6. In these reactions, γ-addition products 5 and α-addition products 7 can be obtained in high yields and with excellent enantioselectivities, respectively [Scheme 4].

The reaction started from the formation of a zwitterionic intermediate derived from the chiral phosphine and allenoate (4 or 6). Intermediate acted as a 1,3-dipole and underwent a [3 + 2] cycloaddition with benzofuranone 1 to give a product 5 *via* γ-addition or product 7 *via* α-addition. The DFT calculations disclosed the origins of the regioselective outcomes for this phosphine-catalyzed [3 + 2] cycloaddition reaction.

The tetrahydroquinoline scaffolds[34-36] can usually be found in natural products and drug molecules. Many of them have been used as therapeutic agents due to their biological activities. In the last few years, the application of squaramide organocatalysts in asymmetric catalysis resulted in the significant development of stereoselective cascade cycloaddition reactions.

In this context, in 2022, Zhang *et al.*[37] developed an asymmetric catalytic cascade reaction of benzolactone-derived olefins 1 and α, β-unsaturated ketones 9, merging the spiro-tetrahydroquinoline with spirobenzolactone into a single new skeleton through asymmetric catalytic cascade reactions catalyzed by a quinine-derived chiral bifunctional squaramide organocatalyst C3. A series of differently substituted spiro[benzolactone-tetrahydroquinoline] hybrids 9 was smoothly obtained with high yields and excellent diastereoselectivities and enantioselectivities (up to 99% yield, > 20:1 dr, and > 99% ee) under mild reaction conditions.
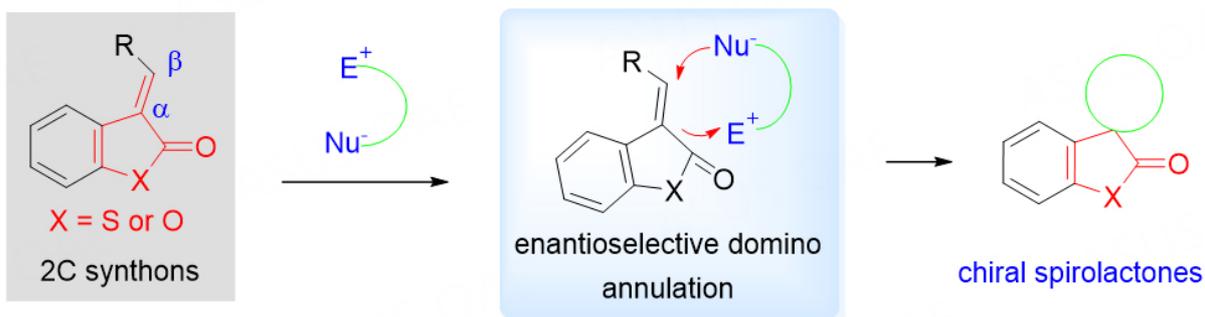
Scheme 2. Benzolactone-derived olefins as 2C synthons for construction of chiral spirolactones.
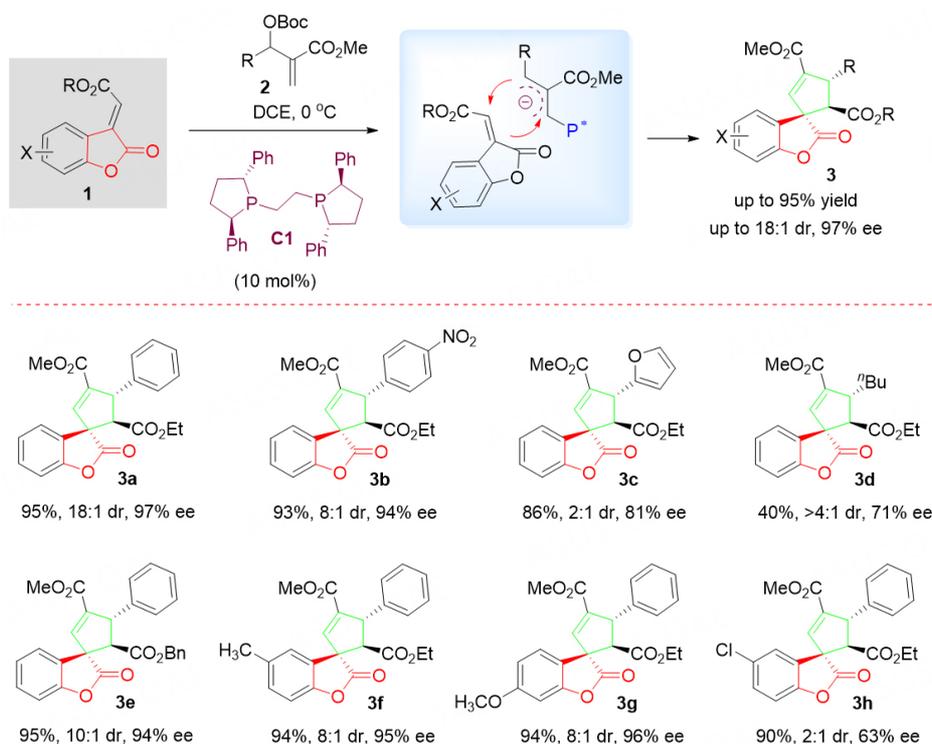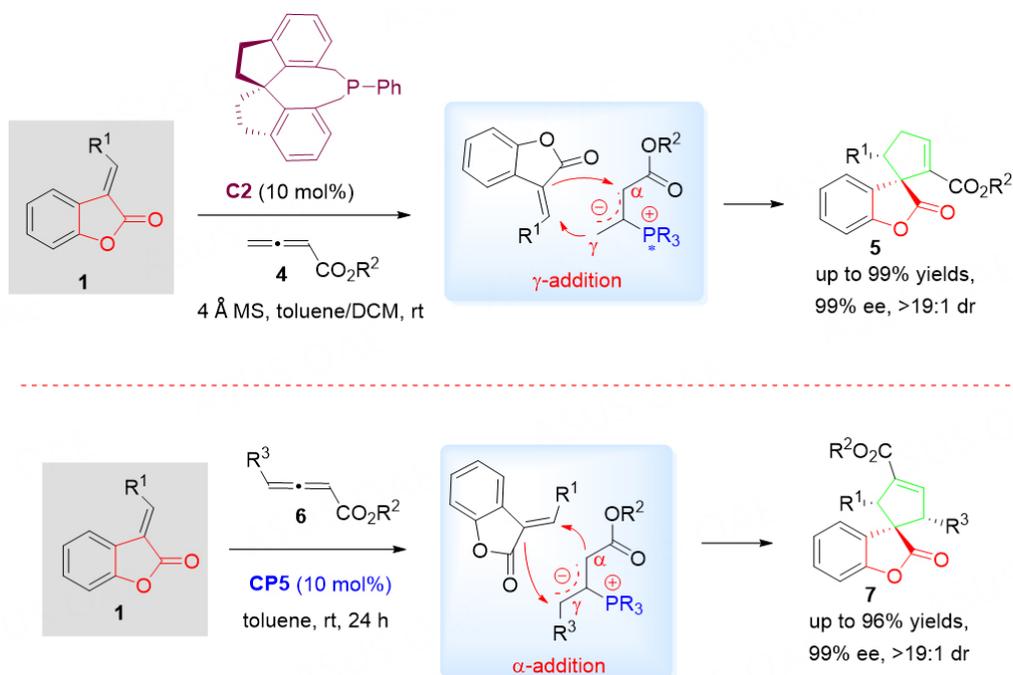

Scheme 3. Asymmetric [3 + 2] cycloaddition reactions of benzolactone-derived olefins **1** and Morita-Baylis-Hillman carbonates **2**. This figure is used with permission from the American Chemical Society[32].

In the proposed reaction mechanism, initially, the bifunctional squaramide catalyst **C3** synergistically activates both **1** and **8** through hydrogen bonds to form the reactive intermediate, followed by an aza-Michael addition process and an intramolecular cyclization, resulting in the final spiro product **9**, accompanied by the regeneration of the chiral catalyst.

Further experiments demonstrated that the reaction of **9a** with *m*-CPBA gave oxidation product **10a** in 95% without damage of the stereo centers (> 20:1 dr and 95% ee, Scheme 5).

Due to the significant medicinal value as well as the structural complexities of spiroheterocyclic hexahydroxanthones, the combination of two or more known pharmacophores could be an efficient and

Scheme 4. Regioselective catalytic asymmetric [3 + 2] cycloaddition of benzolactone-derived olefins **1** and two types of allenic esters **4** and **6**. This figure is used with permission from the Royal Society of Chemistry[33].

powerful method for the synthesis of bioactive natural product-based hybrid molecules[38-43]. Reaction of **1** with bifunctional pyrazolone-chromone **11** in the presence of quinine-derived thiourea catalyst **C4** yielded complicated bispiro[benzolactone-pyrazolone-hexahydroxanthone]s **12** at ambient temperature [Scheme 6][44].

It is believed that the reaction proceeded *via* a domino inter-/intramolecular double Michael cycloaddition reaction, and it serves as a successful strategy for the access of complicate bispiro[benzolactone-pyrazolone-hexahydroxanthone]s **12**, which contains five continuous stereocenters with two quaternary spiro stereocenters. The bis-spiro products **12** were obtained in up to 87% yield with > 20:1 dr and > 99% ee.

In the proposed reaction mechanism, it was revealed that the double hydrogen bonding interaction between **1** and catalyst **C4** played a vital role in controlling the stereoselectivity of this cyclization reaction.

The three-dimensional complexity and diversity of the privileged natural product frameworks could be easily improved by the introduction of contiguous stereocenters[45,46]. In 2020, the synthesis of complicated spiro [benzolactone-hexahydroxanthone] framework **14** was reported.

In situ activation of benzolactone-derived olefin **1** with nitromethane through a [2 + 1] Michael addition generated chiral bifunctional donor-donor 3C synthon **I** with the assistance of quinidine-derived thiourea catalyst **C5**, followed with Michael/Henry cycloaddition with 3-formyl chromone **13** *via* urea-tertiary activation in a "one-pot" fashion, led to structurally diverse spiro [benzolactone-hexahydroxanthone]s **14** with up to six contiguous stereogenic centers, including a quaternary one [Scheme 7][47].
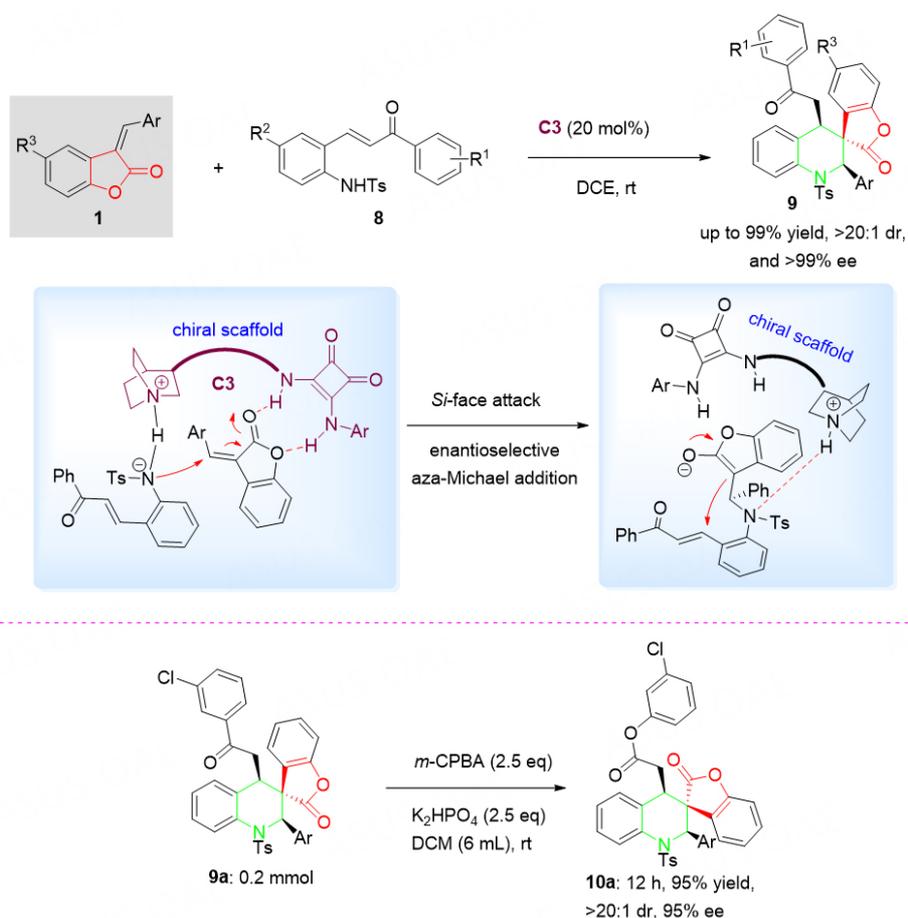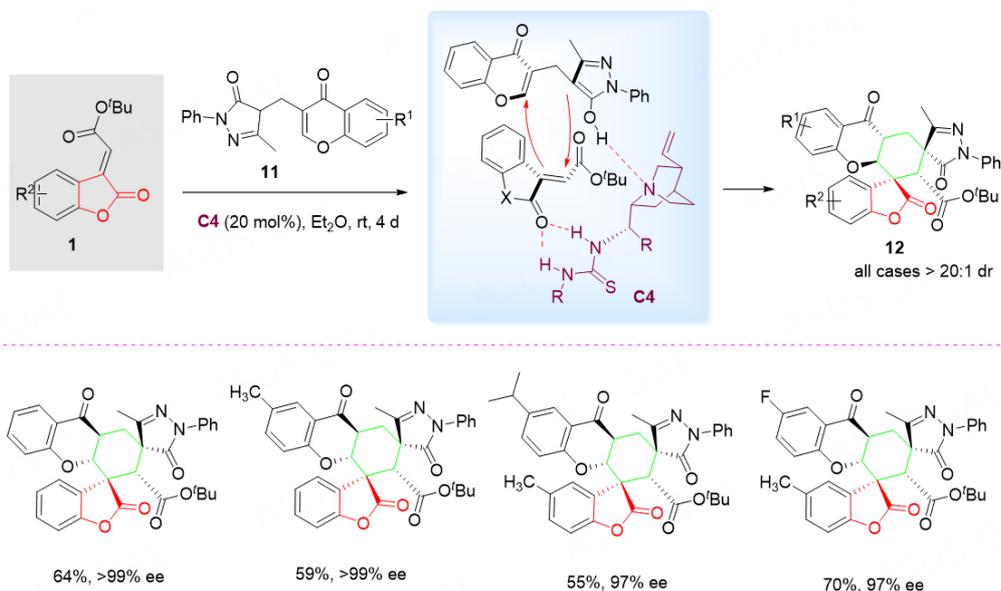
Scheme 5. Asymmetric catalytic cascade reactions of benzolactone-derived olefins **1** and α,β-unsaturated ketones **9**. This figure is used with permission from the Royal Society of Chemistry[37].

It is believed that the enantioselectivity was determined by the first Michael addition. While the Michal addition of **I** to the chromone core *via* hydrogen bonds stabilized intermediate followed by an intramolecular Henry cycloaddition was believed to be the substrate/catalyst-controlled diastereoselective process. All the final products were successfully isolated and characterized in up to 76% yield with > 20:1 dr and 98% ee.

Recently, Li *et al.*[48] developed a highly enantioselective Diels-Alder reaction of benzolactone-derived olefins **1** with polyenals **15** catalyzed by diphenylprolinolsilyl ether **C6** through a trienamine activation strategy, which enabled diversity-oriented synthesis of a series of potentially bioactive multifunctional chiral spirocyclohexenebenzolactone scaffolds **16** with moderate diastereoselectivities and good enantioselectivities. It was demonstrated that this activation strategy lies within the perfect chirality relay over a distance of up to eight bonds by combining trienamine catalysis with enamine activation [Scheme 8A].

To further check the generality of the described work, late-stage chemical modification of the Diels-Alder adduct **16a** was examined. As shown in Scheme 8B, adduct **16a** could be efficiently converted to highly complex scaffolds **17a** and **18a** with good efficiency [Scheme 8B].

Scheme 6. Organocatalytic tandem reaction of pyrazolone-chromone 4C synthons **11** with benzolactone-derived olefins **1**. This figure is used with permission from the Royal Society of Chemistry[44].
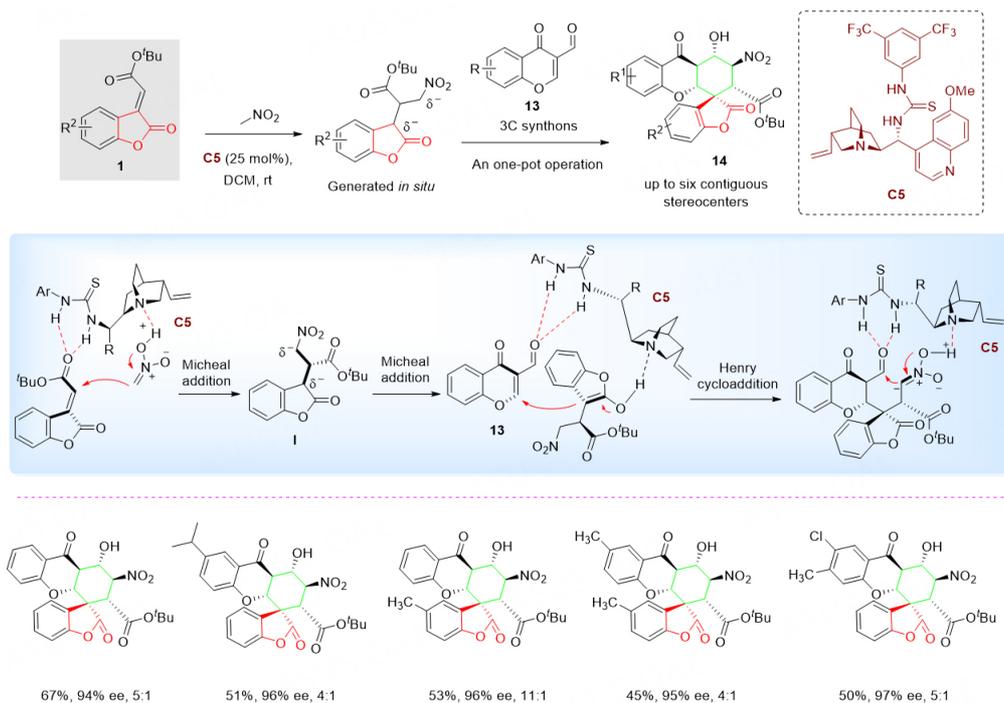
Scheme 7. Organocatalyzed three-component tandem reaction of benzolactone-derived olefins **1**. This figure is used with permission from the Royal Society of Chemistry[47].

Similarly, asymmetric Diels-Alder reaction of 2,4,6-trienals *via* tetraenamine catalysis was also reported by Zhou *et al.*[49]. However, only one example was reported, which utilized benzolactone-derived olefins as a 2C synthon to afford the chiral spirocyclohexenebenzolactone complex in 96% ee and 10:1 dr.

(A) Organocatalytic Diels-Alder reaction for formation of 16
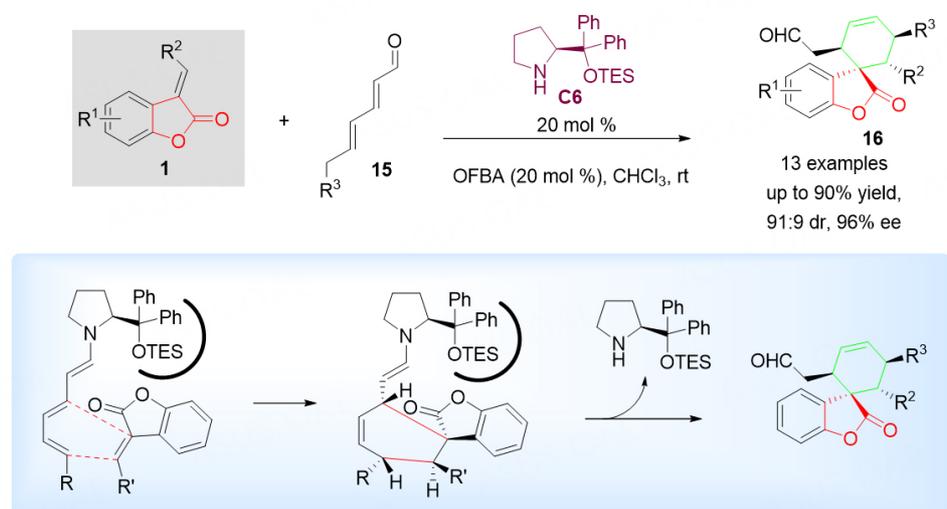
(B) Derivatizations of the product 16a
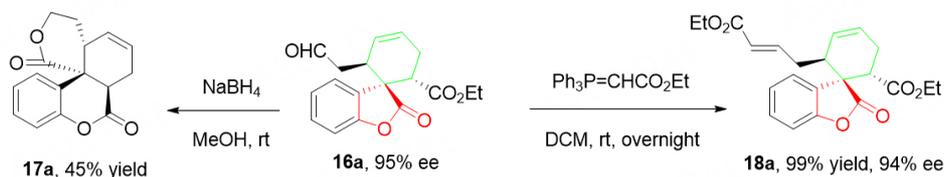

Scheme 8. Organocatalytic Diels-Alder reaction of benzolactone-derived olefins **1** and polyenals **15**. This figure is used with permission from the American Chemical Society[48].

In 2011, Cassani *et al.*[50] developed an organocascade double Michael addition strategy based on the enamine-iminium activation of *α, β*-unsaturated ketones **19**. The highly modified cyclic spiro product **20** was obtained in excellent yields (up to 91%) and enantioselectivity (> 19:1 dr, > 99% ee) in one single chemical step along with the construction of two new bonds and three stereogenic centers [Scheme 9A].

This novel strategy demonstrated the unique ability of primary amine catalyst **C7**, which facilitates the formation of nucleophilic dienamine intermediate and controls the stepwise double-Michael addition. Thus, a variety of complicated spiro-products **20** was successfully isolated with a good diastereomeric and enantiomeric ratio [Scheme 9B].

As a continuation of the above-mentioned strategy, a three-component domino reaction was reported and the spirocyclic benzolactone compounds **23** was obtained by the sequential enamine-iminium-enamine activation of aldehydes **21** and *α, β*-unsaturated aldehydes **22** followed with dehydration as the final step [Scheme 10][50]. A variety of substituents at the *β*-position of the benzolactone-derived olefins **1** is well tolerated, providing fast and easy access to target products **23** with almost perfect control over stereochemistry.

In addition, Chatterjee *et al.*[51] also extended the vinylogous triple cascade reaction of benzolactone-derived olefin. Thus, the three-component domino reaction proceeded by sequential Michael/1,6-addition/vinylogous aldol to give a sole product of spirocyclic benzolactone with six stereogenic centers with perfect control over the stereochemistry.
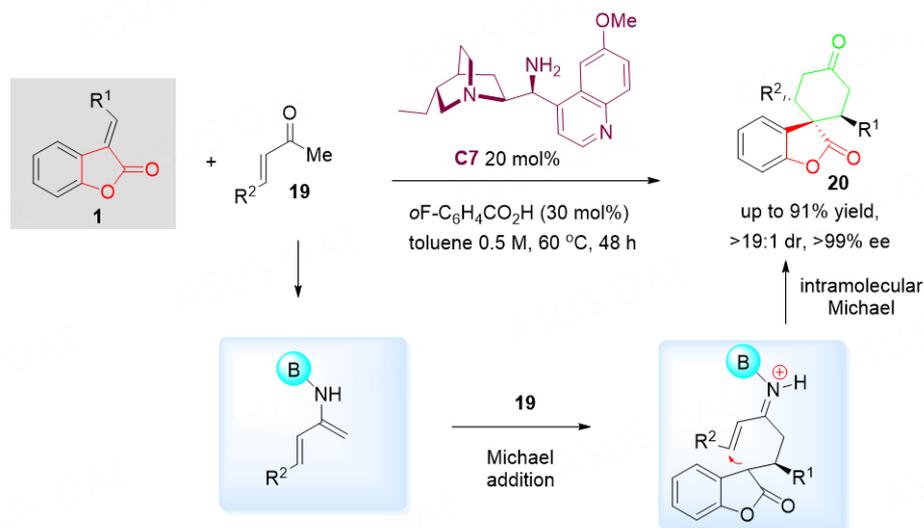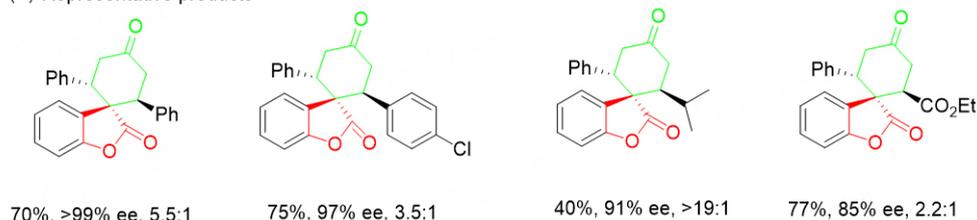
Scheme 9. Organocascade double Michael addition of benzolactone-derived olefins **1** and α,β-unsaturated ketones **19**. This figure is used with permission from the Royal Society of Chemistry[50].

By combining cycloisomerization with trienamine catalysis, in 2016, Chintalapudi *et al.*[52] reported the enantioselective trienamine-organocatalyzed cycloadditions of pyrrolidinyl dienals, prepared by palladium-catalyzed cycloisomerization, successfully delivered two spiro[benzolactone-hexahydroindole] cycloadducts in high enantioselectivity with no preference of endo/exo selectivity.

The development of an efficient and straightforward methodology and enhancement of the structural diversity of these sulfur-containing 3,3'-pyrrolidonyl spirobenzolactones may have a promising impact on the physicochemical and biological characteristics of target molecules.

In this context, an efficient organocatalyzed asymmetric sequential Michael/cyclization of α-isothiocyanato imide **24** with benzothiolactone **1** under mild conditions was reported by Cao *et al.*[53]. However, only two sulfur-containing 3,3'-pyrrolidonyl spirobenzolactones **25** and **26** were reported[53]. Notably, when the oxygen atom of benzolactone-derived olefin **1** was replaced by sulfur, the enantioselective Michael/Cyclization reaction of thiobenzolactone-derived olefin **1** with α-isothiocyanato imide **24** also proceeded smoothly, which provided the spirothiobenzolactone skeleton **26** with greater than 99% ee and moderate distereoselectivity [Scheme 11].

α, β-Unsaturated butyrolactones/valerolactones as 2C synthons
The scaffold-inspired compounds encouraged us further to build a library of molecular complexity around the biologically relevant framework for further biological evaluation. The prevalent spiro
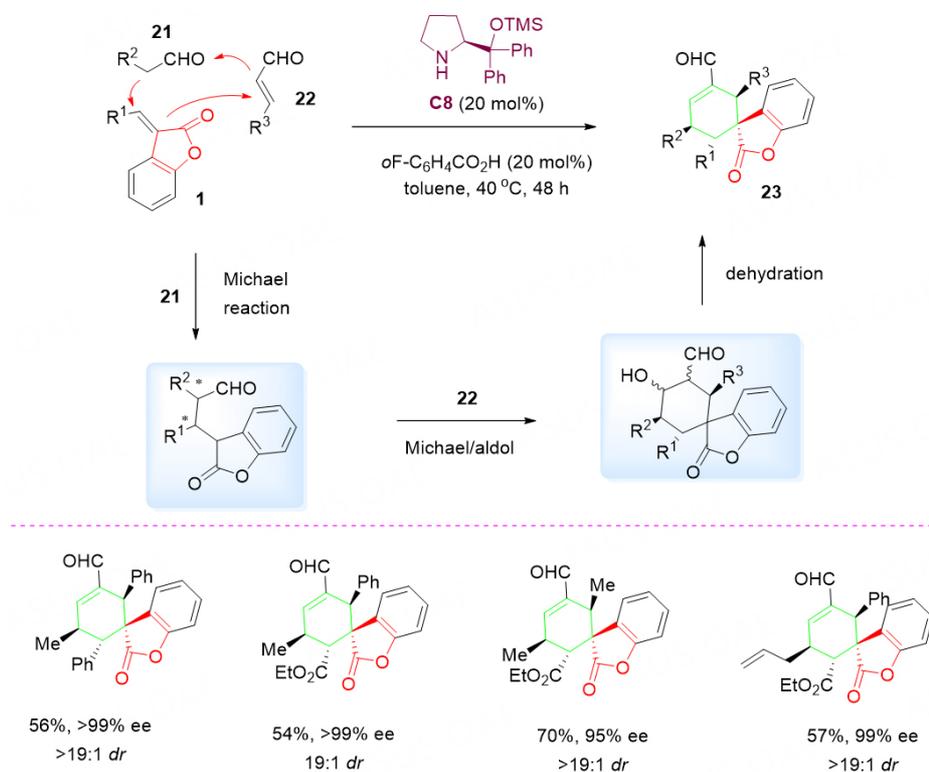
Scheme 10. Organocascade three-component domino reaction of benzolactone-derived olefins **1**, aldehydes **21** and α,β-unsaturated aldehydes **22**. This figure is used with permission from the Royal Society of Chemistry[50].
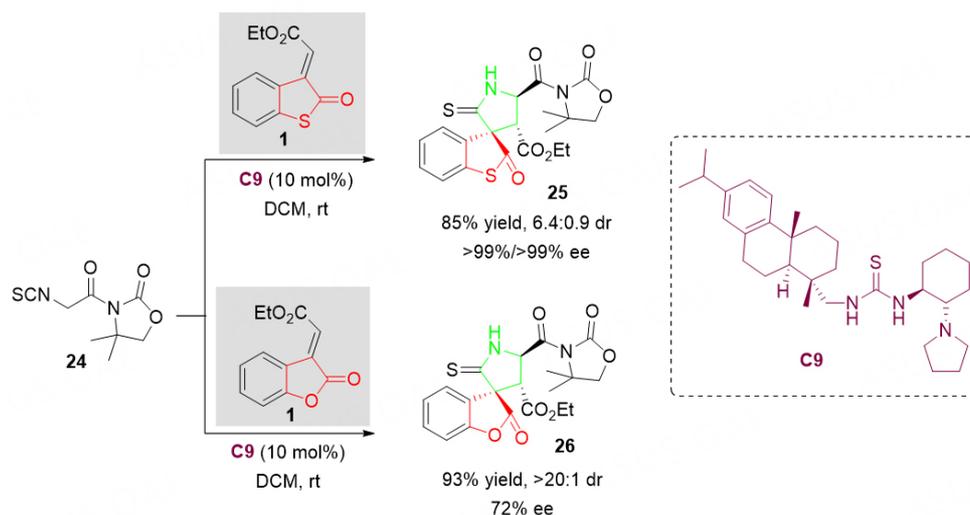
Scheme 11. Organocascade Michael/Cyclization reaction of benzolactone-derived olefin **1** with α-isothiocyanato imide **24**. This figure is used with permission from John Wiley and Sons Ltd[53].

butyrolactone/valerolactone moieties are present in many biologically active molecules and natural products, as shown in Figure 1. To access this type of potentially bioactive compounds, the use of readily available α, β-unsaturated butyrolactones/valerolactones **27** as dipolarophile synthons presents a promising one [Scheme 12]. However, due to the inherent inertness of the α, β-unsaturated esters, the corresponding
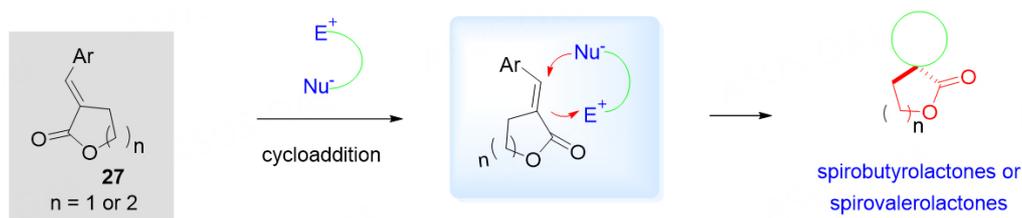
Scheme 12. α, β-unsaturated butyrolactones/valerolactones **27** as 2C synthons for construction of spirobutyrolactone/valerolactones.

report is still limited.

Due to the inherent inertness of the α, β-unsaturated esters, there is no literature report regarding the catalytic asymmetric synthesis. Hence, it is critical to develop a novel organocatalytic system for it. In 2022, our group[54] established a highly efficient strategy for the synthesis of complicated bispiro[butyrolactone-pyrrolidine-indanedione] hybrids **30** in up to 89% yield with excellent selectivity (> 20:1 dr) with three-component reaction of α, β-unsaturated butyrolactones/valerolactones **27**, ninhydrin **28** and proline or thioproline **29** [Scheme 13].

Initially, the intermediate azomethine ylides **A** was generated *in situ* by the reaction of ninhydrin **28** and proline or thioproline **29**, followed by the cyclization addition of α, β-unsaturated butyrolactones/valerolactones **27** to obtain the final spiro product **30**.

It is happy to find out that many of the natural products, e.g., parthenolide, dehydrocostus lactone, and costunolide, could be used as the substrates for described cyclization to give corresponding chiral parthenolide-fused product **30f**, dehydrocostus lactone-fused products **30g-30h**, and costunolide-fused product **30i** with good yields (73%-81%) and enantioselectivity (> 20:1 dr).

The preliminary anti-cancer activity of three selected compounds **30f-h** was performed [Scheme 14]. On the basis of the initial biological experiments results, **30f** and **30g** show significant cytotoxicity to the A549 cells and the K562 cells by inducing apoptosis of tumor cells. Thus, further optimization of the structure and biological data might make them potential candidates for drug discovery.

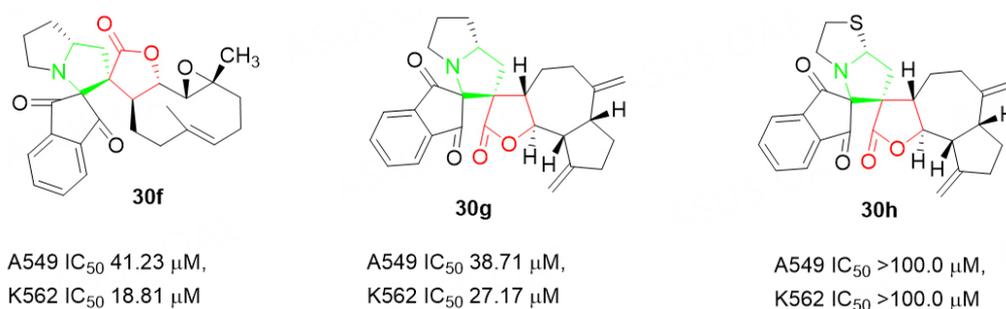### 3-Alkenyl-5-arylbutenolides as 2C synthons
Due to the significant steric hindrance between the two vicinal spiro-quaternary chiral centers, especially in a constrained ring system, it is a great challenge to chemically synthesize such moiety. Hence, it is important to develop an efficient method for the synthesis of vicinal spiro-quaternary chiral centers.

Recently, 3-alkenyl-5-arylbutenolides serving as efficient 2C synthons have been used to generate highly functionalized spiro heterocyclic derivatives under organocatalytic conditions. Wang *et al.*[55] have developed a highly diastereo- and enantioselective [3 + 2] cycloaddition of *N*-2,2,2-trifluoroethylisatin ketimines **32** as efficient azomethine ylide precursors with 3-alkenyl-5-arylbutenolides **31** as efficient 2C synthons with thiourea-tertiary amine **C10** as the catalyst (1 mol%) [Scheme 15].

In this reaction, the tertiary amine of the catalyst **C10** activates the *N*-2,2,2-trifluoroethylisatin ketimines **32** *via* hydrogen bonding and simultaneously the 3-alkenyl-5-arylbutenolides **31** gets activated by thiourea group through hydrogen bonding. This process allows the rapid synthesis of spiro[pyrrolidin-3,20-oxindoles] **33** bearing four consecutive stereocenters, including sterically congested two vicinal quaternary
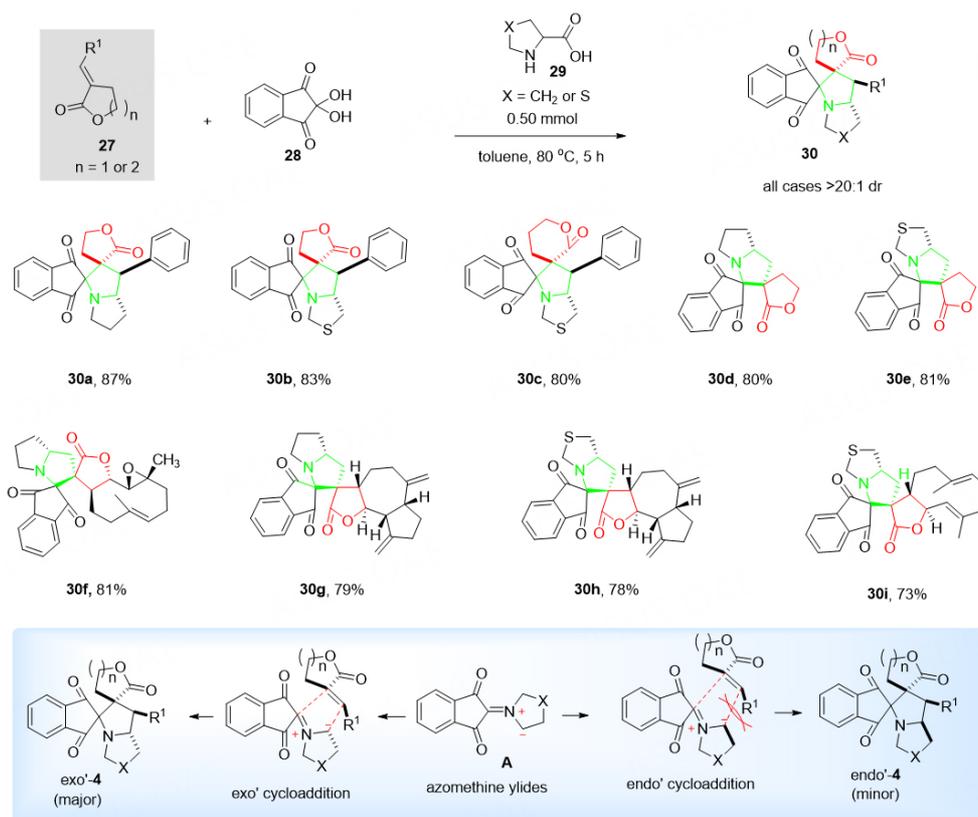
Scheme 13. Domino 1,3-dipolar cycloaddition of butyrolactones/valerolactones **27**, ninhydrin **28** and proline or thioproline **29**. This figure is used with permission from the Royal Society of Chemistry[54].

30f

A549 IC$_{50}$ 41.23 μM,
K562 IC$_{50}$ 18.81 μM

30g

A549 IC$_{50}$ 38.71 μM,
K562 IC$_{50}$ 27.17 μM

30h

A549 IC$_{50}$ >100.0 μM,
K562 IC$_{50}$ >100.0 μM

Scheme 14. The biological evaluation. This figure is used with permission from the Royal Society of Chemistry[54].

spiro chiral centers, with excellent results (up to > 99% yield, > 20:1 dr, and > 99% ee).

The synthetic application of this cascade [3 + 2] cycloaddition was further demonstrated by a diversifying conversion of **33a** into another two functionalized dispirocyclic heterocyclic derivatives **34** and **35** without damage to the stereocenters [Scheme 16].

Benzolactones as 1C synthons
The great synthetic challenge needs to be addressed for the stereo-controlled synthesis of highly functionalized polycyclic spirobenzolactone scaffolds, especially for the efficient installation of novel
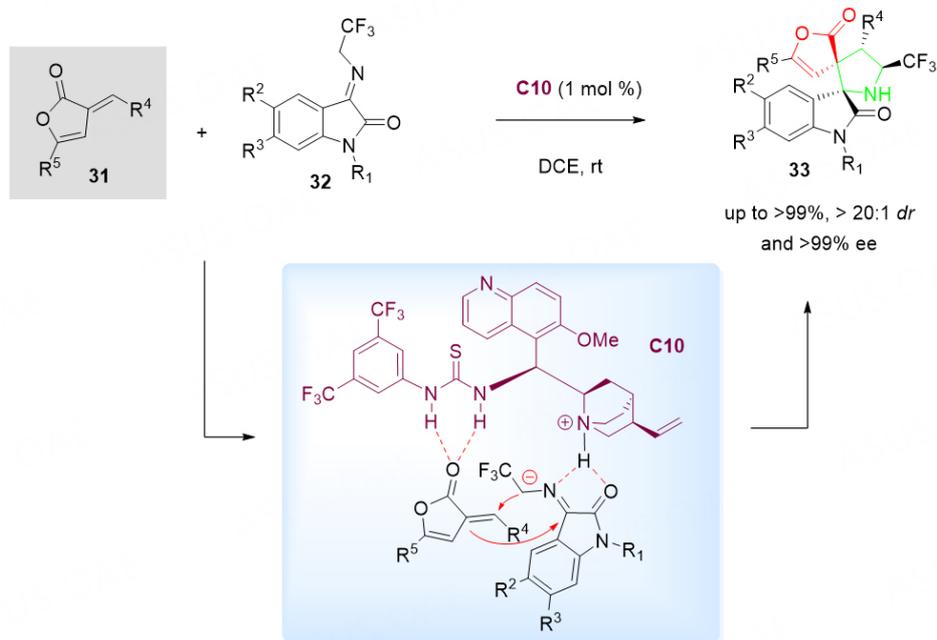
Scheme 15. Organocascade 1,3-dipolar cycloaddition of 3-alkenyl-5-arylbutenolides **31** and *N*-2,2,2-trifluoroethylisatin ketimines **32**. This figure is used with permission from the Royal Society of Chemistry[55].

34, 97%, >20:1 dr, 98% ee   **33a**, >20:1 dr, 98% ee   **35**, 99%, >20:1 dr, >99% ee
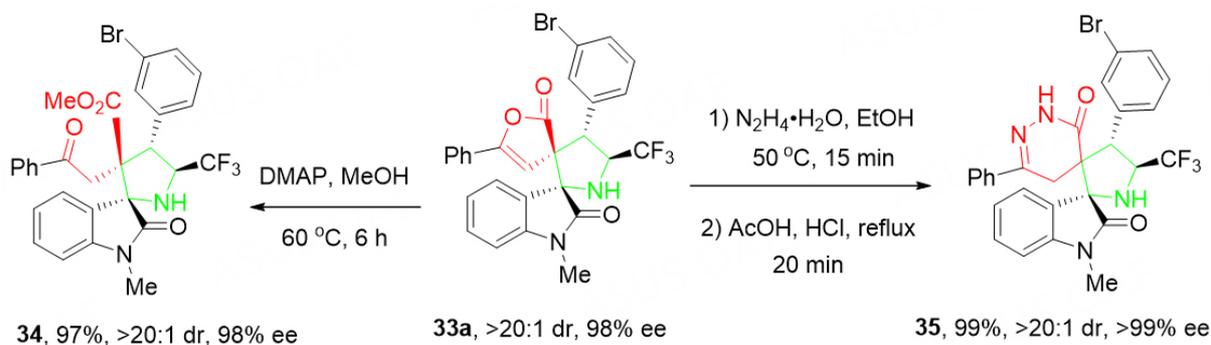
Scheme 16. Representative transformations of product **33a**. This figure is used with permission from the Royal Society of Chemistry[55].

quaternary spiro stereocenters[56-59]. To overcome the synthetic challenge, benzolactones **36** containing a dinucleophilic center, have been utilized as highly efficient 1C precursors in combination with electron-deficient species as electrophiles in organocatalytic annulation systems for the synthesis of complex polycyclic spirobenzolactones [Scheme 17]. A variety of dielectrophiles have been explored over the past years.

In 2011, Chatterjee *et al.*[51] developed a novel amine-catalyzed cascade reaction of benzofuranones **36** with two molecules of enals **37** to access densely functionalized spirobenzolactone molecules **38** [Scheme 18]. The successful isolation and characterization demonstrated the application of organocascade for the synthesis of high degrees of stereochemical and architectural complexity in a single chemical transformation.
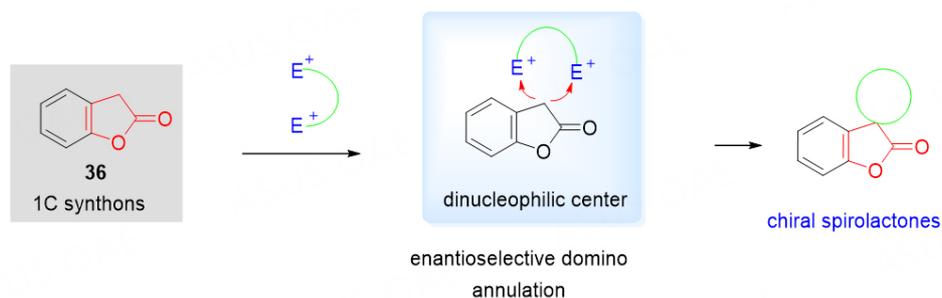
Scheme 17. Benzolactones **36** as 1C synthons for construction of chiral spirolactones.
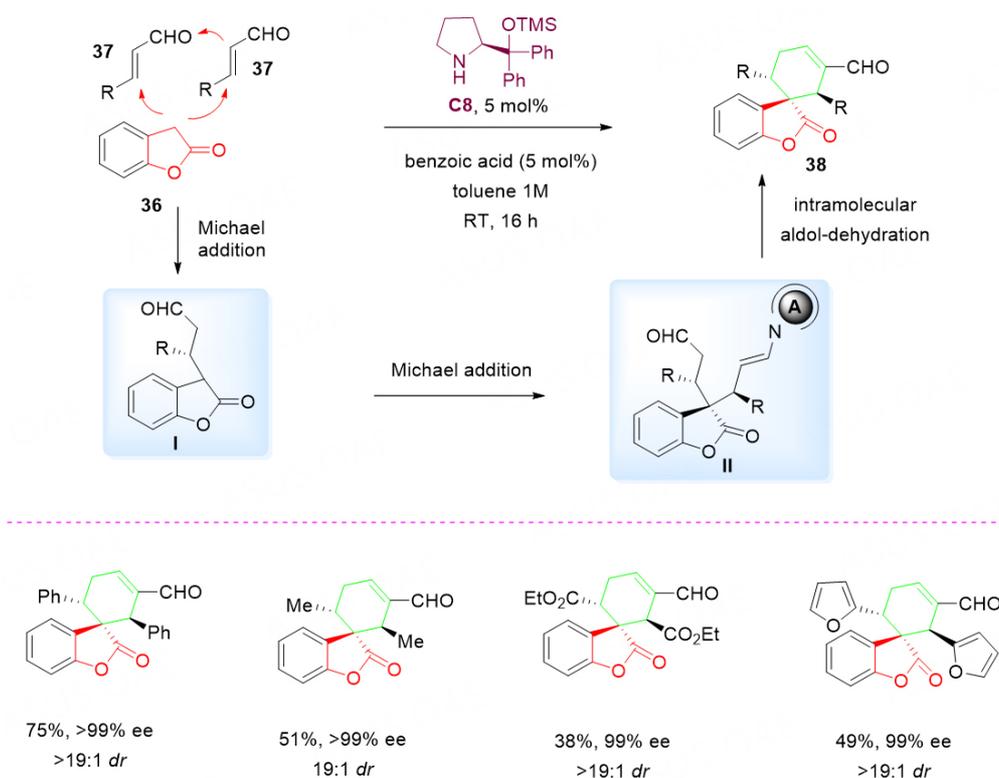
Scheme 18. Aminocatalytic cascade reaction of enals **37** with benzofuranones **36**. This figure is used with permission from Wiley-VCH Verlag[51].

The plausible mechanism for organocascade was proposed. It is initiated with an iminium-catalysed Michael addition of **36** to **37** in the presence of **C8** to give intermediate **I**. A second iminium-mediated Michael addition of the chiral nucleophilic intermediate **I** to another molecule of enal **37** is expected to give intermediate **II**. Lastly, an enamine-driven intramolecular aldol reaction of **II** followed by dehydration led to the formation of spirocyclic benzolactone **38** with excellent stereoselectivities [Scheme 18].

In addition, in 2010, Companyó *et al.*[60] developed an aminocatalytic Michael-Michael-aldol reaction, affording spirocyclic derivatives in good yields and in almost diastereo- and enantiopure form. However, only one example was reported that utilized benzolactone as a 1C synthon to afford the chiral spiro benzolactone compound in 93% ee and > 25:1 dr.

As a complementary above-mentioned organocascade strategy, in 2013, Li *et al.*[61] reported a highly enantioselective double-Michael addition reaction by reaction of benzofuranones **36** containing a dinucleophilic center with divinyl ketones **39** in the presence of tertiary amine-thiourea Cinchona alkaloid organocatalyst **C11** for the construction of a spirobenzolactone scaffolds **40** in very good yields (up to 99%), up to 19:1 dr and 92% ee [Scheme 19A]. A broad substrate scope of spirobenzolactones **40** was obtained.

It was proposed that the tertiary amine of the catalyst **C11** activates the divinyl ketone **39** *via* hydrogen bonding and simultaneously the benzofuranone **36** gets activated by thiourea through hydrogen bonding. The hydrogen bond interaction between the three components locked their conformation and played a critical role in the stereoselectivity of this cyclization reaction. The origin of stereoselectivity was explored and determined by density functional theory (DFT) calculations [Scheme 19A].

To demonstrate the synthetic utility of this process, the enantiomerically enriched compound **40a** obtained by this method can be easily converted into oxime derivative **41** in one step without any loss of enantiomeric excess [Scheme 19B], which is an essential structural motif in a great number of drug molecules[62,63].
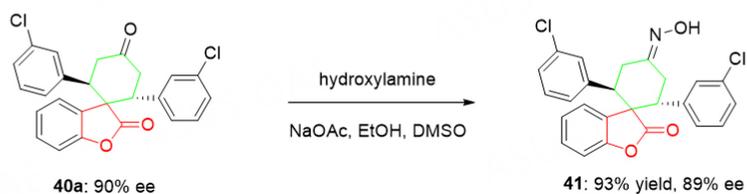
Benzolactone-chromones as 4C synthons

In 2020, our group developed a novel benzolactone-chromone building block **42** and successfully applied it to the organocatalytic Mannich/cyclization reactions of acceptor/donor-based species to give the chiral spirolactone derivatives with excellent structural complexity and diversity, thus facilitating the search for new bioactive entities. After careful analysis of the property of the structure, it is believed that this strategy benefits from the initial intermolecular Michael reaction followed by another intramolecular Michael reaction. The counterbalancing of the lower electrophilicity of these unactivated chromones is critical to facilitate the expected cyclization reaction [Scheme 20].

Due to the special structure of hexahydroxanthone, which contains four or more contiguous stereocenters, it represents a prominent structural motif in many natural products and pharmacologically active compounds. In this context, in 2020, a quinine-derived thiourea **C12**-catalyzed inter-/intramolecular Michael cycloaddition reaction of bifunctional benzolactone-chromone synthon **42** with benzolactone-derived olefins **1** was reported by Zhang *et al.* [Scheme 21][64]. All the desired products **43**, potentially useful in medicinal chemistry, were obtained in good yields (up to 80%) with high diastereoselectivities (up to > 20:1 dr) and enantioselectivities (up to > 99% ee).

Bifunctional benzolactone-chromone synthon **42** was well-tailored to first act as a nucleophilic donor and then to originate as a Michael acceptor; after the conjugate addition, an *in situ* generated intermediate able to continue the intramolecular Michael cycloaddition.

α-Keto lactones as C-O synthons

The spiro-bis-lactone is a crucial synthetic motif found in natural products and biologically active molecules [Figure 1][65-70]. Benzolactone-2-one derivatives are typical *α*-keto lactones, which can serve as a new kind of versatile C-O synthons to react with electron-rich species in annulation, and have attracted much attention in recent years. Treatment of benzolactone-2-ones **43** with NHC-catalyzed generation of homoenolate equivalents from enals **44** in the presence of a convenient catalyst provided a straightforward strategy for the synthesis of spiro-bis-lactones **45** [Scheme 22A][71].

(A) Organocatalytic double-Michael addition reaction for formation of **40**
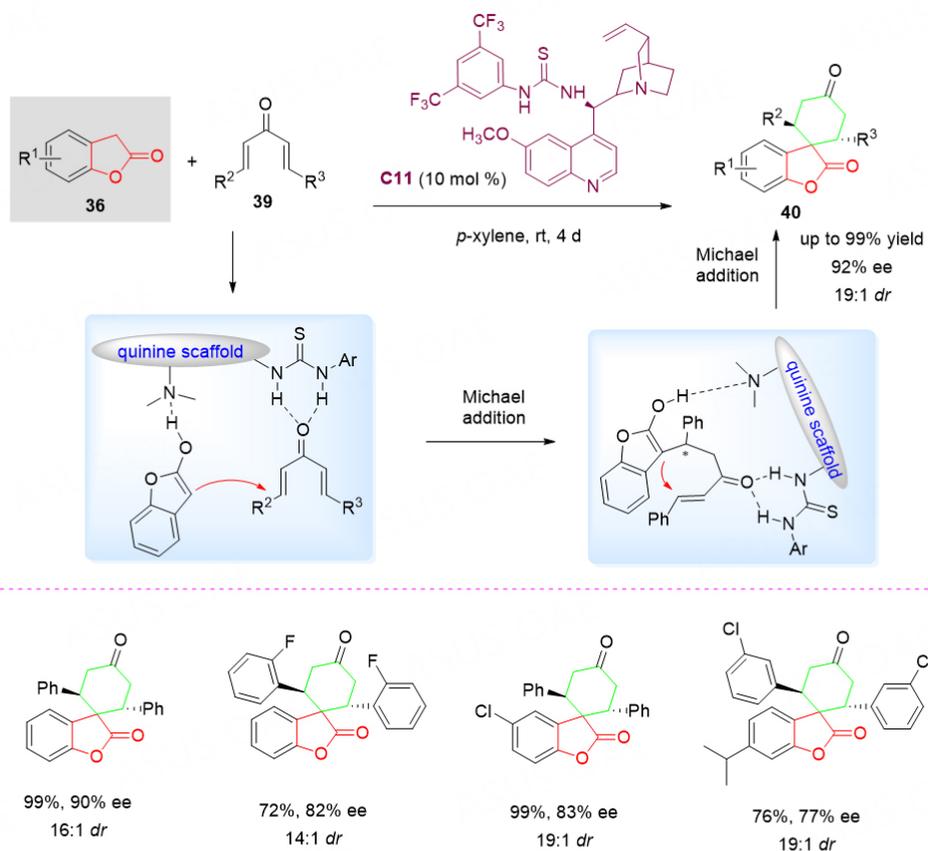
(B) Derivatizations of the product **40a**

Scheme 19. Organocatalytic enantioselective double-Michael addition reaction of benzofuranones **36** and divinyl ketones **39**. This figure is used with permission from John Wiley and Sons Ltd[61].
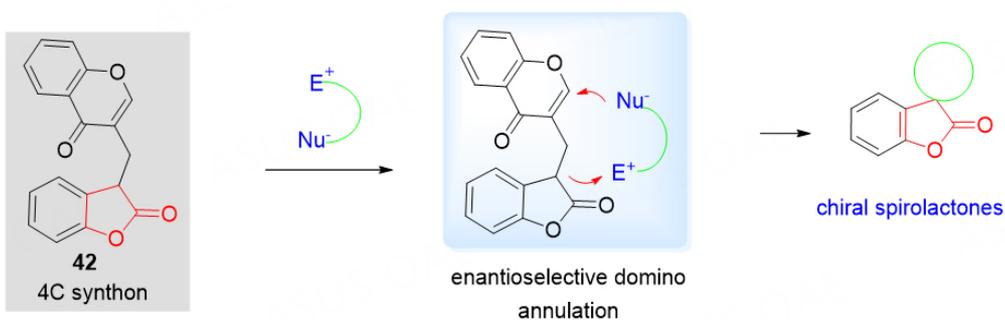
Scheme 20. Benzolactone-chromones **42** as 4C synthons for construction of chiral spirolactones.
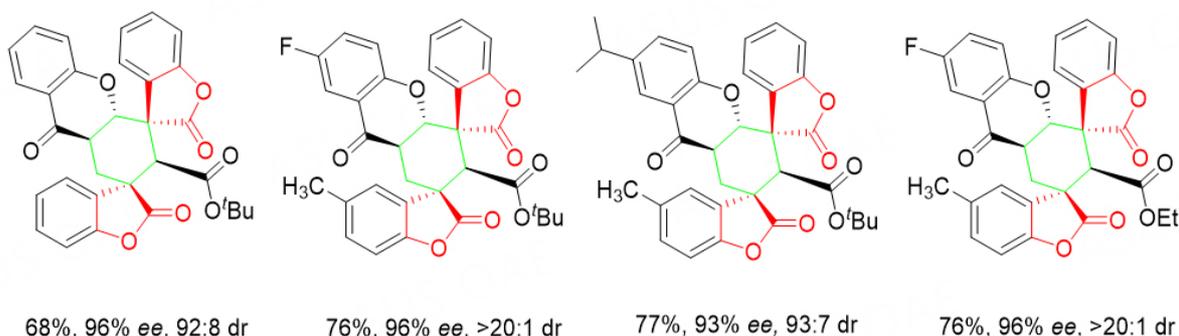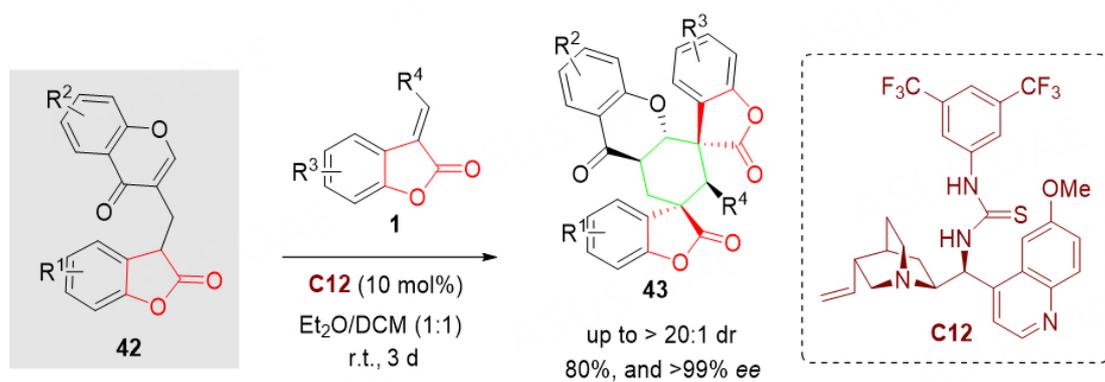
Scheme 21. Organocatalyzed tandem reaction of benzolactone-chromone 4C synthons **42** with benzolactone-derived olefins **1**. This figure is used with permission from Elsevier[64].

It was proposed that the addition of NHC to enal **44** gave an intermediate **I**, followed by nucleophilic addition to the ketone-carbonyl group of benzolactone-2-one **43** to give the intermediate **I**, which was tautomerized to intermediate **III**. Lastly, intermediate **III** underwent intramolecular nucleophilic addition to the activated carboxyl surrogate to close the lactone ring and the regenerated catalyst **C** went to the next circle [Scheme 22B]. It is important to note that no literature report regarding the catalytic asymmetric synthesis of such a molecule was available. Thus, it should be a great research potential for the chiral NHC-catalyzed asymmetric reactions.

Furthermore, α-keto lactone **43** could also serve as a powerful building block in asymmetric cascade [3 + 2] cycloaddition of α-isothiocyanato imide **46** to give the chiral spirolactone derivative **47** with structural complexity and diversity [Scheme 23]. However, only one example was reported[72]. Thus, it should be a great research potential for the aldol/cyclization reaction of α-keto lactone **43**.

3-Isothiocyanato butyrolactones as C-N-C synthons

The structural complexity and richness in the stereogenic centers of spirocyclic compounds are generally important for their potentially useful pharmaceutical properties. Moreover, biological activity seems to be enhanced by replacing oxygen atoms in spirocyclic molecules with sulfur atoms. The isothiocyanates bearing an electron-withdrawing group at the α-position have proved to be particularly critical for the asymmetric synthesis of spirocyclic heterocyclic compounds[73-79]. Recently, 3-isothiocyanato butyrolactone **48** could also serve as a powerful C-N-C synthon in asymmetric [3 + 2] cycloaddition to give the chiral spirothiobenzolactone derivatives [Scheme 24].

(A) N-Heterocyclic carbene-catalyzed annulation for formation of **45**
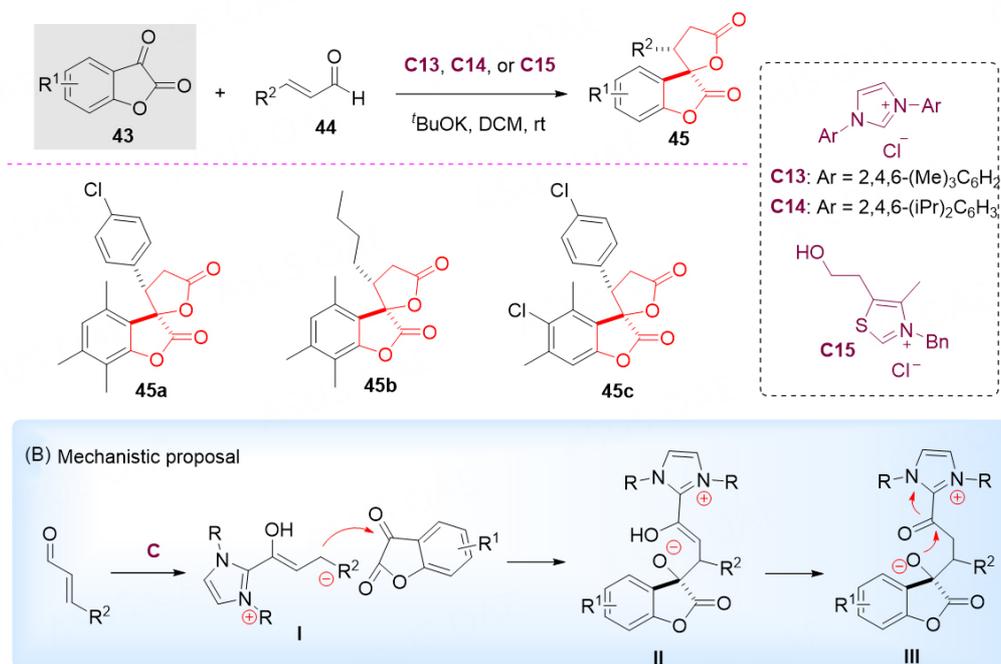
Scheme 22. *N*-heterocyclic carbene-catalyzed annulation of benzolactone-2-ones **43** and enals **44**. This figure is used with permission from the Royal Society of Chemistry[71].
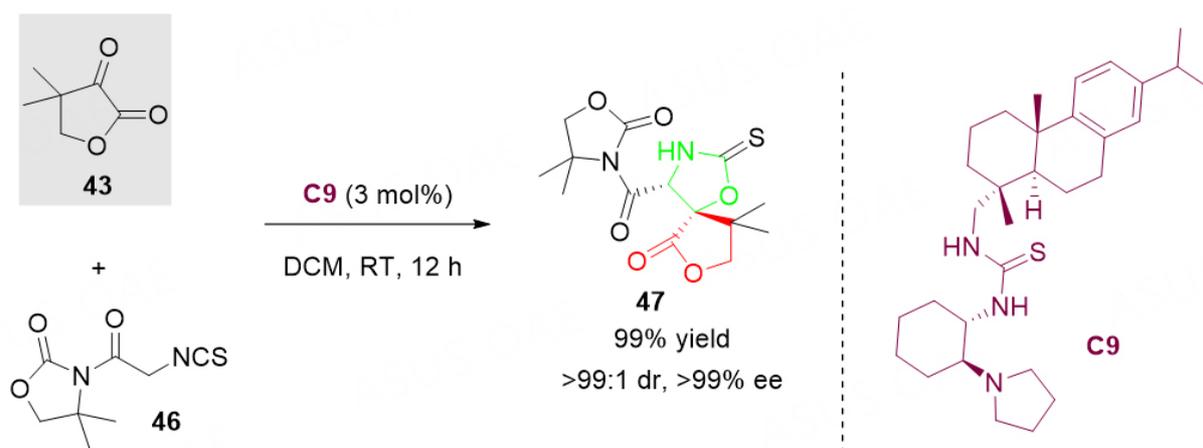
Scheme 23. Organocatalyzed aldol/cyclization reaction of *α*-keto lactone **43** with *α*-isothiocyanato imide **46**. This figure is used with permission from the American Chemical Society[72].

In 2010, a rosin-derived thiourea catalyst **C9** catalyzed asymmetric aldol/cyclization cascade reaction of isothiocyanato butyrolactone **48** as C-N-C synthon with isatins **49** was reported by Jiang *et al.*[72]. It is proposed that, with the dual activation of rosin-based thiourea **C9**, this strategy allowed rapid construction of highly functional bispiro[thiooxazoline/thiocarbamate-butyrolactone-oxindole]s **50** and **51** with moderate diastereoselectivities (70:30-92:8 dr). However, the author did not provide their specific ees [Scheme 25].
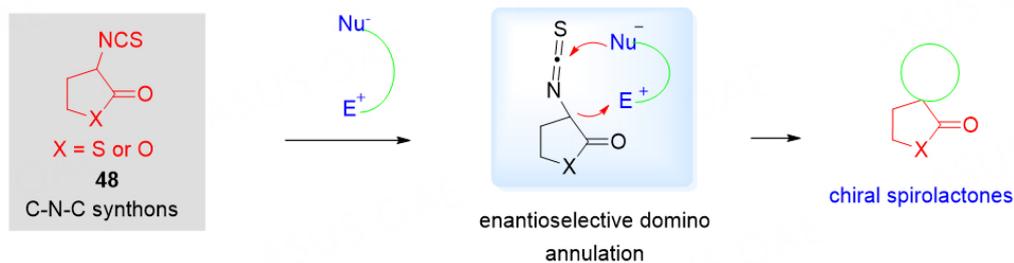
Scheme 24. 3-Isothiocyanato butyrolactone as C-N-C synthons for construction of chiral spirobutyrolactones.
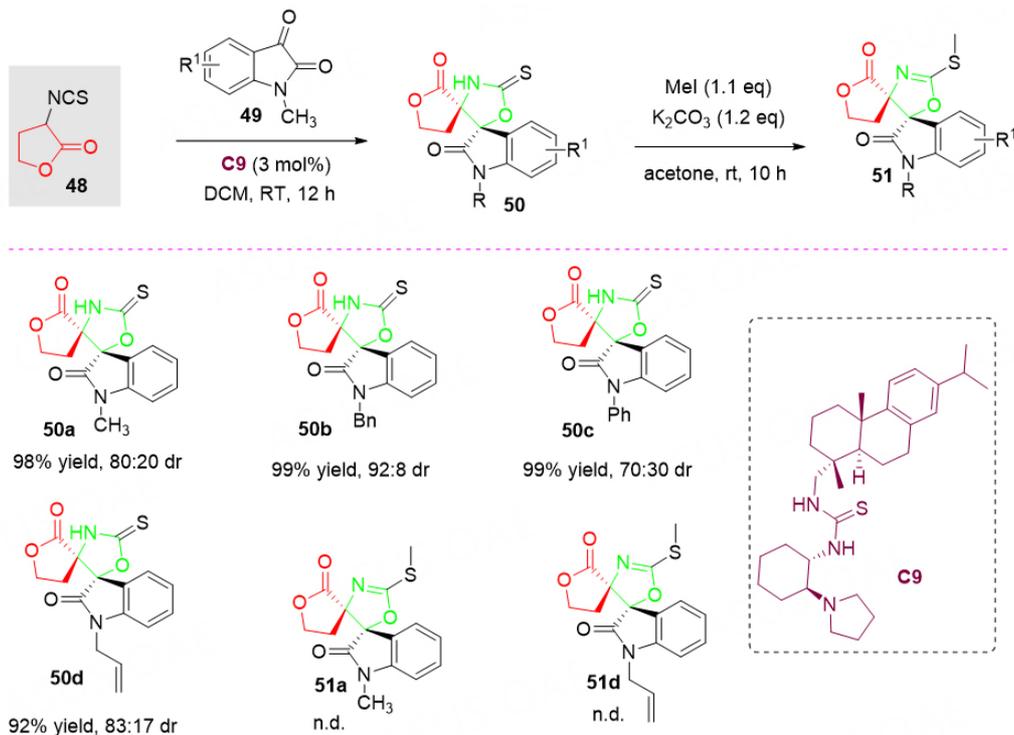
Scheme 25. Organocatalyzed aldol/cyclization reaction of isothiocyanato butyrolactone **48** with isatins **49**. This figure is used with permission from the American Chemical Society[72].

In addition, using *α*-isothiocyanato lactone and methyleneindolinone as the reactants, another organocatalytic synthesis of an optically active bispiro[oxindole-butyrolactone] scaffold was also reported by Cao *et al.*[53] The product having three contiguous stereocenters, including two spiro-quaternary chiral centers, was isolated with > 99% ee, > 20:1 dr and in 80% yield.

In 2011, employing isothiocyanato butyrolactone **48** as a C-N-C synthon, Jiang *et al.*[80] continued to report a highly efficient organocatalyzed Mannich/cyclization reaction of *N*-tosylimines **52** [Scheme 26].

In this reaction, the tertiary amine of the catalyst **C18** activates the isothiocyanato butyrolactone **48** *via* hydrogen bonding and simultaneously the *N*-tosylimines **52** gets activated by thiourea group through hydrogen bonding. This process allows the rapid synthesis of optically active bispiro[thioimidazole-butyrolactone] skeletons **53** with high levels of enantio- and diastereoselectivity (up to 96% ee, and 10:1 dr).
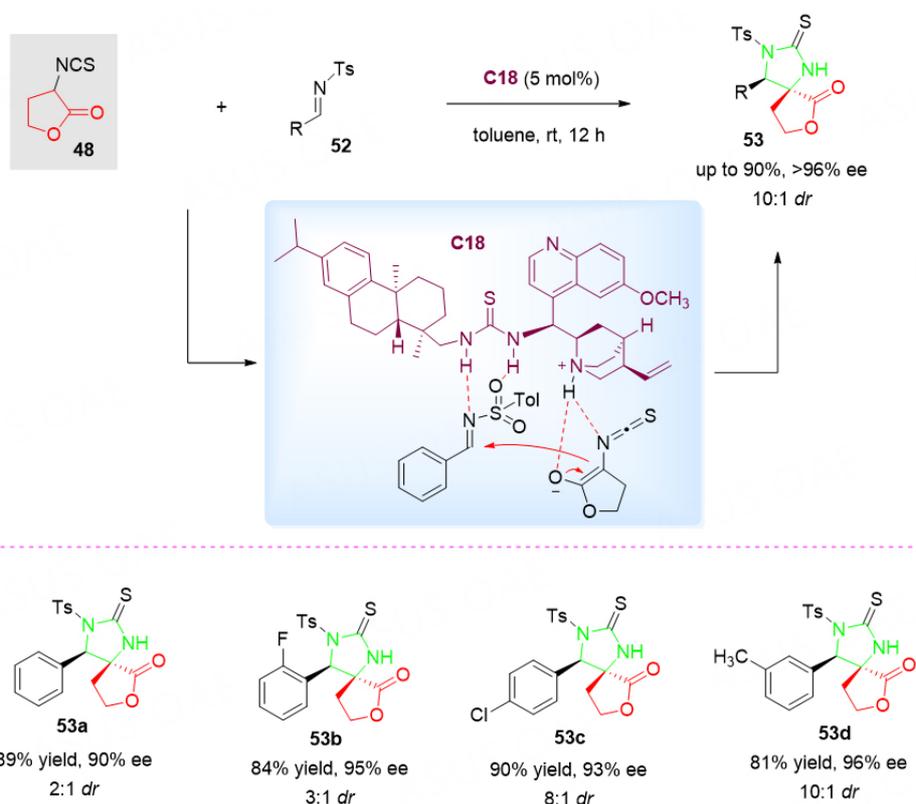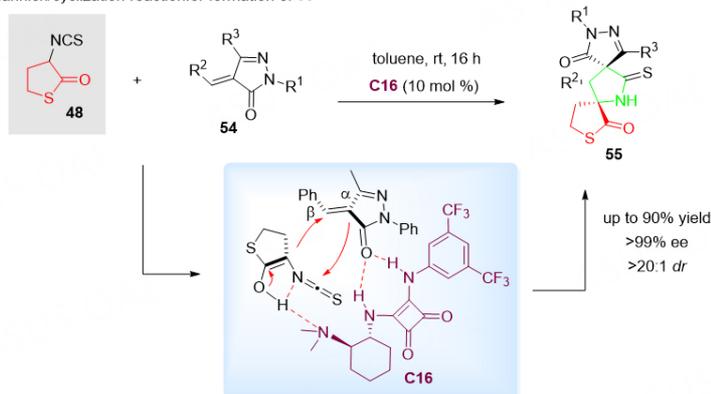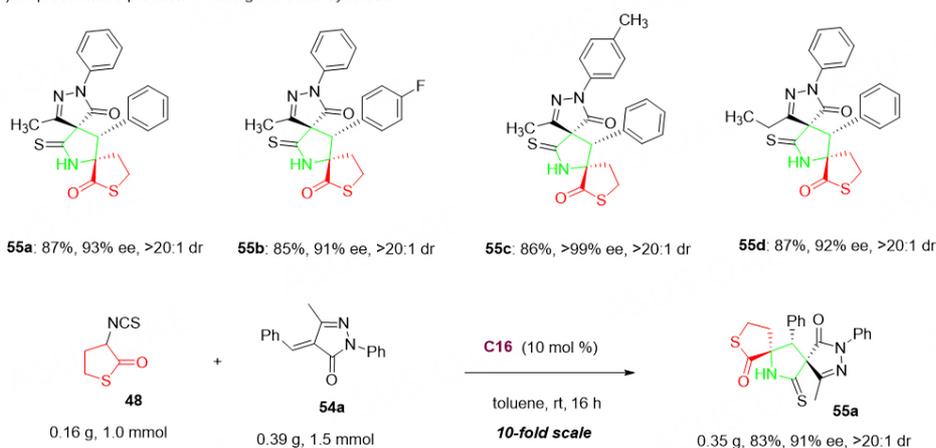
Scheme 26. Organocatalyzed Mannich/cyclization reaction of isothiocyanato butyrolactone **48** with *N*-tosylimines **52**. This figure is used with permission from Wiley-VCH Verlag[80].

Following the work of Jiang *et al.*[80], the reaction of isothiocyanato thiobutyrolactone **48** as a nucleophilic cascade with alkylidene pyrazolones **54** was explored for the squaramide-catalyzed enantioselective synthesis of bispirocyclic bispiro[pyrazolone-thiobutyrolactone] skeletons **55** *via* cascade Mannich/cyclization reaction. A range of structurally diverse products **55** bearing three contiguous stereocenters including two quaternary spiro stereocenters was obtained in up to 90% yield with up to > 20:1 dr and > 99% ee [Scheme 27A][81].

As for the reaction mechanism, we speculated that the tertiary amine of the catalyst **C16** activates the isothiocyanato thiobutyrolactone **48** *via* hydrogen bonding and simultaneously the alkylidene pyrazolones **54** gets activated by squaramide through hydrogen bonding. The hydrogen bond interaction between the three components locked their conformation and played a critical role in the stereoselectivity of this cyclization reaction [Scheme 27A]. To further highlight the synthetic value of this method, the amenability to gram-scale synthesis provided many opportunities for possible industrial applications [Scheme 27B].

To check the potential application of the demonstrated asymmetric synthesis, the reaction of **55e** with MeI and K₂CO₃ in acetone led to the formation of methylated analog **56** without damage to the two quaternary spiro stereocenters [Scheme 27C]. Notably, there are two privileged substructures, butyrolactone and pyrazolone[82-87], in one spirocyclic molecular structure of **55**, which may potentially be useful in medicinal chemistry.
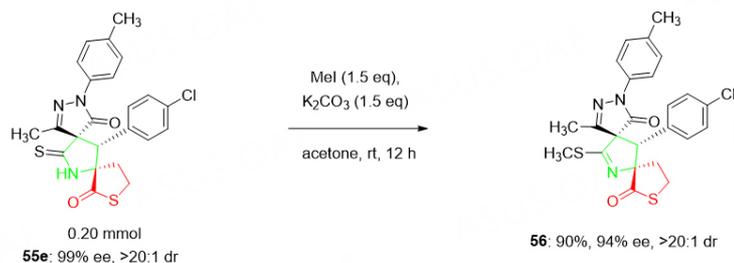
Scheme 27. Organocatalyzed Mannich/cyclization reaction of isothiocyanato thiobutyrolactone **48** with alkylidene pyrazolones **54**. This figure is used with permission from the Royal Society of Chemistry[81].

Butyrolactone-derived cyclic imino esters as C-N-C synthons

The asymmetric 1,3-dipolar cycloaddition of azomethine ylides with electron-deficient olefins is one of the highly powerful methods for the synthesis of various highly substituted pyrrolidine scaffolds widespread in natural compounds. Recently, novel spirocyclic butyrolactone skeletons with multiple stereocenters could be constructed through simple 1,3-dipolar cycloadditions between butyrolactone-derived cyclic imino esters **57** as azomethine ylide precursors and electron-deficient species as dipolarophiles with suitable organocatalysts [Scheme 28].
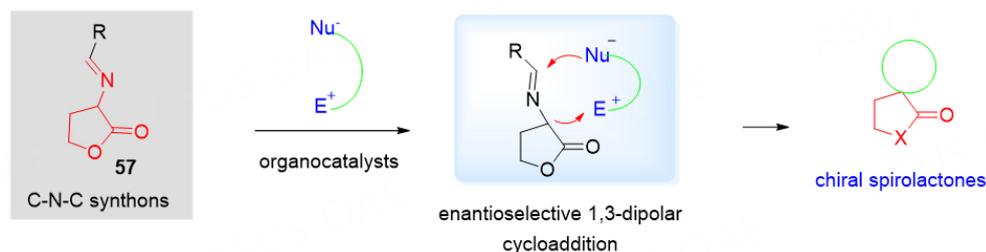
Scheme 28. Butyrolactone-derived imino esters **57** as C–N–C synthons for construction of chiral spirobutyrolactones.

In 2013, a rosin-based thiourea **C9** catalyzed formal 1,3-dipolar cycloaddition of butyrolactone-derived cyclic imino esters **57** and methyleneindolinones **58** as dipolarophiles was reported by Wang *et al.* [Scheme 29][88]. It is proposed that, with the dual activation of rosin-based thiourea **C9**, this process provides a series of highly functional spiro[butyrolactone-pyrrolidin-oxindole] tricyclic skeletons **59** containing four contiguous stereocenters and two spiro-quaternary carbon with excellent yields and stereoselectivities (up to 97% yields, > 20:1 dr and > 99% ee).

In recent years, bispirocyclic scaffolds, which consist of three closed rings with two rigid spirocenters, have been found in many natural products that exhibit important biological activities. Asymmetric 1,3-dipolar cyclization reactions to construct these bispirocyclic scaffolds are highly attractive but extremely challenging. In this context, organocatalytic 1,3-dipolar cycloaddition of butyrolactone-derived cyclic imino esters **57** with alkylidene pyrazolones **60** in the presence of catalyst **C17** in ether at ambient temperature gave highly functionalized bispiro products **61** in high yields (up to 93% yield) and excellent stereoselectivities (> 20:1 dr and > 99% ee, Scheme 30)[89]. Various highly functionalized bispiro[butyrolactone-pyrrolidin-pyrazolone] scaffolds **61** containing two quaternary spirocenters have been successfully obtained in a single reaction. Due to the extensive biological activities of the three structural motifs of butyrolactone, pyrrolidine, and pyrazolone, the author believes that the resulting bispiro[butyrolactone-pyrrolidin-pyrazolone] scaffolds **61** could potentially display enhanced or new bioactivities.

It was explained by the authors that both the intermolecular H-bonding between the catalyst and two substrates as well as the chiral environment created by the bifunctional squaramide catalyst **C17** are critical for the generation of excellent stereoselectivities [Scheme 30].

Dihydrocoumarins and lactones are synthetically useful compounds with various bioactive derivatives and exist in many natural products. Both types of heterocyclic systems occupy a prominent position among the extraordinary richness of various heterocyclic systems. Recently, utilizing butyrolactone-derived cyclic imino esters **57** and *α, β*-unsaturated butenolides **62** as starting materials, Kowalczyk-Dworak *et al.*[90] have developed an organocatalytic approach for the preparation of spiro[butyrolactone-pyrrolidin-dihydrocoumarin] scaffolds **63** with structural complexity and diversity [Scheme 31].

There are two critical annulation processes in the reported synthesis. The first one is the [3 + 2]-dipolar cycloaddition for the construction of a pyrrolidine ring. The second one is the nucleophilic addition-elimination, which led to the butenolide-ring-opening and introduction of a dihydrocoumarin framework in **63**. The polycyclic products **63** have been isolated and characterized in excellent yields and stereoselectivity due to the efficiencies of the bifunctional quinine-derived thiourea catalyst **C18** [Scheme 31].
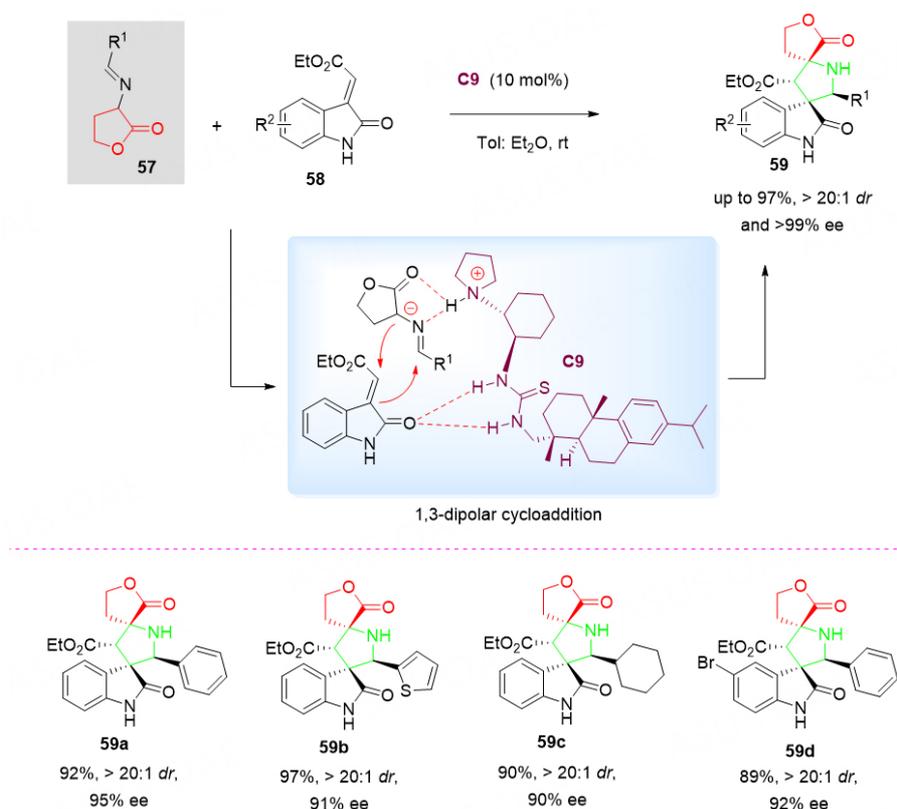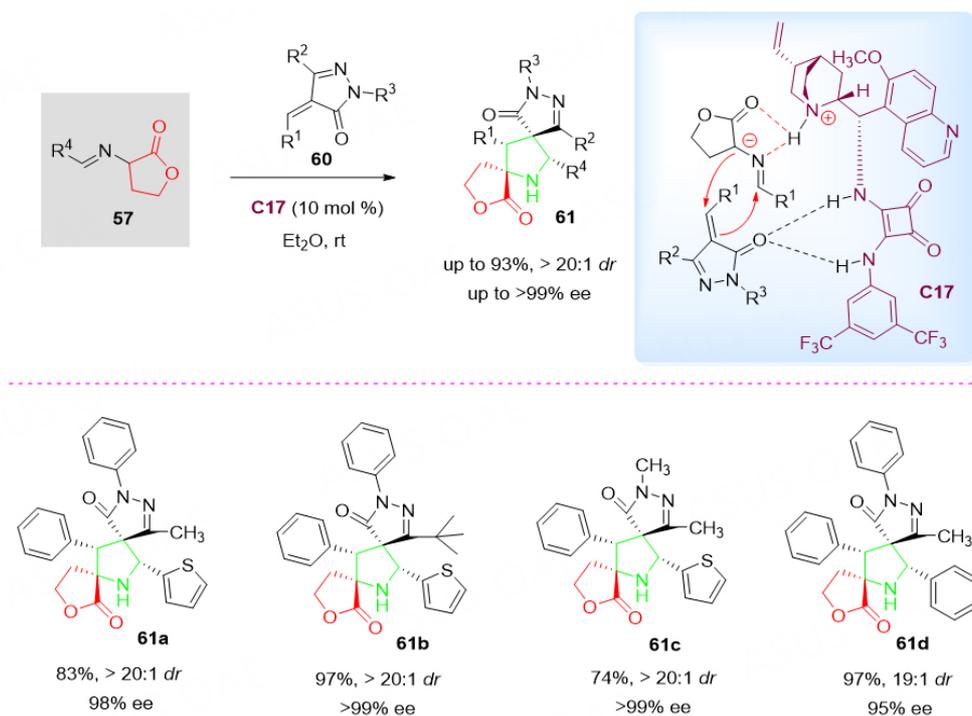
Scheme 29. Organocatalytic 1,3-dipolar cycloaddition of butyrolactone-derived imino esters **57** and methyleneindolinones **58**. This figure is used with permission from the Royal Society of Chemistry[88].

Heterocyclic fused chromanones have attracted lots of attention due to their structural complexity and significant medicinal activities. Inspired by the chemical and biological properties of butyrolactones, pyrrolidines as well as heterocycle-fused chromanones, we have successfully demonstrated the synthesis of novel spiro-[butyrolactone-pyrrolidine-chromanone] hybrids **65** by a simple domino 1,3-dipolar cycloaddition of azomethine ylides **57** with carboxylic acid-activated chromones **64** in the presence of the catalytic amount of Et3N [Scheme 32][91]. The desired products **65** were obtained in moderate to good yields (up to 85%) and selectivity (> 20:1 dr) *via* an exo-transition state. Although no literature report regarding catalytic asymmetric synthesis is available yet, further organocatalytic investigations should have great research potential.

Furthermore, the biological activity of the four selected hybrids **65** was investigated [Scheme 33]. The experimental data shows impressive cytotoxicity to the K562 cells (IC50 < 50.00 μM) for **65a-65d**. It is important to note that **65a** and **65b** also show considerable cytotoxicity to the A549 cells. Both of the promising biological data suggest the possible application of spiro-[butyrolactone-pyrrolidine-chromanone] derivatives **65** for the development of active drugs after further pharmacological studies.

In conclusion, the described works have demonstrated the potential of lactone-related frameworks as building blocks for the diversity-oriented synthesis of chiral spirolactone skeletons. Various complicate products could be easily obtained simply by taking advantage of the existing lactone structure and focusing on its functionalization. Thus, the efficient construction of chiral spirolactone-based libraries for modern probe and drug discovery will be another frontier in the near future.

Scheme 30. Organocatalytic 1,3-dipolar cyclization of butyrolactone-derived cyclic imino esters **57** and alkylidene pyrazolones **60**. This figure is used with permission from Wiley-VCH Verlag[89].
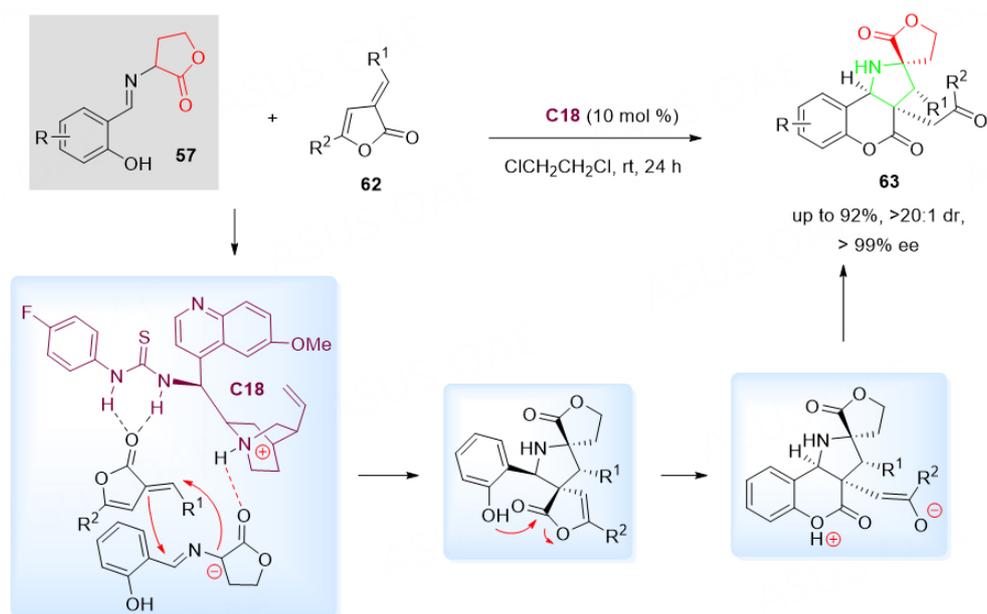
Scheme 31. Organocatalytic annulation cascade reaction of α, β-unsaturated butenolides **62** and butyrolactone-derived cyclic imino esters **57**. This figure is used with permission from the Royal Society of Chemistry[90].

DIRECT SPIROLACTONIZATION REACTION USING VARIOUS REAGENTS IN ORGANOCATALYTIC ASYMMETRIC CASCADE REACTIONS

The efficient construction of chiral spirolactones with broad structural diversity, including spiropropyllactones, spirobutyrolactones and spirovalerolactones from simple substrates, would be valuable for the development of new biologically active molecules.

To achieve this goal, in recent years, the use of readily available lactone-related frameworks as starting materials for the organocatalyzed asymmetric domino annulation reaction is a straightforward strategy. Despite the advancements, the structural diversity is limited by the choice of starting materials. In this context, the eco-friendly, efficient methodologies for the rapid generation of skeletally-diverse chiral spirolactone molecules remain highly desirable but challenging. In addition to utilizing the existing lactone structure as the starting material, another synthetic route is the skeletal construction of the lactone framework from various lactone construction precursors in a direct spirolactonization reaction, providing the structurally and biologically interesting chiral spirolactones with good efficiency [Scheme 34].

Spirolactonization reaction of 3-olefinic oxindoles

Skeletal construction is an important method in synthetic communities for the rapid and reliable construction of core frameworks with various functional groups. In 2018, Guo *et al.*[92] developed a new and promising Michael-initiated Pinnick oxidative spirolactonization reaction for the synthesis of potentially bioactive chiral spirocyclic oxindole-lactone derivatives **68** in up to 97% yield with up to 99% ee [Scheme 35, top]. The corresponding products **68** contain spirocyclic oxindole-paraconic esters and bear three chiral stereocenters.

The mechanism of formation of the spirocyclic oxindole-lactones is presented [Scheme 35, bottom]. Initially, an organocatalytic asymmetric Michael addition of aliphatic aldehyde **67** with 3-olefinic oxindole **66** to generate intermediate 3-oxindolepropionic aldehyde **A**. Then, spirocyclic oxindole-lactone **68** was generated in the presence of sodium chlorite *via* a sequential tandem Pinnick oxidation/chlorination/substitution transformation.

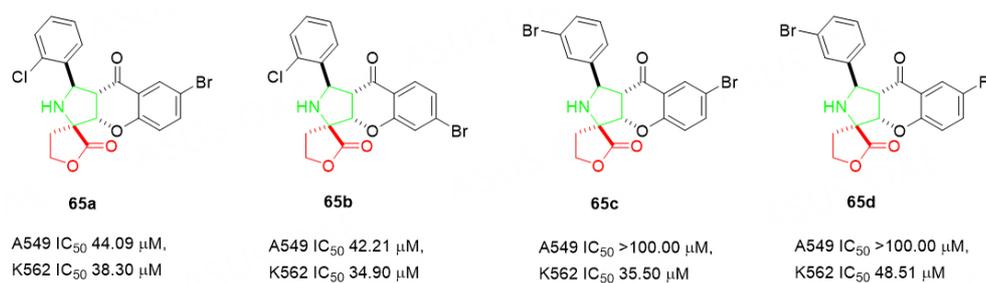### Spirolactonization reaction of 3-hydroxyoxindoles

The spiro[oxindole-lactone] scaffolds are found in a wide range of biologically active natural products and clinical pharmaceuticals [Figure 1]. Because of the correlation between molecular structure and biological activity, it is strongly desired to develop efficient asymmetric synthetic methods for the construction of spiro[oxindole-lactone] derivatives.

For many years, 3-hydroxyoxindoles **69** containing two reactive nucleophilic sites have been successfully applied in the organocatalytic asymmetric synthesis of spiro[oxindole-lactone] scaffolds. Due to the presence of the lone pair electron at the oxygen atom, they are a good candidate to react with electron-deficient species *via* nucleophilic addition reactions. With the presence of the carbonyl group, the sequential intramolecular nucleophilic lactonization reaction is expected *via* the acyl-transfer process [Scheme 36]. Various biselectrophilic species, such as *α, β*-unsaturated *N*-acylated succinimides, *α, β*-unsaturated pyrazoleamides, *α, β*-unsaturated esters, *α, β*-unsaturated acyl phosphonates and *α, β*-unsaturated acyl azoliums generated from enals and NHCs, have been explored over the past years.

The spirolactone is widely present in various natural products, e.g., fungi, plants, and marine species. Some of these products show significant biological and pharmaceutical activities [Figure 1][93,94]. To investigate the diversity-oriented synthesis of the medicinally important spirolactone scaffolds, an efficient tandem spirolactonization reaction of 3-hydroxyoxindoles **69** with olefinic azlactones **70** was reported by Cui *et al.*[95] for the synthesis of structurally diverse spirocyclic oxindole-lactones **71** [Scheme 37]. It is proceeded *via* the
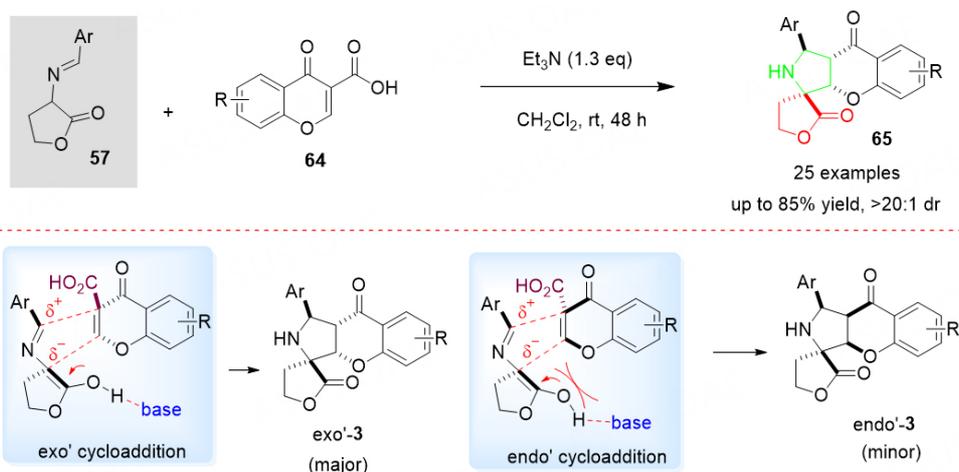
Scheme 32. Organocatalytic domino 1,3-dipolar cycloaddition of butyrolactone-derived cyclic imino esters **57** and carboxylic acid-activated chromones **64**. This figure is used with permission from Georg Thieme Verlag[91].

65a	65b	65c	65d
A549 IC$_{50}$ 44.09 μM, K562 IC$_{50}$ 38.30 μM	A549 IC$_{50}$ 42.21 μM, K562 IC$_{50}$ 34.90 μM	A549 IC$_{50}$ >100.00 μM, K562 IC$_{50}$ 35.50 μM	A549 IC$_{50}$ >100.00 μM, K562 IC$_{50}$ 48.51 μM

Scheme 33. Evaluation of cytotoxicity toward cancer cell lines. This figure is used with permission from Georg Thieme Verlag[91].
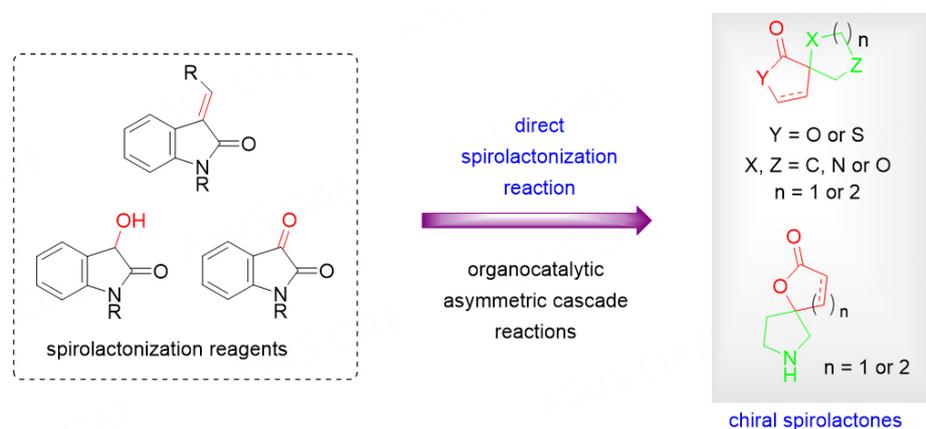
Scheme 34. Direct spirolactonization reaction for construction of chiral spirolactones.

Michael addition of the 3-hydroxyoxindole **69** to the (*Z*)-olefinic azlactone **70** and sequential ring opening and lactonization.
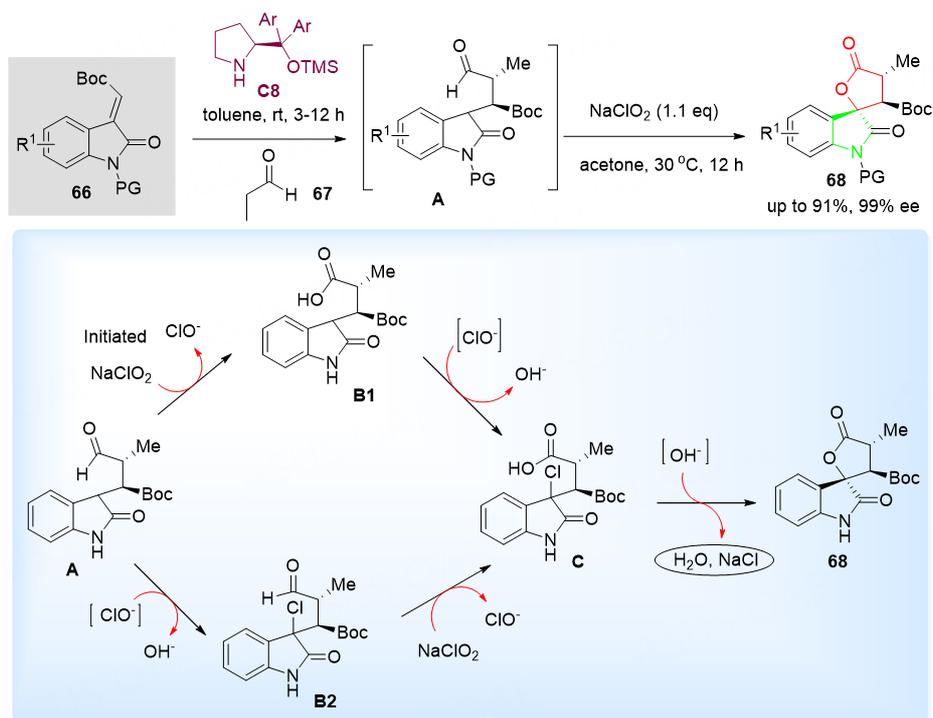
Scheme 35. 3-Olefinic oxindoles as lactone construction reagents **66** in Michael-initiated Pinnick oxidative spirolactonization reactions. This figure is used with permission from the American Chemical Society[92].
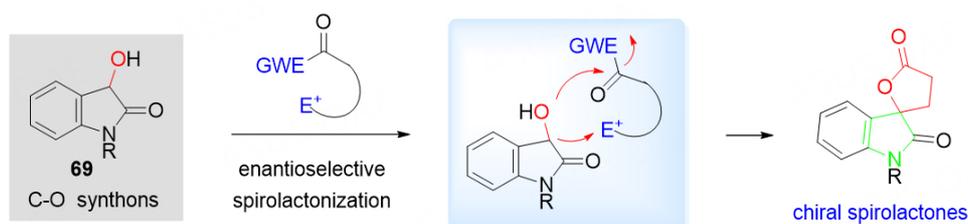
Scheme 36. Spirolactonization reaction of 3-hydroxyoxindoles **69** for construction of chiral spirolactones.
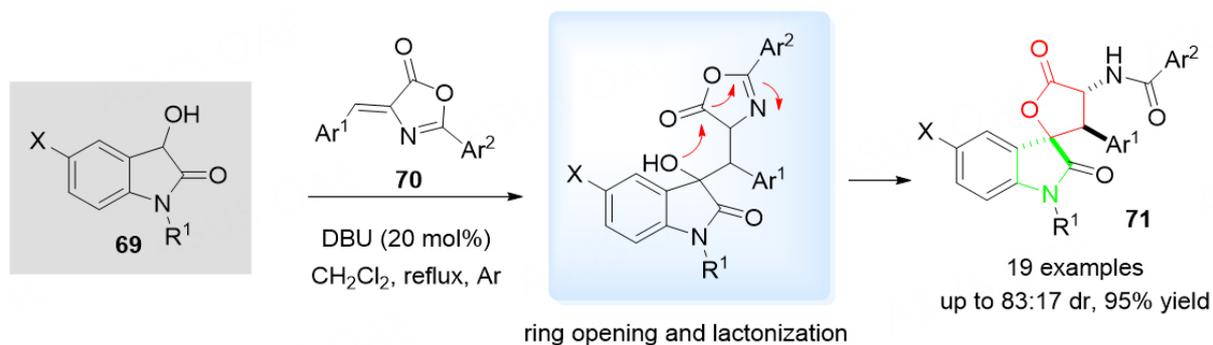
Scheme 37. Spirolactonization reaction of 3-hydroxyoxindoles **69** and olefinic azlactones **70**. This figure is used with permission from the American Chemical Society[95].

With DBU as the catalyst, various spirocyclic butyrolactone-oxindoles **71** were successfully isolated in high

yields with excellent diastereoselectivities. However, no literature report regarding the catalytic asymmetric synthesis of spirocyclic oxindole-lactones 71 was found, which creates great research potential for asymmetric syntheses.

The *α, β*-unsaturated acyl phosphonates have been known as activated ester surrogates for the generation of esters or amides due to the presence of the lability of the C-P bond. In 2017, Chen *et al.*[96] developed a highly enantioselective Michael/lactonization cascade reaction of 3-hydroxyoxindoles 69 with *α, β*-unsaturated acyl phosphonates 72 in the presence of quaramide catalyst C19 under mild conditions (CAN, 25 °C). On the basis of the demonstrated protocol, a serial of spirocyclic oxindole-lactone derivatives 73 were obtained in moderate to excellent yields (up to 98%) with good to excellent diastereo- and enantioselectivities (up to > 99:1 dr and 95% ee) under the optimal conditions [Scheme 38].

It is proposed that, with the dual activation of cinchonine-derived quaramide catalyst C19, Michael addition of the 3-hydroxyoxindoles 69 to *α, β*-unsaturated acyl phosphonates 72 forms the chiral acyl phosphonate intermediate B. Then, a favorable intramolecular cyclization reaction *via* the acyl-transfer led to the formation of spirocyclic oxindole-lactones 73 with excellent yields and selectivities [Scheme 38].

The class of heterocyclic spiro known as oxindole-lactones possesses many biological activities, e.g., tumor necrosis factor-*α* (TNF*α*) induced NF-*κ*B inhibition, antibacterial, and antibiofilm activities[97,98]. Since trifluoromethylated molecules have unique physical, chemical, and physiological properties[99-101], it has been well developed in chemical biology and drug discovery. The structure-activity relationships (SAR) could be a good starting point for drug design. Hence the fusion of fluorinated lactones to oxindole will be discussed.

In this context, Yang *et al.*[102] developed an organocatalytic Michael/lactonization of 3-hydroxyoxindoles 69 with 3-trifluoroethylidene oxindoles 74 in the presence of a cinchona-derived squaramide catalyst C20 for the synthesis of heterocyclic spiro products 75 Scheme 39). The conversion of the chemically inert amide moiety of oxindoles into the lactone was successfully achieved with the delivery of CF_3-containing spiro oxindole-lactones 75 in moderate to excellent yields (up to 97%) and selectivities (up to 98:2 dr and 98% ee). It was explained by the authors that the dual activation of chiral bifunctional squaramide-tertiary amine catalyst C20 is critical for the generation of excellent stereoselectivities [Scheme 39].

In addition, the further late-stage modification of this asymmetric methodology was demonstrated by the treatment of 75a with HCl/MeOH at ambient temperature for 4 h. The 3-hydroxy oxindole 76 was obtained in 93% with 95% ee and 1.2:1 diastereoselectivity [Scheme 40].

Similar to *α, β*-unsaturated acyl phosphonates, the *α, β*-unsaturated *N*-acylated succinimides 77 can also serve as biselectrophilic species in the spirolactonization reaction of 3-hydroxyoxindoles 69. In 2017, Ming *et al.*[103] utilized *α, β*-unsaturated *N*-acylated succinimides 77 as biselectrophilic synthons to undergo a bifunctional squaramide-catalysed asymmetric Michael/cyclization cascade reaction of 3-hydroxyoxindoles 69, affording the desired spiro[oxindole-lactone] derivatives 78 bearing two contiguous stereocenters were obtained in up to 89% with up to > 95:5 dr and up to 99% ee [Scheme 41].

The plausible mechanism for the formation of 78 was proposed [Scheme 41]. Based on the activation of both substrates 69 and 77 with the bifunctional quinine-derived squaramide catalyst C21, the hydrogen bond stabilized intermediate A was obtained. The nucleophilic addition of C3 in the deprotonated 3-hydroxyoxindole 69 to the *α, β*-unsaturated *N*-acylated succinimide 77 *via* Michael addition gave intermediate B. Then, intramolecular lactonization was achieved by nucleophilic substitution of an alkoxide
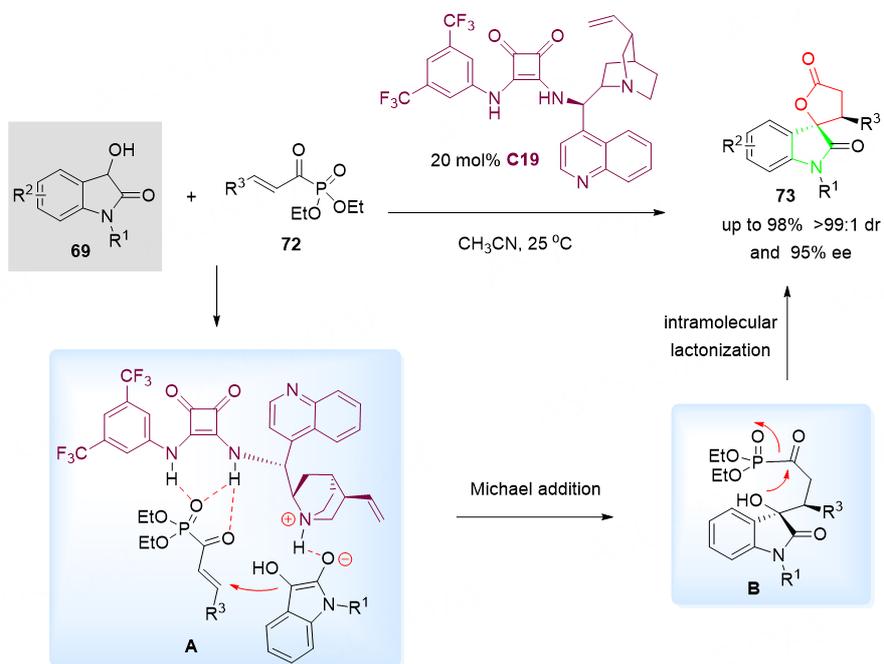
Scheme 38. Spirolactonization reaction of 3-hydroxyoxindoles **69** and α, β-unsaturated acyl phosphonates **72**. This figure is used with permission from the American Chemical Society[96].
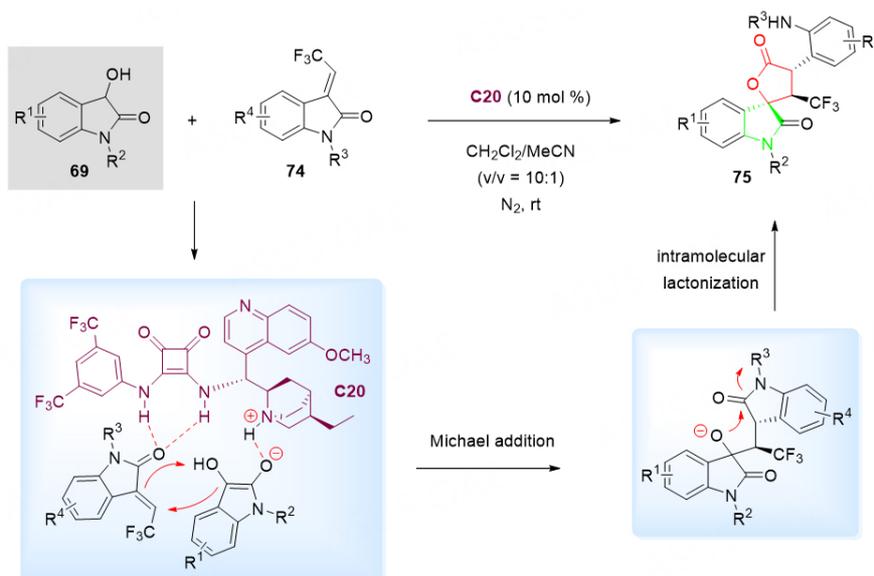
Scheme 39. Spirolactonization reaction of 3-hydroxyoxindoles **69** and 3-trifluoroethylidene oxindoles **74**. This figure is used with permission from the American Chemical Society[102].

anion with the removal of the succinimide group to give the final product **78** [Scheme 41].

The α, β-unsaturated pyrazoleamides, as a class of excellent Michael receptors, have been widely used in asymmetric synthesis. Earlier in 2022, the Zn(OTf)$_2$-catalyzed esterification of coumarin-3-pyrazoleamides **79** and 3-hydroxyoxindoles **69** in the presence of quinine-derived squaramide **C22** for the synthesis of chiral
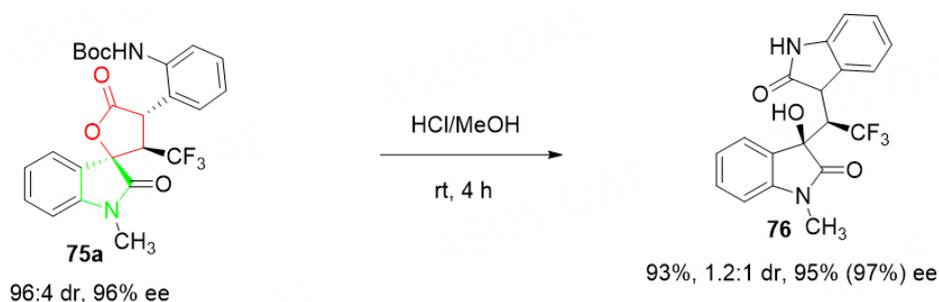
Scheme 40. Chemical Transformation of Compound **75a**. This figure is used with permission from the American Chemical Society[102].
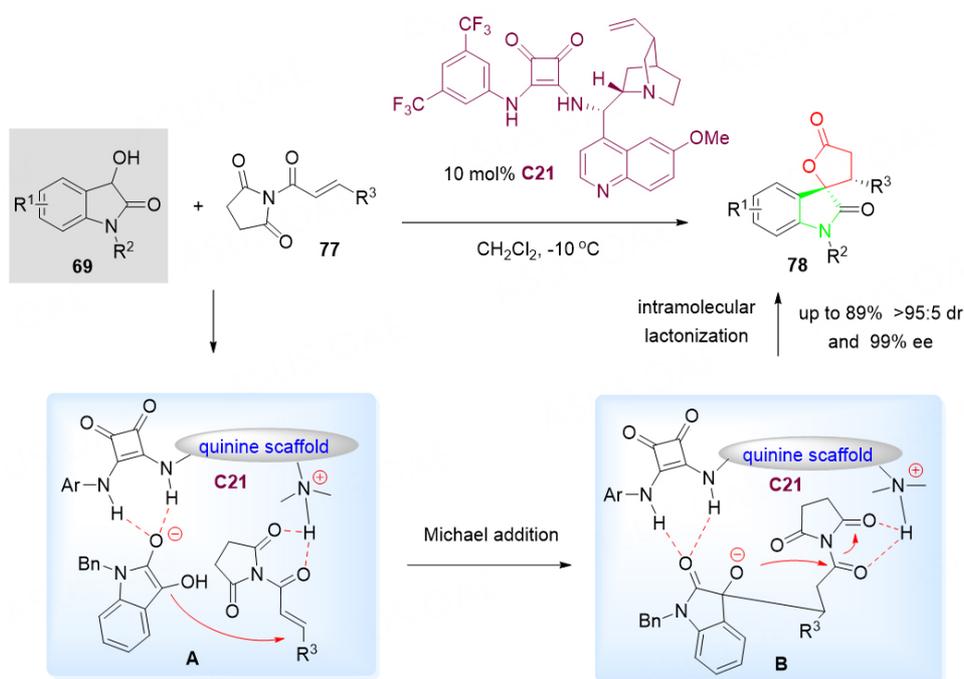
Scheme 41. Spirolactonization reaction of 3-hydroxyoxindoles **69** and *α, β*-unsaturated *N*-acylated succinimides **77**. This figure is used with permission from the Royal Society of Chemistry[103].

spirocyclic oxindole-dihydrocoumarin-lactones **81** was reported by our group [Scheme 42][104]. It is proposed that, with the dual activation of quinine-derived squaramide **C22**, this cyclocondensation was realized by an esterification/asymmetric intramolecular Michael sequence. A serial of chiral spirocyclic product was obtained in excellent yields (up to 91% yield) and enantioselectivities (> 20:1 dr and up to 99% ee).

Further, to highlight the synthetic value of this method, we proceeded with a preparative-scale preparation of **81a** under optimized reaction conditions [Scheme 43], and then obtained the desired product **81a** in 88% yield, > 20:1 dr, 91% ee without deteriorating the stereochemical outcome of the reaction. The potential of the described asymmetric synthesis was further demonstrated by the late-stage modification *via* the ring-opening (DMA/THF, 75 °C, 30 min) or oxidation (DDQ/DCM, r.t. 5 h) to give other spiro-fused lactone derivatives **82** and **83**, respectively [Scheme 43].
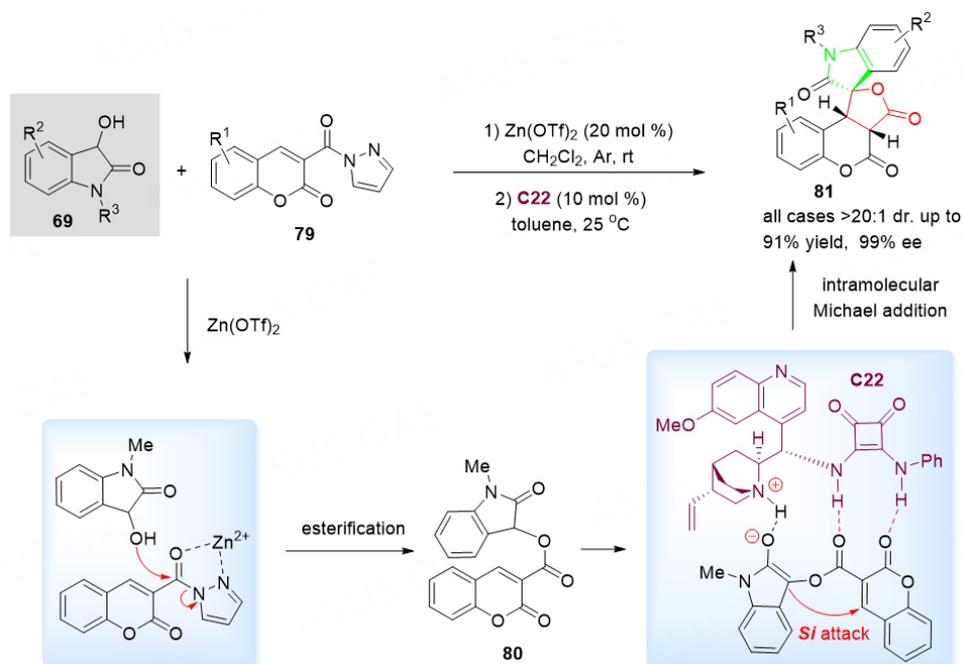
Scheme 42. Spirolactonization reaction of 3-hydroxyoxindoles **69** and α, β-unsaturated coumarin-3-formylpyrazoles **79**. This figure is used with permission from the American Chemical Society[104].

Scheme 43. Preparative-scale experiment and derivatizations. This figure is used with permission from the American Chemical Society[104].

The α-methylene-γ-lactone motif is one of the critical building blocks in organic synthesis. It has been found in a wide range of biologically active natural products and clinical pharmaceuticals[105-107]. It could also bind with specific proteins containing active SH groups from cysteine, which results in a change of the protein structure, thus inhibiting their functions[108-111]. So, the enantiopure hybrid structures combining α-methylene-γ-lactone motifs may pave the way to the generation of more promising covalent inhibitors for drug screening.

In this context, in 2020, the synthesis of highly functionalized spirooxindoles **85** was reported by Wang *et al.*[112] *via* the asymmetric allylic alkylation-cyclization of 3-hydroxyoxindoles **69** with MBH carbonates **84** in the presence of catalyst **C23** in DMC at 5 °C. Due to the presence of α-methylene-γ-lactone decorated moiety in products **85**, there is a possibility for the late-stage chemical modification after spirooxindoles **85** were obtained in good yields with diastereo- and enantioselectivities. It is proposed that nucleophilic addition (allylic alkylation) of 3-hydroxyoxindole **69** to MBH carbonates **84**, which was activated by the cinchona alkaloid **C23**, followed by an intramolecular lactonization to afford the desired spirooxindoles **85** [Scheme 44A].

The potential of this methodology was demonstrated by the facile transformation for the construction of fused butenolide derivatives and their analogues. The cyclization product **85** was unexpectedly isomerized to the fused butenolide **86** in the presence of Pd-C/H$_2$ in 41% yield. A CuCl-NaBH$_4$ complex can successfully reduce **85** to the expected fused dihydrofuran-2(3H)-one derivative **87** in 38% yield and > 99:1 dr [Scheme 44B].

Another organocatalytic synthesis of optically active spirocyclic spirooxindole scaffolds **90** bearing α-methylene-γ-lactone motifs was reported by Jayakumar *et al.*[113]. Instead of 3-hydroxyoxindoles **69**, 3-OBoc-protected oxindoles **88** were employed as a nucleophile, which avoided the possible dimerization of 3-hydroxyoxindole **69** under basic conditions as well as competitive C,O-alkylation. Furthermore, the alkylated product **90** was obtained under trifluoroacetic acid conditions, which is an important supplement to the above-mentioned Wang's strategy [Scheme 45][112].

Recently, the *N*-heterocyclic carbene (NHC)-catalyzed reaction *via* radical intermediate has been well developed and used as a powerful strategy for the synthesis of highly modified molecules[114-116]. A variety of heterocycles including spiro compounds have been successfully synthesized in the presence of *N*-heterocyclic carbene (NHC) based organocatalysis. Besides the above-mentioned α, β-unsaturated substrates, the α, β-unsaturated aldehydes were also known as 3-carbon nucleophilic partners with 3-hydroxyoxindoles **69** for the synthesis of spiro compounds *via* the Michael addition/lactonization sequence.

In this context, in 2017, the *N*-heterocyclic carbene **C25**-catalyzed oxidative [3 + 2] annulation of 3-hydroxyoxindoles **69** and α, β-unsaturated aldehydes **91** was reported by Chen *et al.*[117] in 2017 [Scheme 46, top]. Both challenging alkyl enals and aryl enals **91** worked well under the optimal conditions to give the corresponding spirooxindole lactones **92** in good yields with excellent diastereo- and enantioselectivities.

The cyclization was proposed to proceed *via* radical/radical cross-coupling of homoenolate and enolate, and the single electron transfer is the key step for NHC-catalyzed annulation reaction [Scheme 46, bottom]. Furthermore, both enolate and homoenolate radicals were observed by EPR spectra.

As a continuation of the research, the oxidative N-heterocyclic carbine **C25**-catalyzed [3 + 2] annulation of β, β-disubstituted enals **93** and 3hydroxyoxindole nucleophiles **69** was achieved *via* catalytic coupling of two tertiary radicals[118]. The spirocyclic oxindole-lactones **94**, bearing two contiguous tetrasubstituted stereocenters, were obtained in good yields with excellent diastereoselectivities and good enantioselectivities. This is an important alternative synthetic method to the previously reported NHC catalysis strategy [Scheme 47][117].

The α, β-unsaturated acyl azolium intermediate[119,120] (electrophile) is an important intermediate in this *N*-heterocyclic carbene (NHC)-catalysis. This type of intermediate could be easily obtained from the reaction

(A) Organocatalytic spirolactonization reaction for formation of **85**
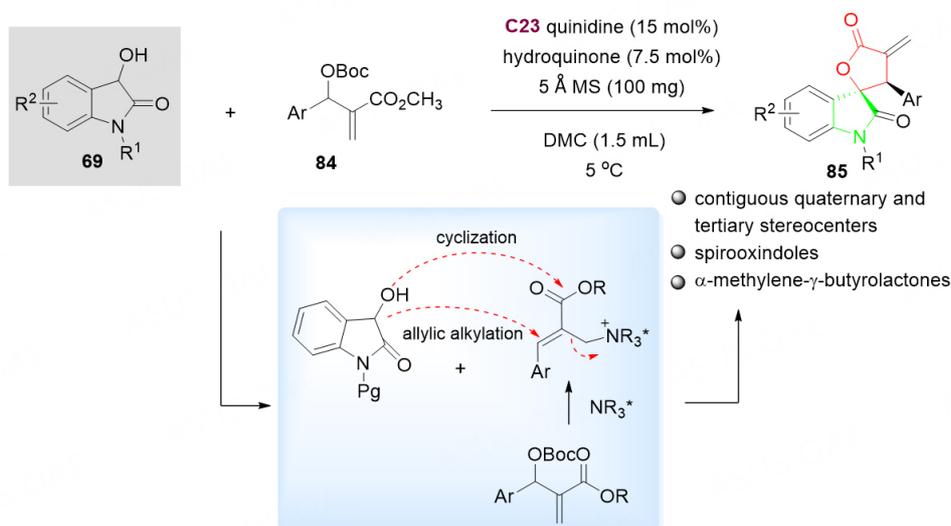
- contiguous quaternary and tertiary stereocenters
- spirooxindoles
- α-methylene-γ-butyrolactones

(B) Derivatizations of the product **85**

86
41% yield, 84% ee

85

87
38% yield, >99:1 dr
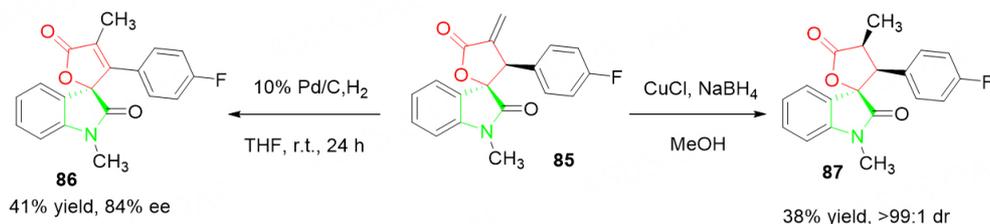
Scheme 44. Spirolactonization reaction of 3-hydroxyoxindoles **69** with MBH carbonates **84**. This figure is used with permission from the Royal Society of Chemistry[112].

88

89

90
14 examples, 76-92%
up to 20:1 dr, 98% ee
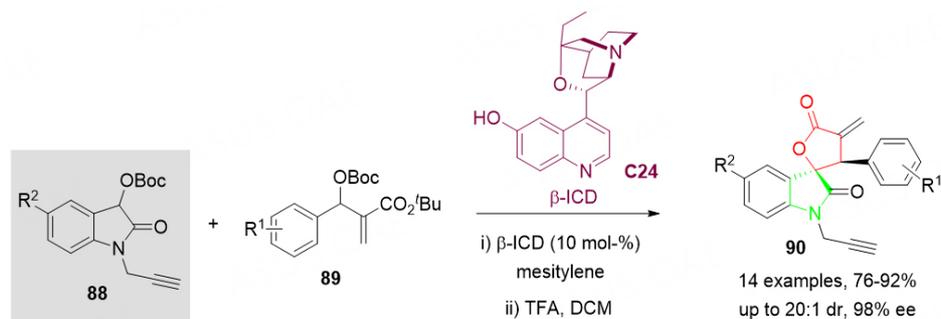
Scheme 45. Spirolactonization reaction of 3-OBoc-oxindoles **88** with MBH carbonates **89**. This figure is used with permission from Wiley-VCH Verlag[113].

of enals and NHCs under oxidative conditions. Since they are good electrophiles, treatment with a variety of bisnucleophiles could give the corresponding heterocycles.

In this context, in 2017, the NHC-catalyzed enantioselective [3 + 2] annulation of α, β-unsaturated aldehydes **95** with 3-hydroxy oxindoles **69** in the presence of **C26** gave spiro oxindole-butyrolactones **97** in moderate to good yields, enantioselectivity and diastereoselectivity [Scheme 48, top][121].
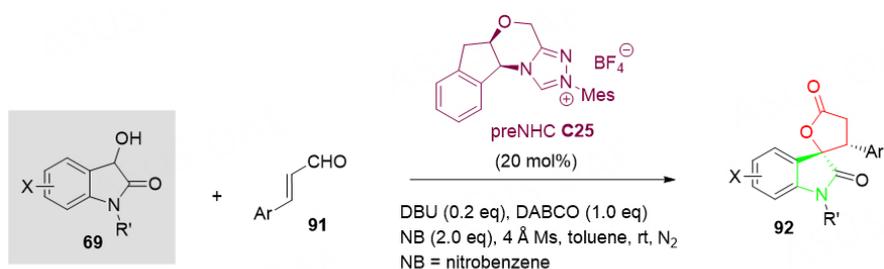
Scheme 46. Spirolactonization reaction of 3-hydroxyoxindoles **69** with enals **91**. This figure is used with permission from the Royal Society of Chemistry[117].
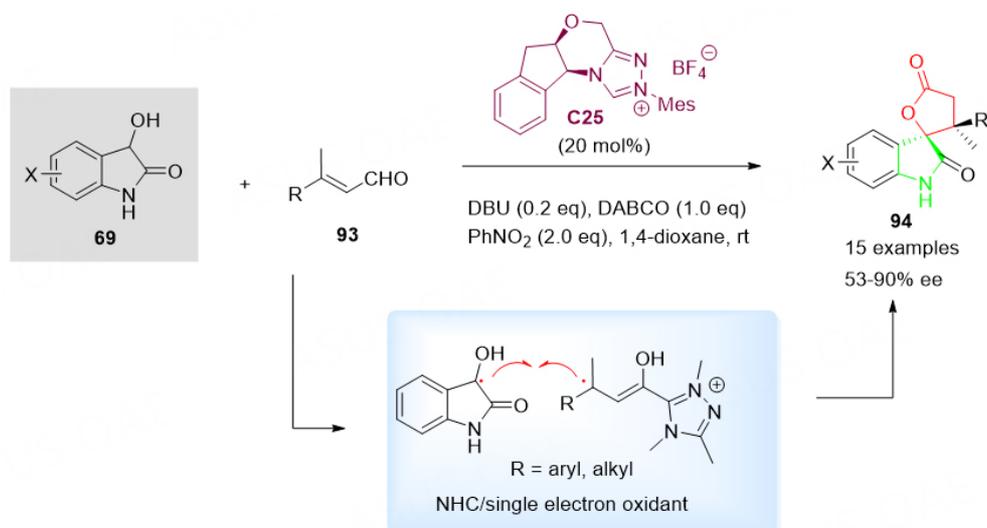
Scheme 47. Spirolactonization reaction of 3-hydroxyoxindoles **69** with β,β-disubstituted enals **93**. This figure is used with permission from the American Chemical Society[118].
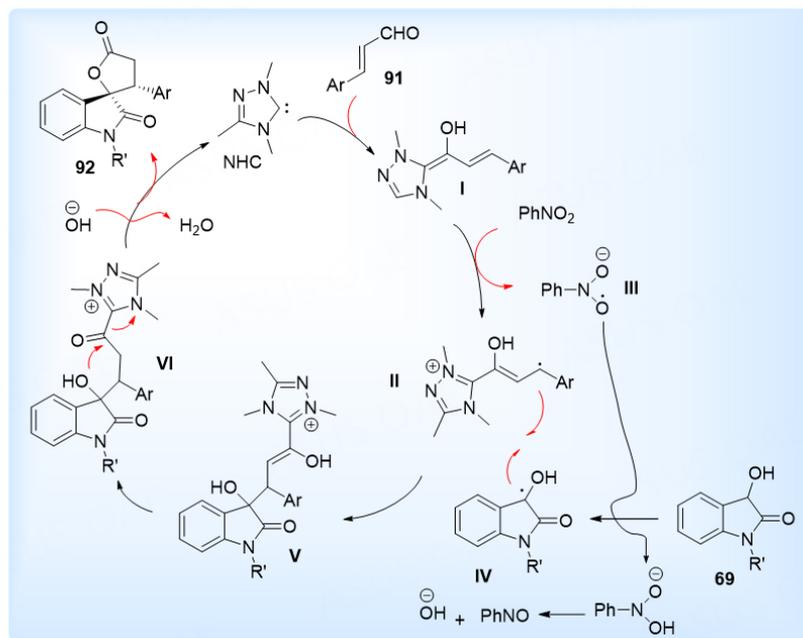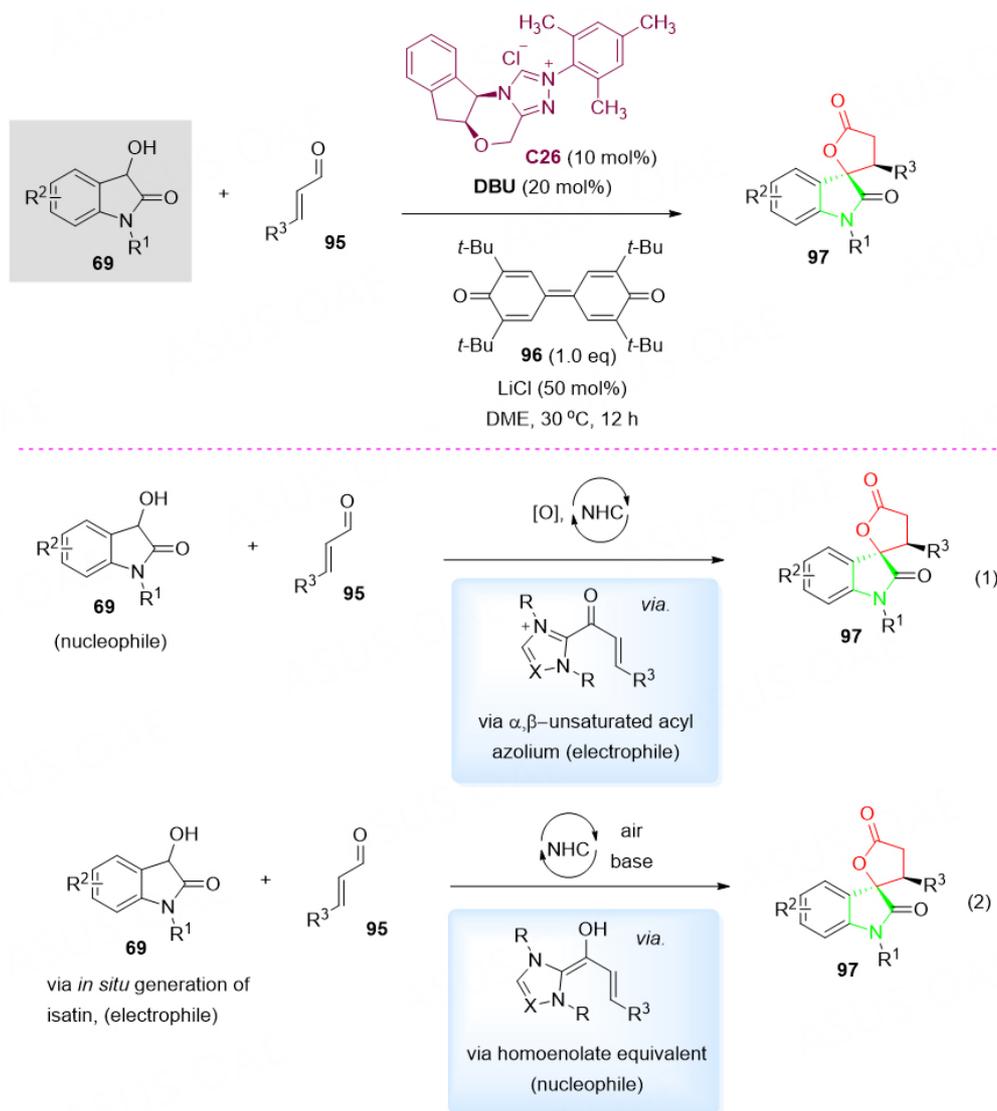
Scheme 48. Spirolactonization reaction of 3-hydroxyoxindoles **69** with enals **95**. This figure is used with permission from the Royal Society of Chemistry[121].

Mechanistic investigation of this reaction revealed that the annulation was initiated with (1) the *in situ* generation of the chiral *α, β*-unsaturated acyl azolium intermediate or *via* (2) a formal [3 + 2] pathway to give the corresponding spirocyclic product **97** [Scheme 48, bottom].

Maremycin A, a diketopiperazine alkaloid, was isolated from the culture broth of marine Streptomyces species B 9173[122]. The application of a new synthetic strategy for the total synthesis of complex natural products is generally considered an important validation of its synthetic potential and usefulness.

In 2012, Bergonzini *et al.*[123] established a chiral secondary amine **C8**-catalyzed enantioselective [3 + 2] annulation of *α, β*-unsaturated aldehydes **98** with 3-hydroxy oxindoles **69**, generating spiro oxindole-butyrolactones **99** and **100** in high enantioselectivities and low diastereoselectivities [Scheme 49A]. Although the diastereoselectivity is not as good as expected, the diastereomerically pure compounds **99** and
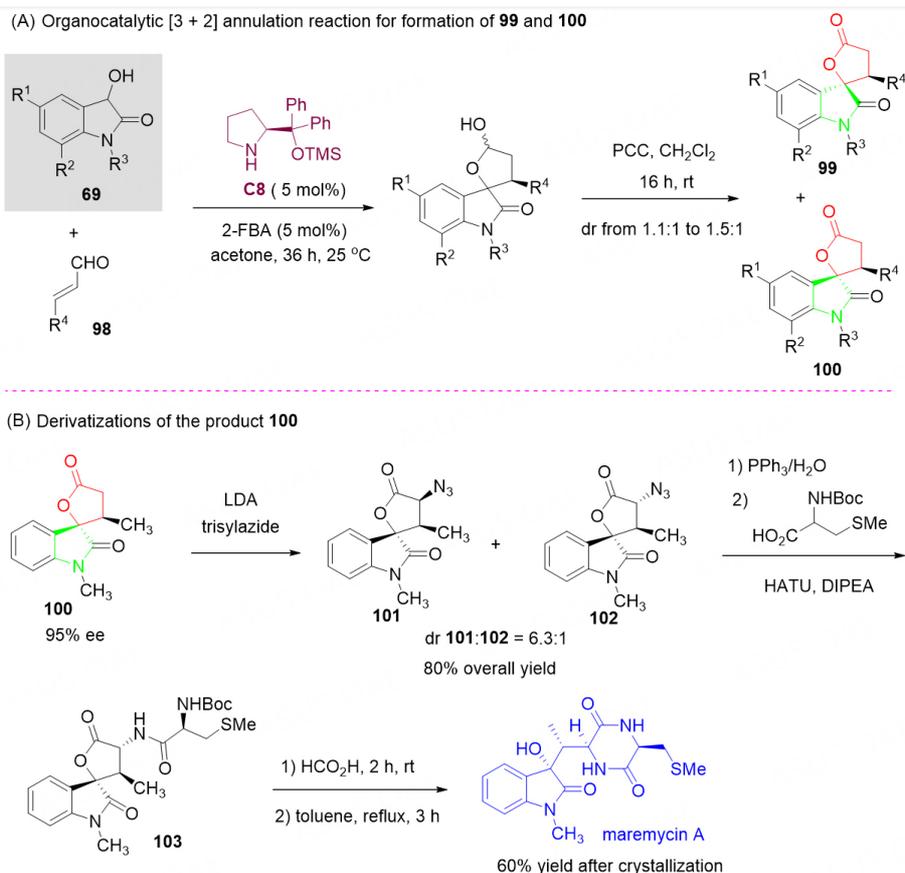
Scheme 49. Stereocontrolled synthesis of spiro oxindole-butyrolactones and maremycin A. This figure is used with permission from John Wiley and Sons Ltd[123].

100 can be easily separated by silica column chromatography. It is important to note that the described method could be used for the synthesis of the complex natural product Maremycin A in three steps from chiral spirolactone synthon **100** [Scheme 49B]. Thus, this elegant protocol helps elucidate the absolute structure of the chiral spirolactone frameworks, and it is a critical building block in the total synthesis of natural products.

Although direct activation of the β-C^{sp3} of saturated carbonyl compounds using NHCs has been successfully developed, due to their chemical inertness, great challenges remain in this field. Saturated acid chlorides are known to be highly reactive and prone to hydrolyze. Thus, activation of the saturated acid chlorides under mild conditions is desired.

In 2019, Zhu *et al.*[124] developed a new chiral NHC **C27** catalyzed annulation of **69** with acyl chloride **104** in the mixture of toluene and DCM (1:1, v/v) at ambient temperature for the synthesis of cyclic spiro product **105** with high yields, excellent diastereo- and enantioselectivities [Scheme 50].

The plausible mechanism for the formation of **105** was proposed. First of all, the β-C^{sp3} of 3-substituted saturated acid chlorides **104** was activated by the deprotonation to give the intermediate bearing an active electrophilic carbon. Oxidation of Breslow intermediates to the α, β-unsaturated acyl salt intermediate is a key step to the formation of functionalized spirocyclic oxindole-lactones **105**.
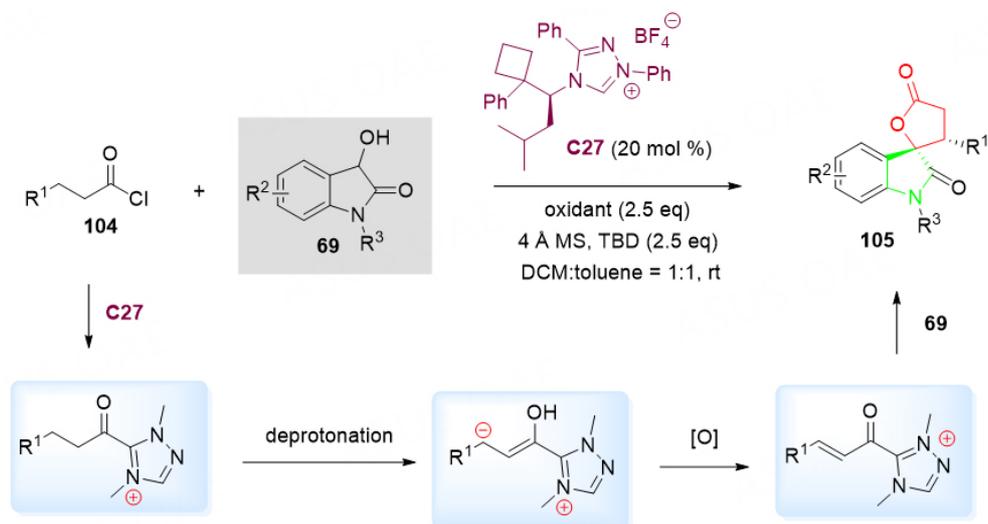
Scheme 50. Spirolactonization reaction of 3-hydroxyoxindoles **69** with 3-substituted saturated acid chlorides **104**. This figure is used with permission from the Royal Society of Chemistry[124].

The spirocyclic oxindole-lactone **105** could be applied to the synthesis of the 3-hydroxy-indole natural product maremycin B according to the literature methods [Scheme 51][125].

Spirolactonization reaction of isatins

The development of efficient strategies for the stereoselective construction of highly modified heterocyclic molecules is always a key goal in chemical synthesis. Isatins, also known as tribulin, are an important class of heterocyclic compounds. The germinal carbonyls are as exceptional electrophiles in asymmetric catalysis. Thus, reaction of isatins with electron-rich species *via* nucleophilic aldol addition followed by an intramolecular lactonization could give the spirocyclics products [Scheme 52].

Recently, the 3-alkylidene oxindoles could act as vinylogous nucleophiles to functionalize at the γ-position with electrophiles[126,127]. The research involving vinylogous reaction of enolates derived from 3-alkylidene oxindole derivatives is one of the most efficient protocols in organic synthesis. Many efficient and elegant methodologies have been created using 3-alkylidene oxindoles as nucleophiles for the direct formation of allylic compounds, which is a key structural element in a number of natural products and synthetic bioactive molecules.

Pentenelactone scaffolds are widely present in a number of natural and unnatural compounds which possess potent biological activities. Oxindoles are also regarded as one of the privileged skeletons in bioactive compounds; thus, there is an urgent need for the combination of an oxindole scaffold and a pentenelactone motif in one molecule, which will be interesting not only to synthetic but also to medicinal chemists.

In 2016, a direct enantioselective organocatalytic reaction of 3-alkylidene oxindoles **107** with isatins **106** in the presence of **C28** was developed by Han *et al.* for the synthesis of spirocyclic product **108** *via* vinylogous aldol/ring opening and subsequent intramolecular lactonization [Scheme 53][128].
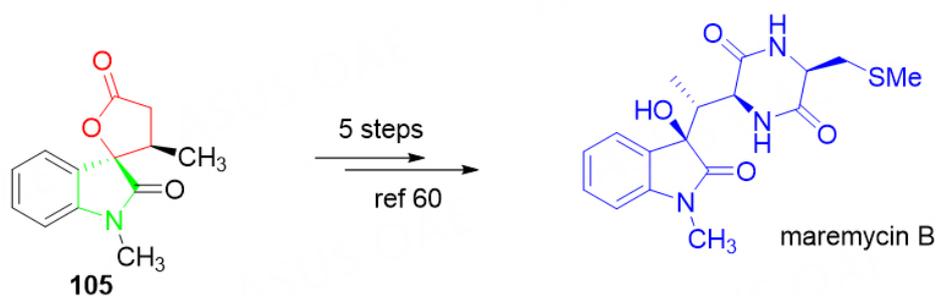
Scheme 51. Application of compound **105** in the total synthesis of maremycin B. This figure is used with permission from the Royal Society of Chemistry[124].
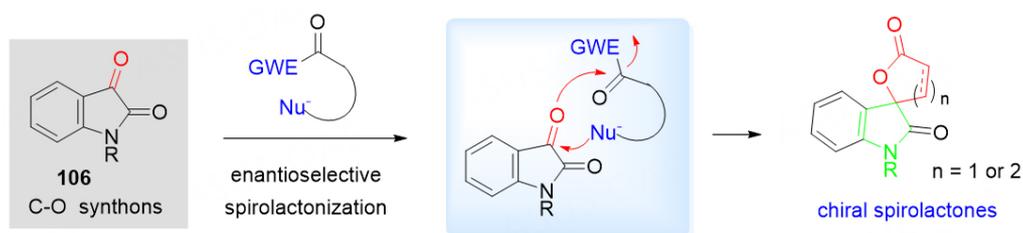
Scheme 52. Spirolactonization reaction of isatins for construction of chiral spirolactones.
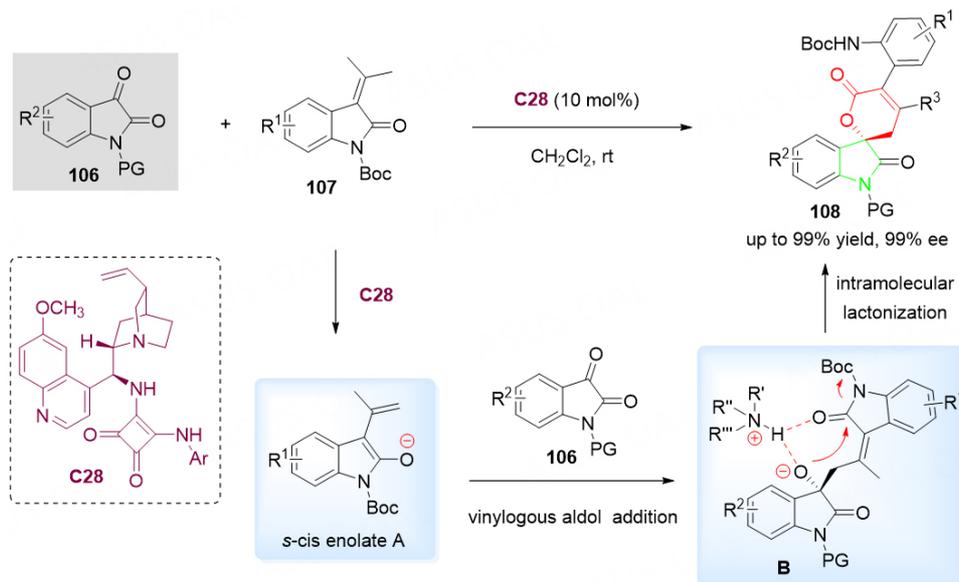
Scheme 53. Spirolactonization reaction of isatins **106** with 3-alkylidene oxindoles **107**. This figure is used with permission from the Royal Society of Chemistry[128].

With the help of alkaloid-squaramide bifunctional organocatalyst **C28**, the cyclization was initiated with the adol reaction between activated intermediate s-cis enolate A and **106** led to the formation of intermediate **B**. Subsequent intramolecular lactonization, leading to the cleavage of the oxindole ring and generation of a broad range of enantioenriched spirocyclic oxindole-pentenelactone derivatives **108** in good to excellent yields with high enantioselectivities [Scheme 53].

In recent years, due to the presence of multiple functional groups, the α, β-unsaturated butenolides have been known as versatile candidates for the synthesis of various oxygen-containing heterocyclic analogues[129,130]. The privileged moiety has been found in several bioactive compounds as well.

Similar to the work of Han *et al.*[128], another synthetic route toward the enantioenriched functionalized spirocyclic oxindole-pentenelactone scaffolds **110** was reported by Wang *et al.* [Scheme 54][131]. Treatment of α, β-unsaturated butenolides **109** with isatins **106** in the presence of Takemoto's amine-thiourea catalyst **C29** in toluene at 0 °C gave the desired spirocyclic product **110** in good to excellent yields (73%-99%) and enantioselectivities (71%-97% ee).

A similar mechanism of the sequential vinylogous aldol reaction/ring opening and subsequent intramolecular lactonization was proposed. It is important to mention that the intermolecular hydrogen bonding between the **C29** and two substates plays a critical role in the control of the stereoselectivity [Scheme 54].

Moreover, in order to further expand the application of α, β-unsaturated butenolides **109** in the construction of chiral spirocyclic pentenelactone scaffolds, the spirolactonization of α, β-unsaturated butenolides **109** with other electrophiles were also attempted. Upon using phenanthrenequinone **111** instead of isatin **106** as an electrophile, desired products **112** and **113** were obtained in excellent yields and good selectivities. So it is an attractive combination of pharmacologically significant phenanthrenequinone and pentenelactone units [Scheme 55].

The hetero-Diels-Alder (HDA) reactions of the carbonyl group with α, β-unsaturated carbonyl has been developed for the rapid generation of six-membered oxygen-containing heterocycles. Azlactones, as versatile reactants, are great candidates for the synthesis of potentially bioactive α,α-disubstituted α-amino acids.

In 2017, Gao *et al.*[132] reported a catalytic asymmetric hetero-Diels-Alder (HDA) reaction olefinic azlactones **113** with isatins **106** in the presence of **C30** in DCE at 30 °C for 48 h for the synthesis of spirocyclic product **114** [Scheme 56].

It was found that the vinylogous reactivity of azlactones **113** was realized hydrogen-bond directed activation of both of the reaction partners *via* γ-addition of **113** to **106**, and the desired medicinally important spirocyclic oxindole-pentenelactone scaffolds **114** were obtained in good yields and enantioselectivity [Scheme 56].

In recent years, the NHC-bonded intermediates' generation and their corresponding reaction with polar double bonds moiety of the substrates have drawn a lot of attention since a variety of highly functionalized molecules could be easily obtained in such a simple reaction.

In 2015, using the HOBt esters of carboxylic acids and isatins as substrates, an attractive alternative NHC-catalyzed cascade synthetic route toward the potential biological enantioenriched spirocyclic oxindole-pentenelactone scaffolds was reported by Que *et al.* [Scheme 57, top][133]. The spirocyclic oxindole-pentenelactones **116** were obtained in good yields with high enantioselectivity.
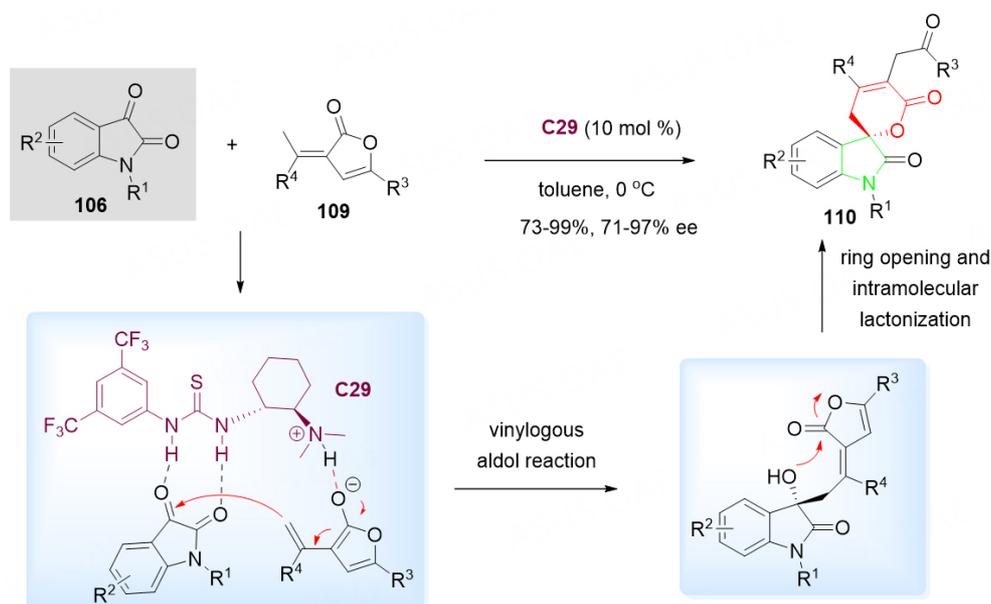
Scheme 54. Spirolactonization reaction of isatins **106** with α, β-unsaturated butenolides **109**. This figure is used with permission from the Royal Society of Chemistry[131].
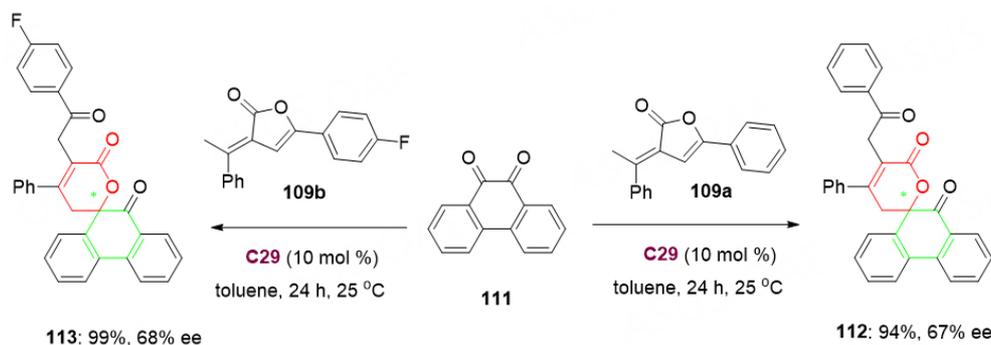
Scheme 55. Experimental results using phenanthrenequinone **111** as an electrophile. This figure is used with permission from the Royal Society of Chemistry[131].

It was found that the HOBt esters of carboxylic acids can be transformed into the NHC-bonded intermediate, followed by the reaction with activated C-O double bond of isatins **106** provided a new alternative method for the synthesis of spirocyclic oxindole-pentenelactones **116** [Scheme 57, bottom].

Aromatic moiety exists almost in every single bioactive molecule and natural product. The catalytic functionalization of aromatic Csp² and the attached Csp³ is fundamental to organic chemistry and therefore an important subject of research.

Notably, the compounds containing isatin units, which exhibit interesting biological properties, such as anticonvulsant, antimicrobial, antitumor, antiviral, anti-HIV and antitubercular activities. In 2013, Chen *et al.*[134] developed an NHC-derivative **C25** catalyzed annulation of isatins **106** with indole 3-carboxaldehydes **117** in the presence of quinone oxidant **96** to give spirocyclic lactones **118** containing isatin units in good to excellent yields and ees [Scheme 58].
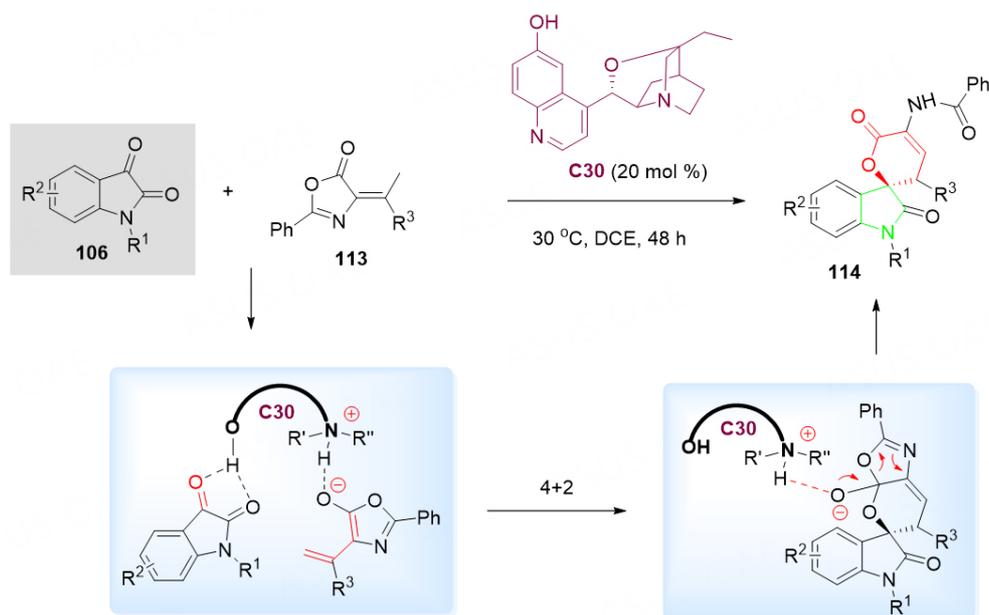
Scheme 56. Spirolactonization reaction of isatins **106** with olefinic azlactones **113**. This figure is used with permission from the Royal Society of Chemistry[132].

In the proposed reaction mechanism, the **C25**-catalyzed **96**-oxidized activation of the Csp³ of α-methylindole-3-carboxaldehydes **117** to give *ortho*-quinodimethane intermediates, which undergoes formal [4 + 2] cycloaddition with an isatin **106** to give a spirocyclic oxindole-pentenelactone **118** [Scheme 58]. Both the pre-catalyst **C25** and oxidizer **96** play a critical role in the activation of the **117**.

Recently, pyrazoleamides have been used as special donors in enantioselective Mannich and Michael reactions. In these reactions, the versatile pyrazoleamide functions as an activating group, a directing group for enhancing stereocontrol, as well as a good leaving group for subsequent transformations.

In 2014, the synthesis of optically active spirocyclic oxindole-pentenelactones **120** was reported by Li *et al.*[135] *via* the enantioselective vinylogous aldol-cyclization cascade reaction of allyl pyrazoleamides **119** with isatins **106** in the presence of Takemoto catalyst **C29** in acetonitrile at ambient temperature. Various spirocyclic products **120** were obtained in excellent yields (93%-99%) and enantioselectivities (82%-97% ee). It is worth mentioning that the protection of the nitrogen atom in the indole ring is not necessary, although the yield and enantioselectivity of the product **120d** are relatively lower. Thus, the reported method establishes a new protocol for the asymmetric construction of structurally novel spirocyclic oxindole-pentenelactones **120** employing β, γ-unsaturated aldehyde derivatives [Scheme 59].

Recently, Zhang *et al.*[136] reported a series of NHCs derived from L-pyroglutamic acid. Due to the high enantioselectivity of L-pyroglutamic acid NHCs, in 2011, further exploration of the chiral NHCs catalyzed enantioselective umpolung reactions of enals **121** was performed.

It was found that the proximal hydroxyl group of L-pyroglutamic acid **C31** was an efficient catalyst for the activation of isatins **106** by the formation of intermolecular hydrogen bonds between the two geminal carbonyl groups. It also plays a role in directing the addition of the homoenolate to the carbonyl group of isatin **106**. Thus, followed by the [3 + 2] annulation of enals **121** and activated isatins **106**, the corresponding
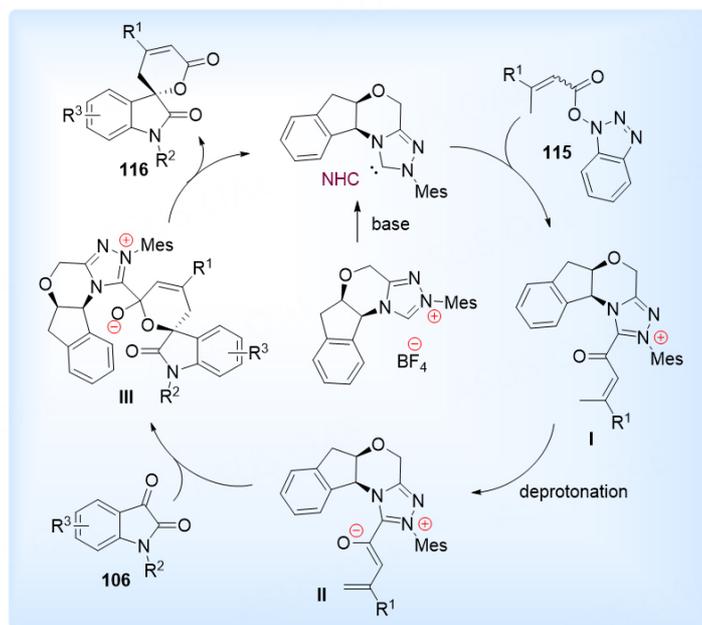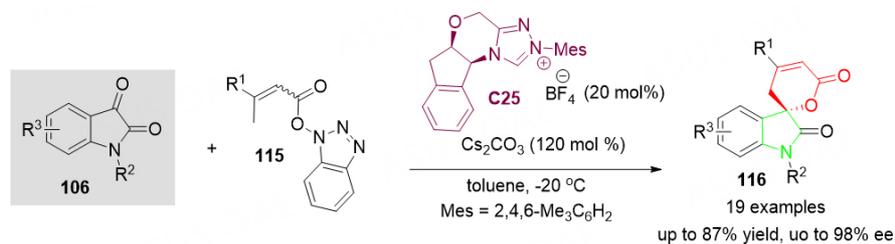
Scheme 57. Spirolactonization reaction of isatins **106** and HOBt esters of carboxylic acids **115**. This figure is used with permission from the American Chemical Society[133].

spirocyclic oxindole-butyrolactones **122** were obtained in good yield with good diastereo- and enantioselectivities [Scheme 60][137].

In 2011, a chiral *N*-heterocyclic carbenes **C32**-catalyzed cyclization of *α, β*-unsaturated *β*-methylacyl chlorides **123** with isatins **106** for the synthesis of optically active spirocyclic oxindole-pentenelactones **124** was also developed by Shen *et al.* [Scheme 61, top][138].

The proposed catalytic cycle was described in Scheme 61, bottom part. The addition of *in situ* generated NHC intermediate to the carbonyl carbon of the vinyl ketene **123′**, which is generated *via* base-promoted halo dehydrogenation of the acyl chloride **123**, gave the diene intermediate **A**. The reaction of **A** and isatin **106** proceeded *via* either hetero-Diels-Alder reaction or stepwise vinylogous aldol reaction to give the zwitterionic **B** after a spontaneous intramolecular cyclization **B**, which could be explained by the formation of the stable six-member ring to reduce the steric hindrance. Regeneration of the NHC catalyst **C32** for next catalyst circle led to the formation of spirocyclic oxindole-pentenelactone **124** [Scheme 61, bottom].

Over the last decade, despite significant advancements in the area of *N*-heterocyclic carbene-catalyzed homoenolate equivalents have achieved, activation of NHC catalysis in the presence of Lewis acid and transition metal catalysis is still underdeveloped for the access of hetero- and carbocyclic structures.

Scheme 58. Spirolactonization reaction of isatins **106** and α-branched indole 3-carboxaldehydes **117**. This figure is used with permission from John Wiley and Sons Ltd[134].
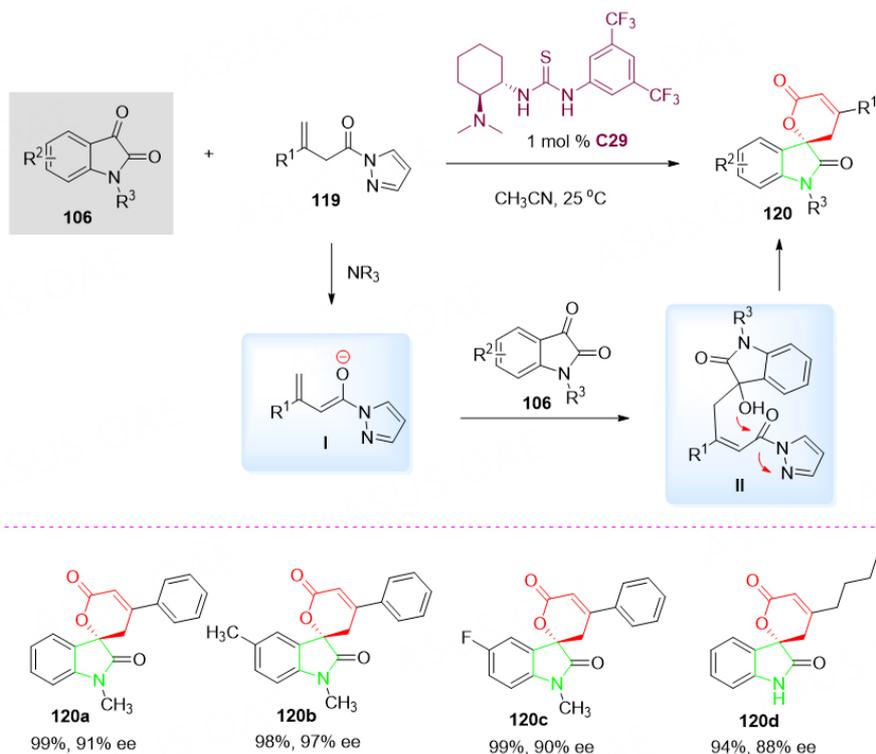
Scheme 59. Spirolactonization reaction of isatins **106** and α-branched indole 3-carboxaldehydes **119**. This figure is used with permission from the Royal Society of Chemistry[135].

122a
90%, 98% ee, 20:1 dr

122b
86%, 93% ee, 17:1 dr

122c
97%, 86% ee, 30:1 dr

122d
38%, 85% ee, 20:1 dr
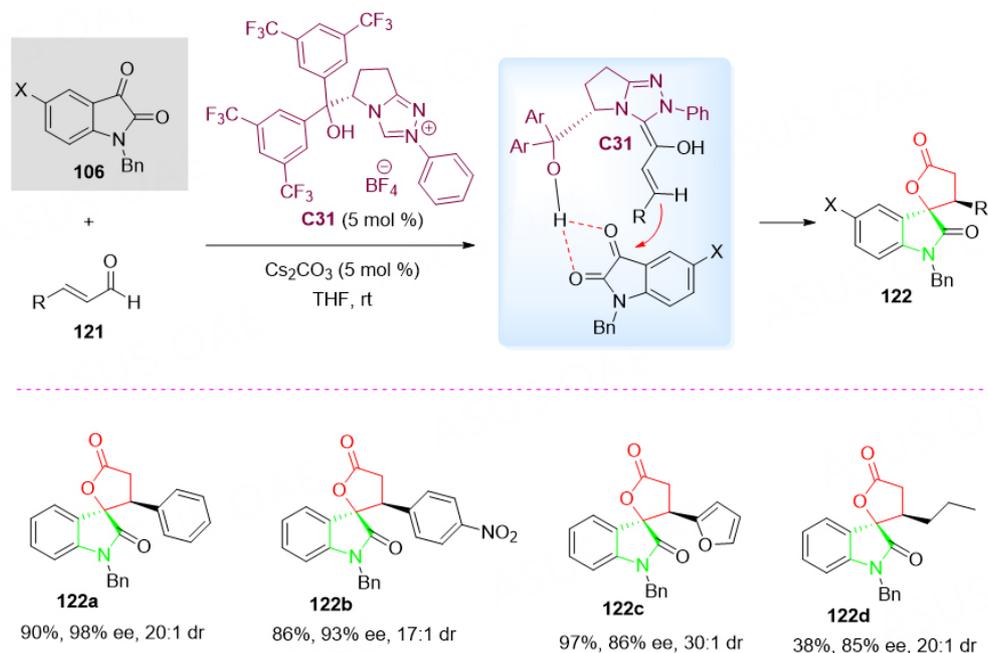
Scheme 60. Spirolactonization reaction of enals **121** and isatins **106**. This figure is used with permission from Wiley-VCH Verlag[137].
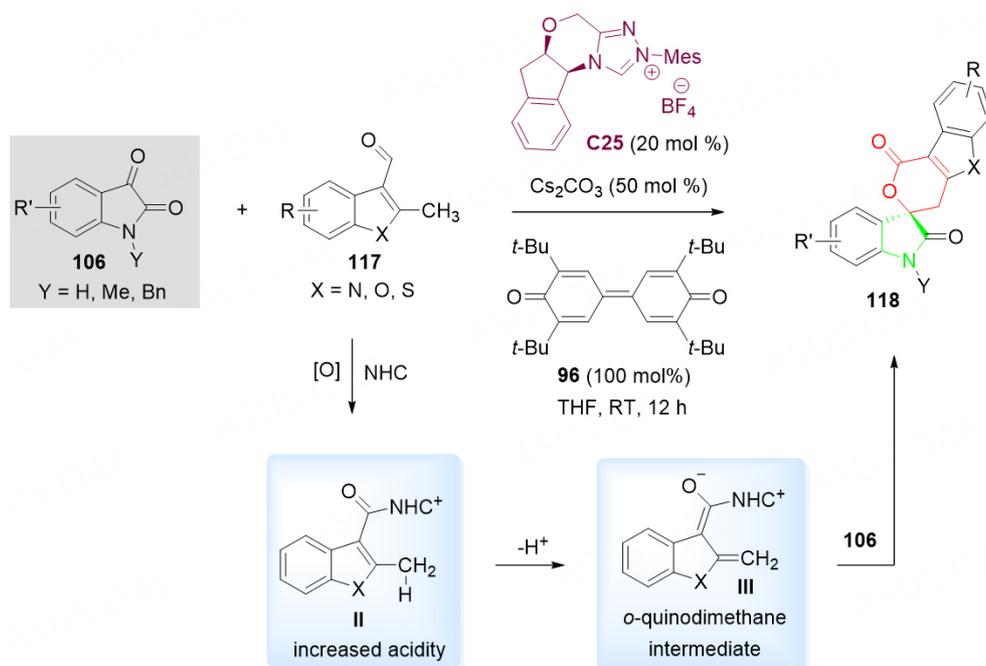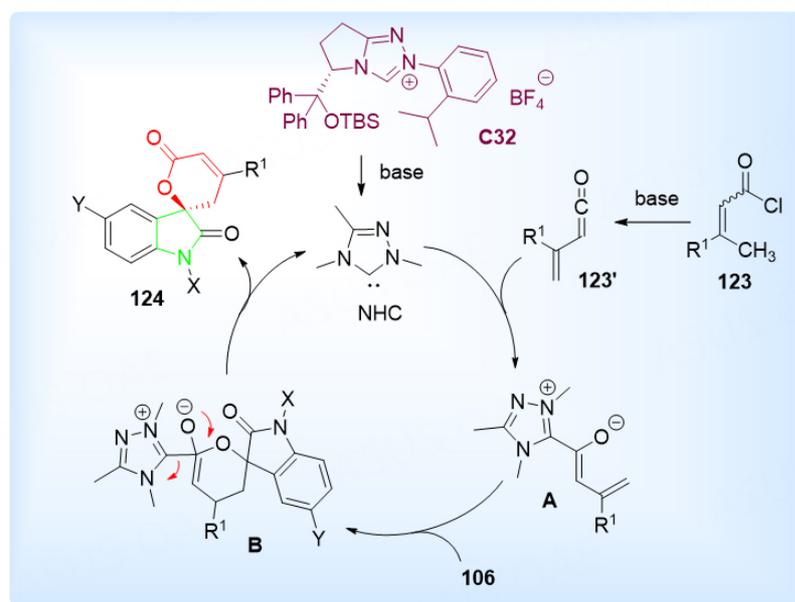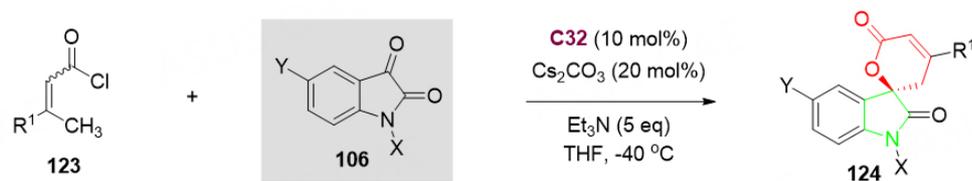

Scheme 61. Spirolactonization reaction of isatins **106** and unsaturated acyl chlorides **123**. This figure is used with permission from Wiley-VCH Verlag[138].

In 2012, the enantioselective annulation of enals **125** with isatins **106** in the presence of cooperative catalysis NHC/Lewis acid (LiCl) in THF at ambient temperature was reported by Sun *et al.*[137] for the synthesis of spirocyclic oxindole-lactone products **126** [Scheme 62].

It was proposed that the initial activation of **125** with NHC catalyst **C33**, while the isatins **106** was activated by LiCl at the same time. Those two activated substrates were further stabilized by the π-π stacking and O-Li-O covalent bonds. The alkali salt significantly enhances the enantioselectivity by securing the confirmation of substrates to give the spirocyclic oxindole-lactone products **126** [Scheme 62, bottom].

More importantly, the total synthesis of Maremycin B was successfully achieved in a few steps *via* the described highly selective formal [3 + 2] annulation methodology, which is a great example of the possible application for chemists [Scheme 63].

Due to the electronegativity of the fluorine atom, the sigma bond between carbon and fluoride is generally considered the strongest single bond for the carbon atom. Thus, the reduction of fluorocarbons or the transformation of fluorocarbons into non-fluorinated organic molecules under mild conditions is extremely challenging but still has drawn much attention.

In 2018, the reaction of γ-fluoroenals **130** with isatins **106** in the presence of chiral NHC catalyst **C34** in toluene at 0 °C gave spirocyclic oxindole-pentenelactone scaffolds **131** in up to 91% yield with up to > 99% ee [Scheme 64][139].

Upon the activation of the γ-fluoroenals **130** with *in situ* generated NHC, the Zwitterion intermediate **I** was obtained. Followed by the 1,2-H shift and tautomerization, along with the cleavage of the C-F bond, intermediate **III** was obtained. Sequential 1,5-H shift, base-promoted hydrogen abstraction and [4 + 2] cyclization gave the final spiro product **131**. It is worth mentioning that the C-F bond cleaved without the help transition-metal catalyst and elevated temperature was not required. To further understand the mechanism, Density functional theory (DFT) calculations were performed to elucidate the C-F bond cleavage process [Scheme 64].

In 2015, an NHC **C25**-catalyzed annulation of **106** and aldehyde **132** in THF was developed by Cheng *et al.*[140]. The corresponding spirocyclic oxindole-pentenelactones **133** were obtained in moderate to good yields and enantioselectivities [Scheme 65].

It is proposed that the addition of *in situ* generated NHC to **132** initially gives the vinyl Breslow intermediate **A**, which decomposes to the NHC-bound unsubstituted dienolate **B** in the presence of base. Subsequently, the γ-addition of the dienolate intermediate **B** to the isatin **106** affords the acyl azolium adduct **C**. Finally, the lactonization leads to the desired spirocyclic oxindolodihydropyranone **133** and regenerates the NHC catalyst **C25** [Scheme 65].

CONCLUSION AND OUTLOOK

The catalytic asymmetric synthesis of chiral spirolactone skeletons is an important topic in synthetic chemistry and medicinal chemistry. This review has summarized the efficient organocatalytic asymmetric cascade reactions for the synthesis of desired chiral spirolactone molecules with structural diversity and complexity. However, this research is still in its early stage. The below-listed challenges need to be addressed as well. (a) The organocatalytic asymmetric cascade synthesis of chiral spirolactone scaffolds is confined to the two major organocatalytic asymmetric synthetic routes as discussed above. Thus, the constructed
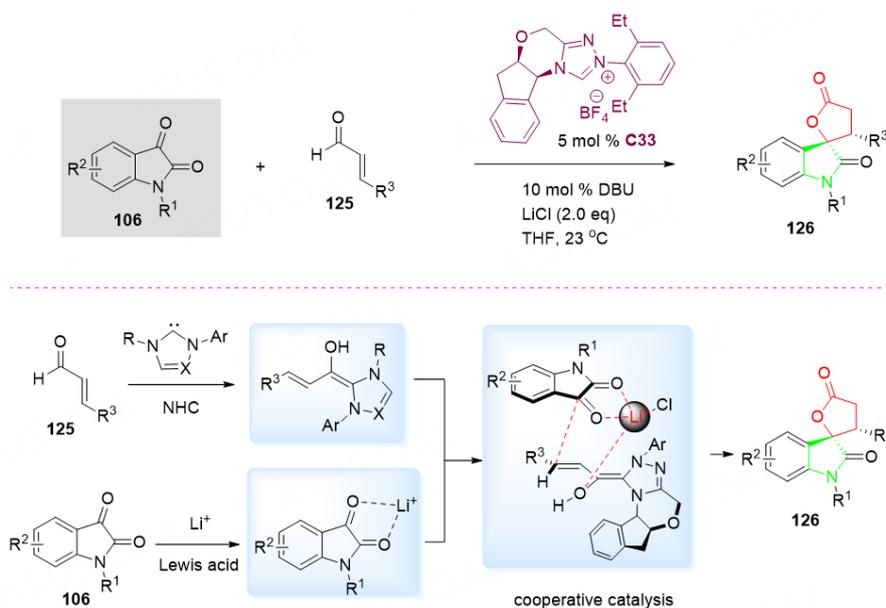
Scheme 62. Spirolactonization reaction of isatins **106** and *α, β*-unsaturated aldehydes **125**. This figure is used with permission from the Royal Society of Chemistry[137].
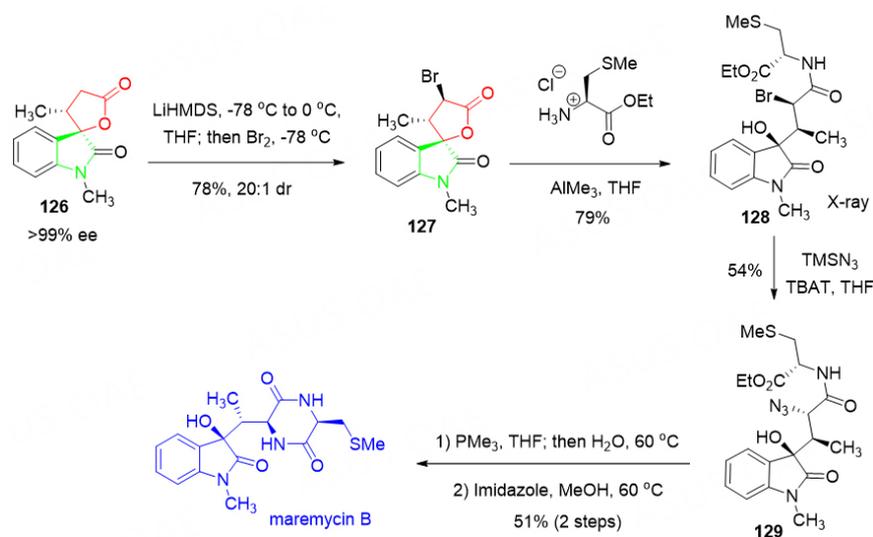
Scheme 63. Total synthesis of maremycin B. This figure is used with permission from the Royal Society of Chemistry[137].

scaffolds are mainly limited to spirobutyrolactones and spirovalerolactones derivatives. At the time of this writing, there are no other cascade reactions available for the catalytic asymmetric construction of chiral spiropropyllactones. So, the careful design of specific reagents to develop an efficient and versatile platform for organocatalytic asymmetric cascade synthesis is highly desired. (b) Although spirolactone moiety exists in lots of natural products, the successful application of organocatalytic asymmetric cascade reactions in the total synthesis of natural products is still limited. (c) Although controlling the enantioselectivity in catalytic asymmetric radical reactions remains a great challenge, it is highly valuable to have new activation models for the synthesis of spirolactones by the combination of asymmetric organocatalysis with visible light photoredox and electrochemical synthesis. (d) The biological properties of spirolactone derivatives need to

Scheme 64. Spirolactonization reaction of isatins **106** and γ-fluoroenals **130**. This figure is used with permission from the Royal Society of Chemistry[139].
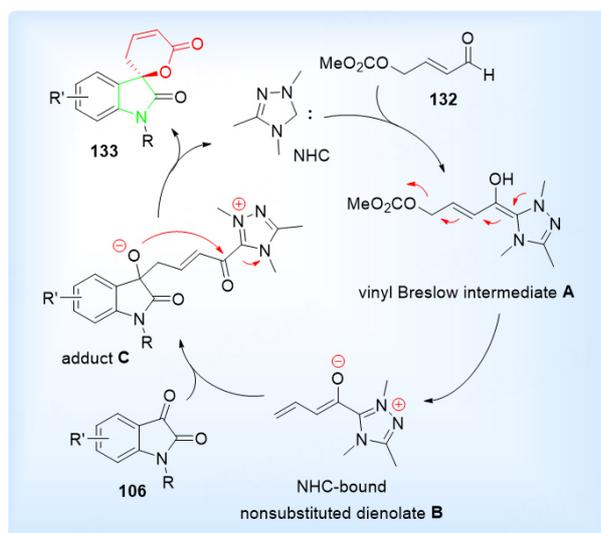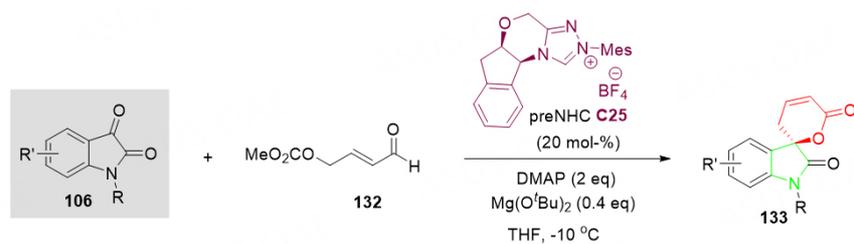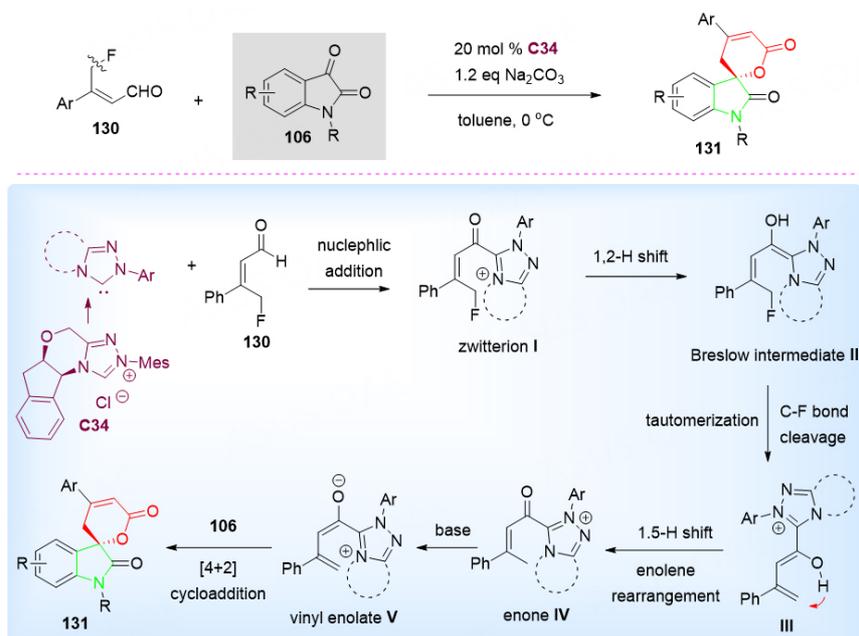
Scheme 65. Spirolactonization reaction of isatins **106** and γ-preoxidized enal **132**. This figure is used with permission from Wiley-VCH Verlag[140].

be further explored and there is still extensive room to address the biological activity issues. We are proud to work in this fascinating area and are sure it will be even better with the continuous endeavors of every chemist.

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All authors declared that there are no conflicts of interest.

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