Stereoselective domino reactions in the synthesis of spiro compounds

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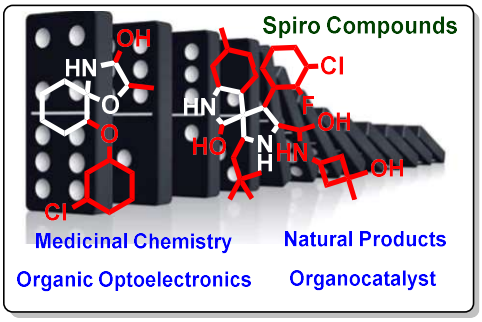


Received:
Accepted:
Published online:
DOI:

Abstract This review aims to summarize the latest developments in asymmetric domino reactions, with the emphasis on the preparation of spiro compounds. Discussions on the stereoselectivity of the transformations, the reaction mechanisms, the rationalization of the stereochemical outcome, and the applications of domino reactions to the synthesis of biologically active molecules and natural products are included when appropriate.

Key words Domino reactions; Spiro compounds; Stereoselective synthesis; Organocatalysis; Natural products.

1. Introduction

One of the main goals of organic synthesis is the complete control of stereochemistry and, in this framework, recently a special attention has been given to the challenging preparation of highly complex 3D chiral structures. Arguably, the most important defiance is the regio- and stereo-controlled generation of spiro compounds.[1]

These compounds are formally known as bicyclic organic compounds, include rings connected through just one atom (spiro atom) and present unique characteristics, such as: intrinsic complexity, 3D structural properties and conformational rigidity of their scaffold. Notably, spiro compounds display a broad range of biological activities (**Figure 1**).[2] Therefore, these molecules have attracted attention as framework in modern drug discovery.

The 3D orientation and the structure rigidity of spiro compounds represent an exceptional starting point in medicinal chemistry, providing a more efficient design of the pharmacophore and, consequently, being a promising tool for rational optimization of H-bonding, hydrophobic, and π-stacking interactions. These benefits can increase the recognition between the drug and its target, and change the physico-chemical properties of the drug, including its solubility and lipophilicity.[3] Moreover, synthetically 3D/sp^3-rich scaffolds provide more possibilities for functionalization compared to common flat/aromatic scaffolds, overrepresented in many fragment libraries.[3]

While spiro compounds are gaining increasing attention in the drug discovery field, they are still underrepresented in screening libraries and suffer from low diversity. The relatively low occurrence reflects the need for new strategies for their efficient synthesis and derivatization.

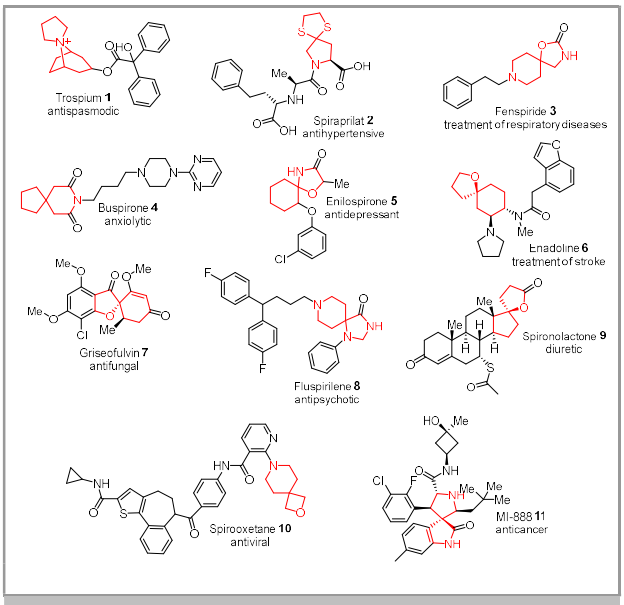


Figure 1 Selected examples of biological active spiro compounds

Another important use of spiro compounds is in organic optoelectronics.[4] Organic semiconductors as active materials in thin film electronic devices offer several major advantages over their inorganic counterparts. They can be processed by different methods, the most important being vapor deposition and solution-based processes, such as spin-coating and different printing techniques.[4] This process can be carried out at room temperature, and low costs. Nevertheless, the reproducibility control of device performance and their stability become the major challenges in organic optoelectronics devices. Thus, improving the morphological stability while retaining their electronic properties can be achieved based on the concept of connecting two more or less extended *ð*-systems with identical or different functions (emission, charge transport) via a common sp^3-hybridized atom. This is the basic idea of the spiro concept.[7] Some examples of spiro compounds used as organic optoelectronics are shown in **Figure 2**.[4]

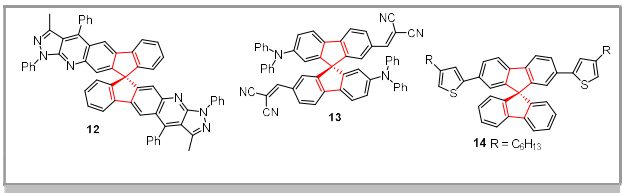


Figure 2 Spiro compounds as organic optoelectronics.

Spiro compounds are part of the structure of many natural products isolated from plants, frogs, marine sponges and other natural fonts. One of the earliest isolated spiro natural products was β-vetivone **15**, extracted from vetiver oil in 1939 by Pfau and Plattner.[5a] Alkaloids have special prominence and, for example, marine alkaloid (+)-discorhabdin A **26** and the fused tetracyclic lycopodium alkaloid nankakurine A **30** are shown in **Figure 3**, with other selected natural products.[5]

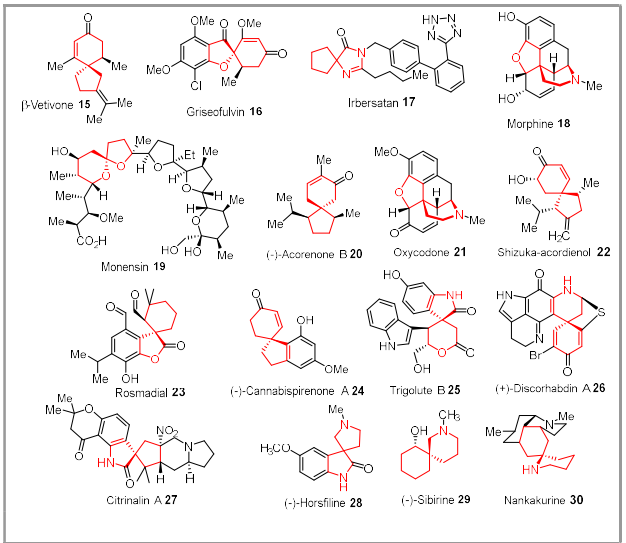


Figure 3 Examples of natural products containing spirocycles framework.

Finally, spirocyclic compounds have emerged as one of the most attractive ligand and catalyst motifs in asymmetric synthesis. The increased rigidity, restricted rotation at the spiro centre and extremely precise 3D structure can assist in improving enantiomeric excess in asymmetric reactions. Some organocatalysts, such as spirobiindane (spinol) **31**, spirobis(oxazoline) **32**, spinol-derived phosphoric acid **33**, diphosphine spirOP **34**, and the spiroketal diphosphine **35** are illustrated in **Figure 4**.[6]

The challenge associated with the synthesis of spiro compounds are many and can be briefly described as: functional-group incompatibility, difficulty to add useful functionality into the newly formed ring system for further synthetic manipulation and, from the stereoselective perspective, the presence of the quaternary and generally stereogenic spiro atom. Furthermore, the asymmetric characteristic of the molecule is one of the important criteria of the biological activities.

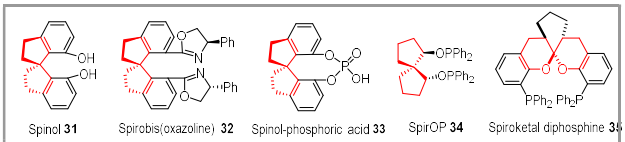


Figure 4 Spiro compounds as chiral organocatalysts.

Domino reactions have been undergoing great developments, as witnessed by the numerous review papers dedicated to this topic.[7] However, as far as we know, no previosu publication was dedicated specifically to the asymmetric synthesis of spiro compounds. Therefore, the present review aims to describe the recent advances in asymmetric domino reactions developed specifically for the synthesis of spiro compounds.

According to the Tietze definition, domino reaction involves two or more bond-forming transformations which take place under the same reaction conditions, without adding extra reagents including catalysts. Furthermore, the subsequent reactions are a consequence of the functionality formed by bond formation or fragmentation in the previous step.[8] However, it is important to highlight that experimentally a small difference exists between domino and consecutive cascade or tandem. The difference between the two lies in the point along the sequence at which one or more catalysts or reagents had to be added to effect either the initiation of a sequence (that is, domino reaction) or propagation to the next step (that is, consecutive reaction).

It should be noted that this definition was used as a basis for bibliographic research and for the manuscript preparation. In addition, the domino reactions will be classified in this review based on the reaction types involved in the first synthetic step.

2. Asymmetric domino reactions

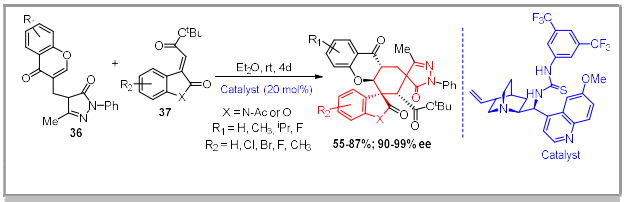
2.1 Domino reactions initiated by Michael reaction

Michael-type reactions can be considered as one of the most powerful and reliable tools for the stereocontrolled formation of carbon–carbon and carbon–heteroatom bonds. Undoubtedly, the domino reactions initiated by Michael reaction have been highlighted in the spiro compounds synthesis as depicted in the following chapters.

2.1.1 Michael-Michael domino reactions

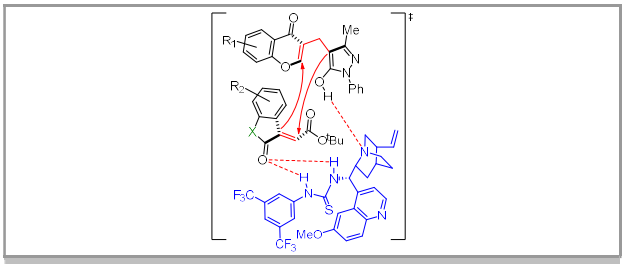
The Michael-Michael domino reaction is a powerful tool in forging ring systems common to many natural products. For

example, a recent work of Zhou and coworkers reports for the first time the bifunctional pyrazolone–chromone synthon directed organocatalytic double Michael domino reaction, a valuable strategy to access structurally diverse hexahydroxanthone derivatives, bearing five continuous stereocenters, including two all-carbon quaternary spiro-stereocenters. These products were obtained in 55-86% yield, dr >20:1 and 90-99% ee, under mild conditions (**Scheme 1**).[9]



Scheme 1 Asymmetric organocatalytic double Michael domino reaction.

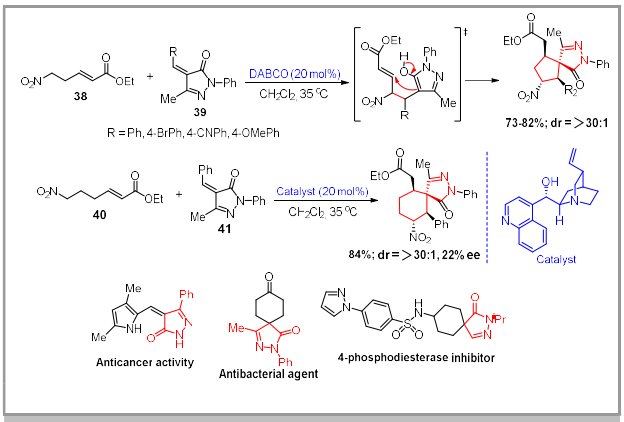
The proposed transition state for chirality induction is shown in **Scheme 2**. The tertiary amine of the catalyst activates the enolated pyrazolone **36** by deprotonation. Meanwhile, the double hydrogen bonding interactions between the thiourea hydrogen atoms of the catalyst and the carbonyl group **37** occurred simultaneously. Subsequently, the *Re*-face of **37** was preferably attacked by the *Si*-face of enolated pyrazolone **36**, delivering the desired Michael adduct under the control of catalyst by an efficient shielding effect.



Scheme 2 Transition state for double Michael.

Spiropyrazolone-based cyclohexanes, cyclohexanones and cyclohexenones have attracted interest due to their various biological activities as phosphodiesterase inhibitors,[10a] and antimicrobial, anticancer, and anti-inflammatory agentes.[10]

An efficient diastereoselective Michael-Michael domino reaction of δ-nitro α,β-unsaturated esters **38** with alkylidenepyrazolones **39** catalyzed by DABCO as the organocatalyst under mild conditions was made by Singh and workers to offer a wide range of carbocyclic spiro-pyrazolones with three tertiary stereogenic centers and a quaternary stereocenter in high yields and excellent diastereoselectivities (**Scheme 3**).[11]

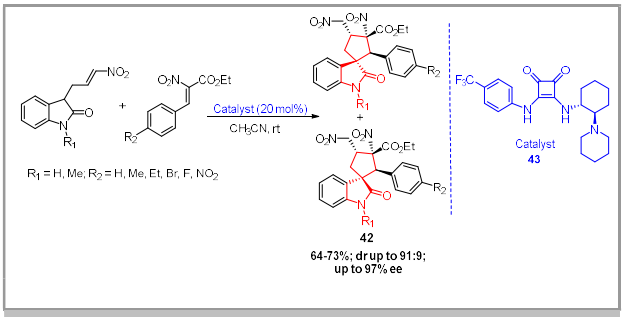


Scheme 3 Diastereoselective and enantioselective double Michael reaction.

Studies on the asymmetric variant of this reaction between **40** and N-phenyl benzylidene pyrazolone **41** was also investigated using several cinchona alkaloids and their derivatives, but low enantiomeric excess was obtained.

The synthesis of functionalized pyrazolones, like the previously described, attract considerable attention because of their potent bioactivities in medicinal chemistry.[12] Some structures are descripted in the **Scheme 3**.

The naturally occurring spirooxindoles as citrinalin B **27** and horsfiline **28** (see **Figure 3**) have diverse biological activities and for this have been attracting great interest among chemists for decades. Inspired by the natural-product-derived spirooxindoles, new therapeutic agents have been discovered from a variety of derivatives and have led to some clinical trials or preclinical studies.[13] In this sense, a series of spirocyclopentaneoxindoles **42** with four consecutive stereocenters including quaternary α-nitro esters were prepared in good yields (up to 73%) and excellent enantioselectivities (up to 97% ee), through enantioselective Michael–Michael domino reaction using nitroolefins.[14] The reaction was realized and optimized with the aid of a chiral squaramide-amine catalyst **43**. (**Scheme 4**).

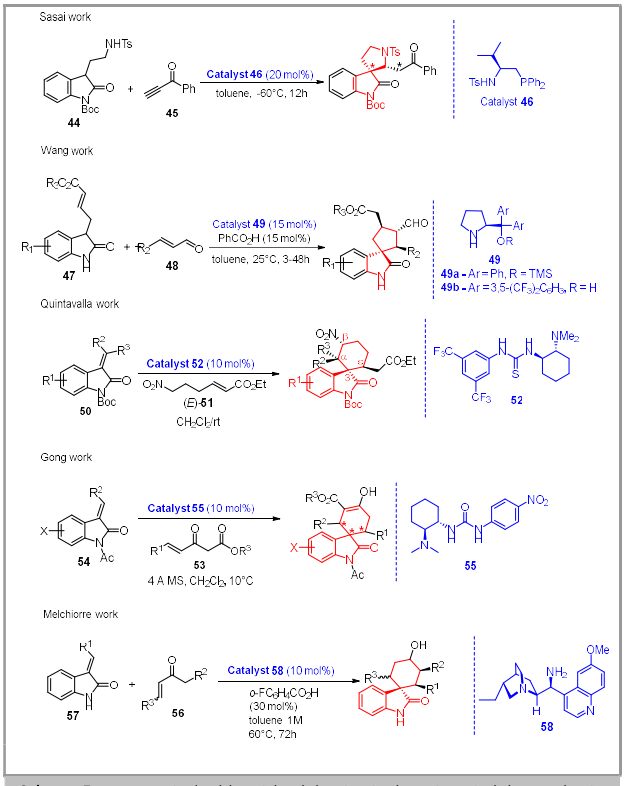


Scheme 4 Asymmetric double Michael in the synthesis of **42**.

Five similar examples, were reported by Sasai, Wang, Quintavalla, Gong and Melchiorre research group, respectively (Scheme 5).[15]

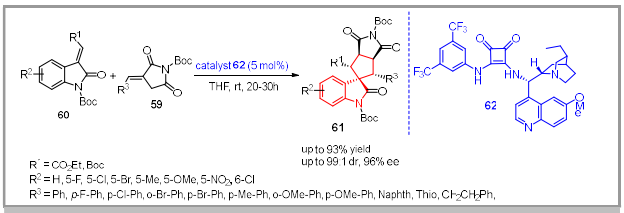
In Sasai's work the reaction of a α-substituted oxindole **44** with phenylprop-2-yn-1-one **45**, was promoted by the chiral multifunctional phosphine catalyst derived from (*S*)-valine **46**, giving the respective spiro compound, in good yield and high enantioselectivity.[15a] In Wang's work, 5-membered spirooxindole containing four consecutive stereocenters, including a spiro quaternary center, were constructed through

reaction between 3-substituted bifunctional oxindoles **47** and α,β-unsaturated aldehydes **48**, catalyzed by a chiral secondary amine **49**. High diastereo- and enantioselectivities can be obtained via an organocatalytic iminium Michael-enamine Michael.[15b] A new domino Michael-Michael reaction between 2-(2-oxoindolin-3-ylidene) acetic esters **50** and nitroenoates **51** catalyzed by chiral bifunctional thioureas **52**, for the synthesys of 5- and 6-membered spirooxindoles, was satisfactorily described by Quintavalla and coworkers.[15c] Gong's research group carried out the asymmetric synthesis of spiro[4-cyclohexanone-1,3′-oxindoline] derivatives with excellent enantioselectivity, using a bifunctional organocatalytic double Michael reaction (formal [4 + 2] cycloaddition) between the Nazarov reagents **53** and methyleneindolinones **54**.[15d] Finally, Melchiorre and coworkers developed an organocatalytic enamine Michael/iminium Michael domino reaction between α,β-unsaturated ketones **56** and oxindole derivatives **57**, for the synthesis of complex spiro-oxindolic cyclohexanes, with extraordinary levels of stereocontrol. In addition, they also developed an enamine Michael/iminium, Michael/enamine intramolecular aldol strategy, for the preparation of spirooxindoles using α,β-unsaturated aldehydes instead of ketones.[15e]



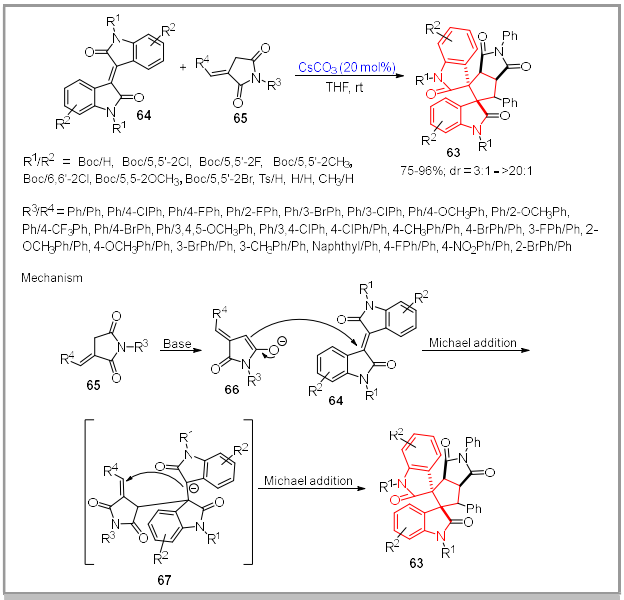
Scheme 5 Asymmetric double Michael domino in the spirooxindoles synthesis.

The construction of five-membered spirooxindoles was developed by Du and Zhao through a bifunctional squaramide-catalyzed Michael-Michael domino reaction. The corresponding products **61** with five contiguous stereocenters including a quaternary center, were obtained in good to excellent yields with excellent stereoselectivities (**Scheme 6**). Moreover, the potential of this methodology was confirmed by a gram-scale synthesis, of the resulting adduct by a one-pot four-component reaction.[16]



Scheme 6 Asymmetric double Michael reaction in the synthesis **61.**

Bispirooxindoles **63** with two adjacent quaternary carbon centers and four consecutive cycles, were efficiently prepared by Wang and coworkers using a Michael–Michael domino cycloaddition reaction (**Scheme 7**).[17a] The spiro compounds were obtained with excellent yields and diastereoselectivities, under mild conditions and in a few minutes. Also in this case, a scale-up was performed with excellent results. A mechanism for the double Michael domino reaction is proposed in the **Scheme 7**. Initially, the enolate **66**, formed in the presence of the base, reacts with the isoindigo **64** *via* a Michael addition generating the adduct **67**. This latter reacts with the double bond of the alkylidene succinimide, *via* a second Michael addition, providing the final product **63**.



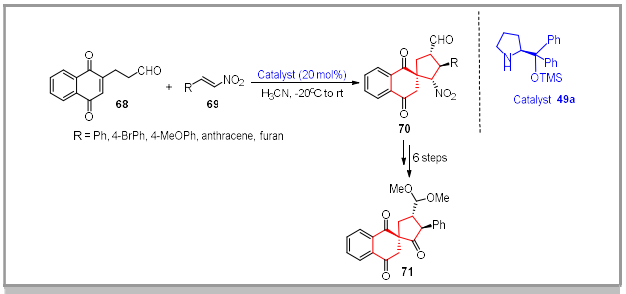
Scheme 7 Asymmetric double Michael reaction in the synthesis of bispirooxindoles.

Isoindigos bearing various R^1 and R^2 groups were tested. It is worth mentioning that the reaction did not occur when R^2 was an H atom or a methyl group, possibly due, according to the authors, to the poor solubility of the isoindigos. Furthermore, by varying the substituents R^3 and R^4 on α-alkylidene succinimides, it was found that, substituents on the *ortho* position provided low yields, while substituents on the *para* position provided better yields. Notably, electron-withdrawing groups were more favorable.

Bispirooxindoles and spiroaziridine oxindoles were also efficiently prepared by Wang and coworkers using double Michael domino reaction between methyleneindolinones and N-tosyloxycarbamates.[17b] Similarly, Zhou and coworkers have prepared bispirooxindoles-based hexahydroxanthones with five

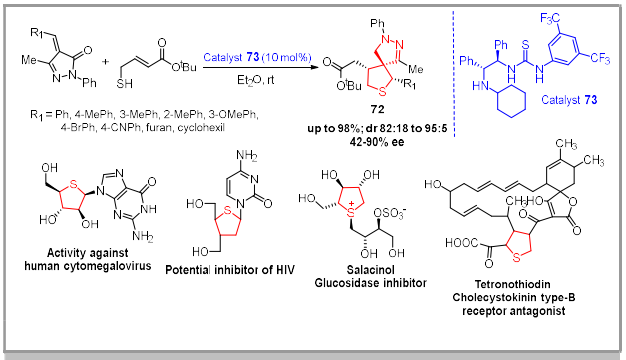
contiguous stereocenters. Antitumor activity evaluation of these compounds revealed that they exerted good cytotoxic effects on human K562, A549, and PC-3 cells.[17c]

A remarkably example of double Michael reaction with naphthoquinone and nitroolefins was recently presented by Hayashi and coworkers.[18] In this work functionalized spiro[cyclopentane-1,2′(1′*H*)-naphthalene] derivatives with four continuous stereocenters were synthetized with excellent diastereo- and enantioselectivities (**Scheme 8**). The reaction consists of the domino Michael-*exo*-Michael reaction of 2-(2-formylethyl)-1,4-naphthalenedione **68** and nitroalkene **69** catalyzed by diphenylprolinol silyl ether **49a**. To determine the absolute configuration, the obtained compound **70** was converted into diketone **71** through a 6-step synthesis.



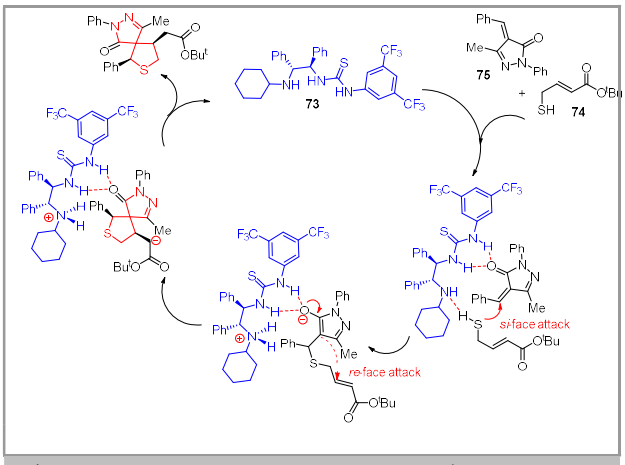
Scheme 8 Michael/Michael domino reaction in naphthoquinone derivative.

A domino reaction, based on an organocatalysed sulfa-Michael-Michael sequence, was applied in the asymmetric synthesis of spiropyrazolone tetrahydrothiophenes **72** bearing three consecutive stereocentres in good yield and good diastereo- and enantioselectivity (**Scheme 9**).[19] Tetrahydrothiophenes represent a fundamental class of heterocyclic compounds endowed with several biological activities,[20] illustrative structure is shown **Scheme 9**.



Scheme 9 Enantioselective sulfa-Michael/Michael domino reaction.

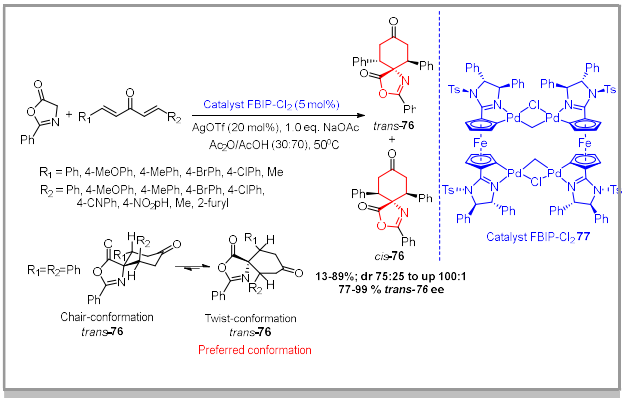
A catalytic cycle for the sulfa-Michael-Michael domino reaction catalyzed by **73** is given in the **Scheme 10**. The bifunctional organocatalyst deprotonate the pronucleophile 4-mercapto-2-butenoate **74**, whereas the pyrazolone **75** is steered by the thiourea group via hydrogen bonding. In this complex, the nucleophilic thiol attacks the *si*-face of the Michael acceptor to give the (*S*)-configured adduct. Then, the adduct enolate would attack the *re*-face of the enoate acceptor to give the (5*R*,6*S*,9*R*)-configured product.



Scheme 10 Proposed catalytic cycle for the sulfa-Michael/Michael reaction.

In 2014, the Zhao group also developed a domino sulfa-Michael-Michael reaction catalyzed by cinchona-derived thioureas to construct spiro[oxindole-tetrahydrothiophenes] with high stereoselectivity.[21] Another enantioselective organocatalytic domino sulfa-Michael-Michael reaction, described by Li an coworkers, between 2-arylidene-1,3-indanediones and 4-mercapto-2-butenoates in the presence of a tertiary amine–thiourea organocatalyst, gave access to chiral spiro[indane-1,3-dione–tetrahydrothiophene] skeletons.[22]

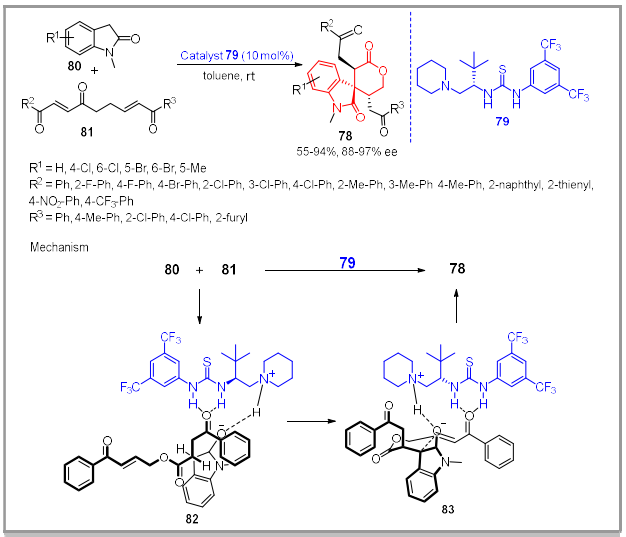
Spirocyclic azlactones are usual precursors of cyclic quaternary amino acids. These compounds are of interest as building blocks for the synthesis of artificial peptide analogues, with controlled geometry in the peptide backbone.[23] Peters and coworkers performed a catalytic asymmetric synthesis of spirocyclic azlactones **76** in moderate diastereoselective, but high enantioselective by a double Michael addition approach (**Scheme 11**).[24]



Scheme 11 Double Michael addition to form spirocyclic **76** and their respective preferred conformations.

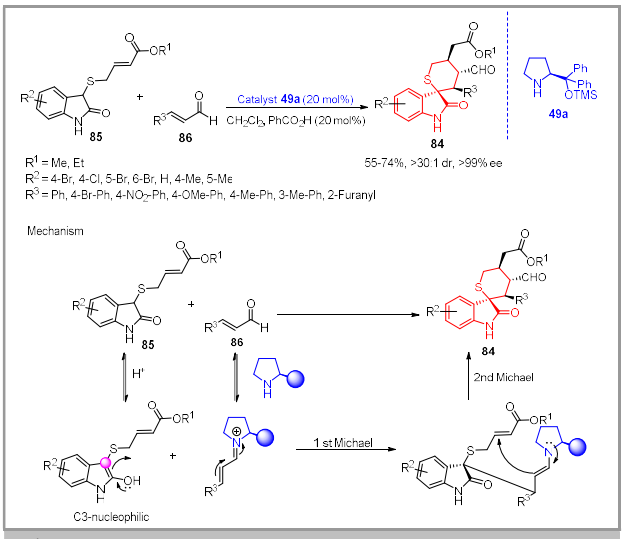
This protocol involves a Pd^{II}-catalyzed double 1,4-addition of an *in situ* generated azlactone intermediate to the dienone (a formal [5+1] cycloaddition). The catalyst used, a planar chiral ferrocene bispalladacycle **77**, suggested a monometallic reaction pathway.[24] Spectroscopic studies showed that the spirocycles prefer a twist over a chair conformation of the cyclohexanone moiety.

Chiral spirooxindoles δ-lactones **78** with three contiguous stereocenters including an all-carbon quaternary center, was obtained by Xu and coworkers through a novel bifunctional thiourea **79** that catalyzed formal [5 + 1] cycloaddition of oxindoles **80** and ester-linked bisenones **81** (**Scheme 12**).[25] This methodology involved a double Michael addition and provided the desired compounds in high diastereoselectivities and enantioselectivities. Based on experimental results, the authors proposed a mechanistic route for the reaction controlled by the catalyst. As shown in **Scheme 12**, oxindole and enone are activated by bifunctional thiourea generating intermediate **82**, which after undergoing an intramolecular Michel addition, becomes intermediate **83**. Then, another intramolecular Michael addition of the oxindole with the *si*-face of the enone provides the product of interest and regenerates the catalyst.



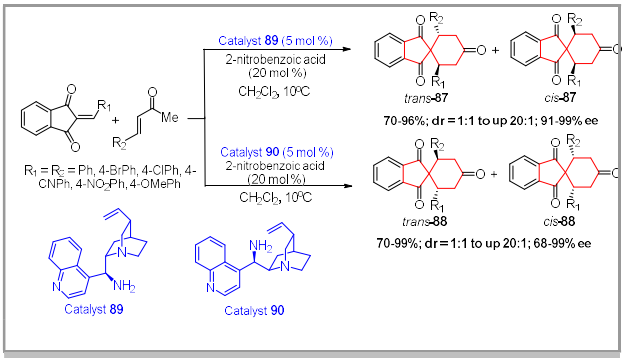
Scheme 12 Double Michael addition to form spirooxindoles δ-lactones.

Sheng and coworkers developed a double Michael domino reaction for the preparation of oxindole–spiro-tetrahydrothiopyrans **84** from **85** and diverse enals **86**. The reactions were catalyzed by amine **49a**, in the presence of $PhCO_2H$ as an additive (**Scheme 13**).[26] The products were obtained in moderate to good yields and with excellent diastereo- and enantioselectivies. The spiro-oxindoles were validated as a new class of p53-MDM2 protein–protein interaction inhibitors with good antitumor activity. According to the proposed mechanism (**Scheme 13**), first Michael addition occurs between the nucleophilic oxindole-C3 of **85** and the conjugated double bond of the iminium ion, formed from the reaction of **86** and **49a**. Then, the second Michael addition (intramolecular) provide the desired compound. It is worth mentioning that this work was the continuation of an earlier work developed by Sheng's research group about antitumor oxindole–spirotetrahydrothiopyran derivatives.[27]



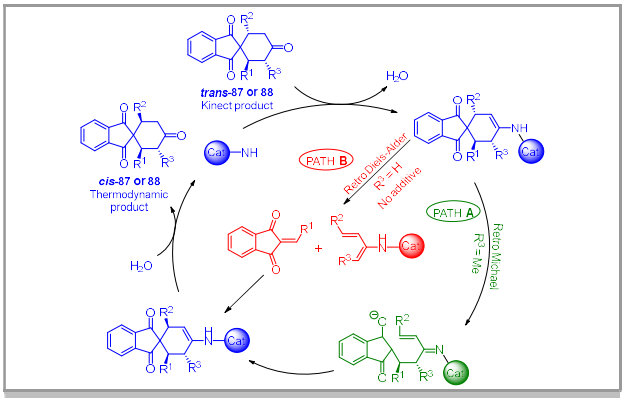
Scheme 13 Michael–Michael domino reaction for the preparation of novel oxindole–spiro-tetrahydrothiopyrans.

The stereoselective synthesis of indanedione-fused 2,6-disubstituted *trans*-spirocyclohexanones, was realized by Lin and coworkers.[28] In this paper, two chiral cinchona-alkaloid derivatives catalyzed the synthesis of the thermodynamically less stable 2,6-*trans*-disubstituted spirocyclohexanones **87** and **88**. Both the enantiomeric forms of the *trans* isomer are obtained in excellent yields and enantioselectivities (**Scheme 14**).



Scheme 14 Synthesis of Indanedione-Fused 2,6-disubstituted *trans*-spirocyclohexanones.

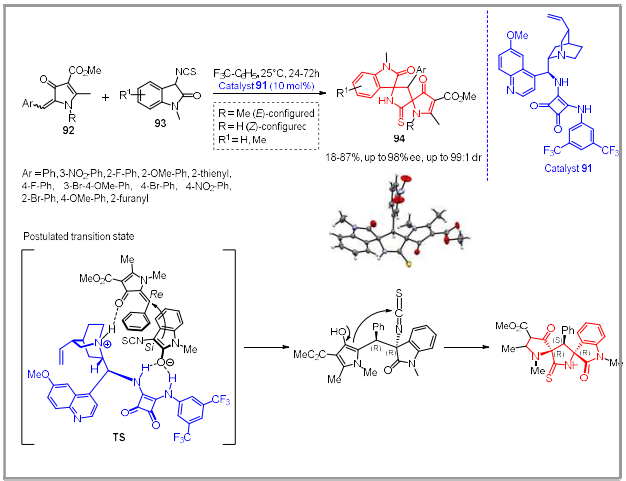
An important objective of this paper was to transform the kinetic *trans*-spiranes, into the thermodynamically stable *cis* congeners, thus demonstrating the generality of this method for the synthesis of all four stereoisomeric forms of the product. Mechanistic investigations revealed two competing pathways: a concerted Diels–Alder reaction, and a stepwise Michael addition, (**Scheme 15**).



Scheme 15 Spirocycles **87** and **88** isomerization.

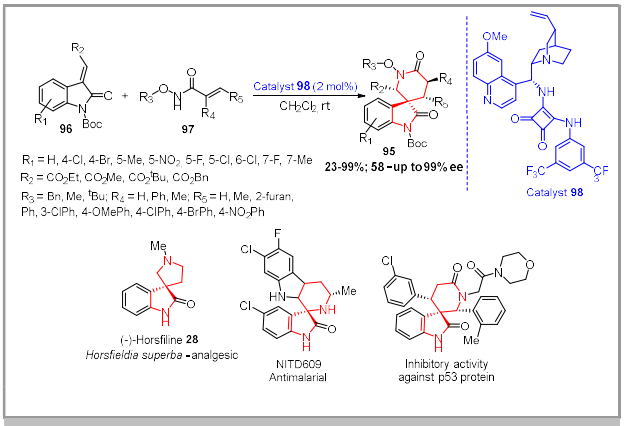
Another similar example of spiroindandiones synthesis was reported by Zhang and coworkers. An organocatalytic cascade Michael-Michael reaction between curcumins and 2-arylidene-1,3-indandiones to prepare multicyclic spiro-1,3-indandiones has been studied. Prolinol, chiral thiourea-tertiary amines, and cinchona alkaloids were evaluated as catalysts, and quinine was identified as the best choice for the transformation.[29]

A quinine derivative **91** was also used as an organocatalyst by Grošelj and coworkers in the double spirocyclization of arylidene-Δ^2-pyrrolin-4-ones **92** with 3-isothiocyanate oxindoles **93** through a Michael-Michael domino reaction (1,4/1,2-addition sequence). The goal was to construct oxindole-thiopyrolidinone-Δ^2-pyrrolin-4-one bis-spiroheterocycles **94** (**Scheme 16**).[30] The products containing three contiguous stereocenters were obtained with ee up to 98% and dr up to 99:1. The absolute configuration of the major diastereomer was determined by single crystal X-ray analysis. A plausible transition state to justify this configuration was proposed in **Scheme 16**, where the protonated catalyst activates, and coordinates, the pyrrolone electrophile through the protonated quinuclidine moiety, while squaramide functionality orients and activates the nucleophile for the attack. The *si*-face of the nucleophile attacks the *re*-face of the electrophile, then spirocyclization occurs, yielding the desired compound.



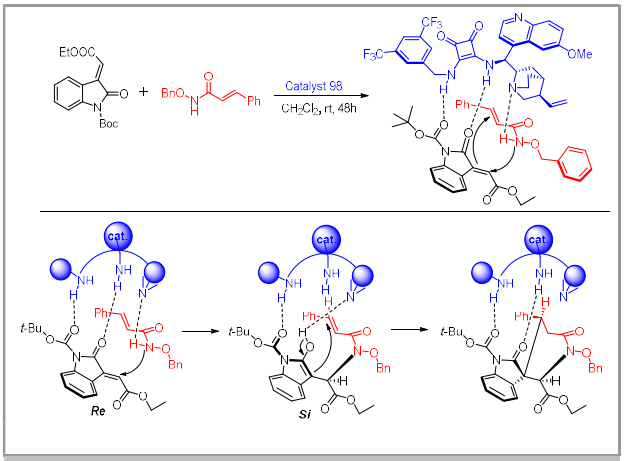
Scheme 16 Preparation of oxindole-thiopyrolidinone-Δ^2-pyrrolin-4-one bis-spiroheterocycles **94.**

Recently a simple, direct, and highly enantioselective synthesis of spiro-oxindole piperidin-2-one derivatives **95**, was achieved through a domino aza-Michael-Michael reaction using a squaramide catalyst. The desired products were obtained in excellent yields (up to 99%) and good to high stereoselectivities (up to >20:1 dr and up to 99% ee) under mild conditions (**Scheme 17).**[31] A spiro-oxindole scaffold bearing a quaternary carbon stereocenter at the 3-position, especially with an N-heterocycle, is a ubiquitous structural moiety in many bioactive natural products and synthetic compounds.[32]



Scheme 17 Synthesis of Spirooxindoles **95**.

With the optimized conditions, the reaction scope of various 3-methyleneindolinones **96** and N-protected acrylamides **97** were also examined. The steric hindrance at both α and β positions of acylamides led to a decreasing in yields, albeit with excellent stereoselectivities. The transition state and mechanism were proposed to rationalize the outcome of stereoselectivities (**Scheme 18**).



Scheme 18 The transition state and mechanism of synthesis **95**.

The squaramide moiety of the catalyst, orients and activates methyleneindolinones via hydrogen bonding. Simultaneously, the α,β-substituted acylamides were activated by the tertiary amine of the quinine component of the catalyst, leading to N-Michael *re*-face addition of α,β-substituted acylamides to activated 3-methyleneindolinone succeeded by the

intermolecular *si*-face Michael addition, resulted in an irreversible cyclization, furnishing the desired enantioenriched and less steric hindered product.

Another examples of diastereo- and enantioselective domino aza-Michael-Michael reaction are described in the literature by Du research group to prepare spiro-pyrrolidine-pyrazolones,[33a] spiropyrazolone tetrahydroquinolines,[33b] spirooxindole tetrahydroquinolines,[33c] spiro[pyrrolidine-3,3'-oxindole] scaffold.[33d] It is important to highlight that in all these reactions, the best results were obtained when a chiral bifunctional tertiary amine squaramide was used as a catalyst.

Spirooxindole tetrahydroquinolines was also synthesized by Zhao research group, using an efficient amine acid-derived thiourea catalyzed asymmetric aza-Michael-Michael domino reaction of various methyleneindolinones with ortho-(p-methylbenzenesulfonamide)-α,β-unsaturated ketones.[34]

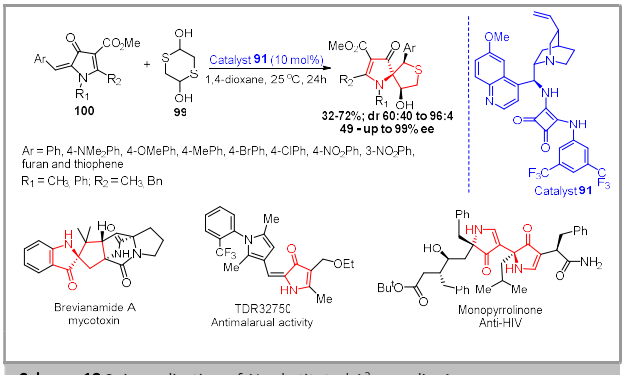
As the last example in this section, a chiral amine-catalyzed oxa- and aza-Michael-Michael domino strategy was used by Zhu and coworkers to synthesize enantiomerically enriched spiro[chroman/tetrahydroquinoline-3,3'-oxindole] scaffolds. The processes provided excellent etherocontrol (dr> 20: 1,> 99% ee) in moderate conditions depending on the different Michael donors (Ar-OH / Ar-NHR) employed.[35]

2.1.2 Michael-Aldol domino reactions

Another domino methodology initiated by Michael reaction widely described in the literature is the Michael-aldol sequence. The following will be showing some examples of this methodology.

In 2019 Ričko and coworkers developed a new methodology to organocatalyzed sulfa-Michael/aldol domino spirocyclizations with mercaptoacetaldehyde dimer 99 using Δ²-Pyrrolin-4-ones **100** as substrate.[36] In this work unsaturated-Δ²-pyrrolin-4-ones are easily transformed into the corresponding spirocyclic derivatives in high stereocontrol (*ee* up to >99%, *dr* up to 95:5) in good yields under organocatalyzed conditions (**Scheme 19**).

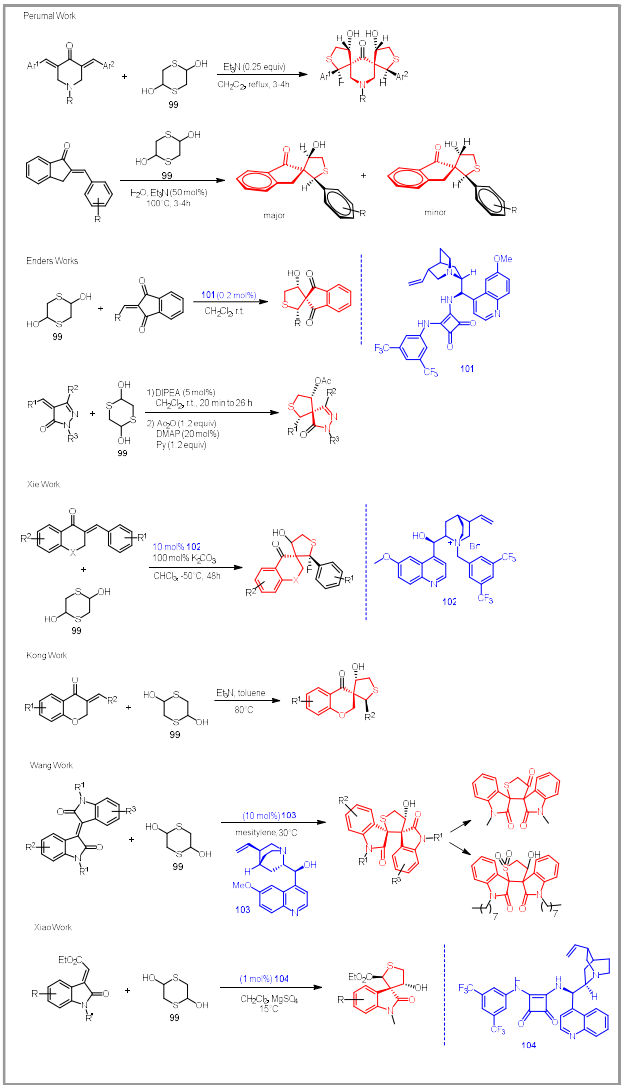
The absolute configuration of the product is dependent the configuration of the exocyclic double bond in the starting material. These results point to the possibility of a widespread use of these building blocks in various domino transformations for accessing libraries of 3D-rich pyrrolone-based spiro heterocycles.



Scheme 19 Spirocyclization of *N*-substituted Δ²-pyrrolin-4-ones.

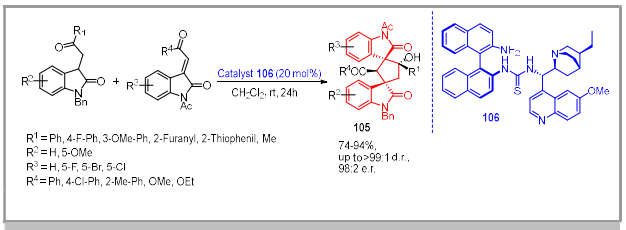
The Δ²-pyrrolin-4-one core is an interesting motif prominent in several natural products like brevianamide A,[37a] bioactive molecules as modulators of opioid receptors,[37b] antimalarials,[37c] HIV-1 protease inhibitors[37d] and herbicides.[37e] Examples are reported in **Scheme 19**.

Tetrahydrothiophene spirocycles have attracted a great attention due to their presence as building blocks in natural products, bioactive compounds, and materials. To synthesize them diastereo- and enantioselective sulfa-Michael-aldol domino reactions were used by Perumal, Enders, Xie, Kong, Wang, Xiao and their respective coworkers (**Scheme 20**).[38]



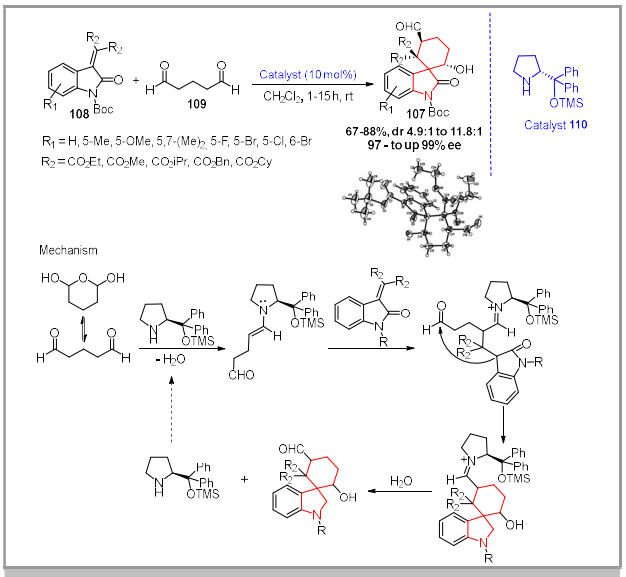
Scheme 20 *D*iastereo- and enantioselective sulfa-Michael/aldol domino reactions.

Barbas III and coworkers developed a highly efficient organocatalytic domino Michael-Aldol approach for the construction of bispirooxindoles derivatives **105**, containing four chiral centres, including three quaternary carbons chiral centres. The methodology carried out in mild conditions and catalyzed by a cinchona alkaloid **106**, provided excellent stereocontrol (up to >99:1 d.r. and 98:2 e.r.) (**Scheme 21**). In addition, catalyst reconfiguration provided access to the opposite enantiomer.[39]



Scheme 21 Michael/Aldol reaction in the synthesis of bispirooxindoles.

Wang research group realized the synthesis of enantiopure spirocyclohexaneoxindoles **107** through domino Michael–Aldol reactions between isatin derivatives **108** and pentane-1,5-dial **109** in the presence of diphenylprolinol silyl ether **110** as an aminocatalyst. As a result, a series of multistereogenic and functionalized spirocyclohexaneoxindoles have been obtained in good yields with moderate diastereoselectivities but excellent enantioselectivities (**Scheme 22**). The mechanism proposed by the authors is described in the same scheme.[40]

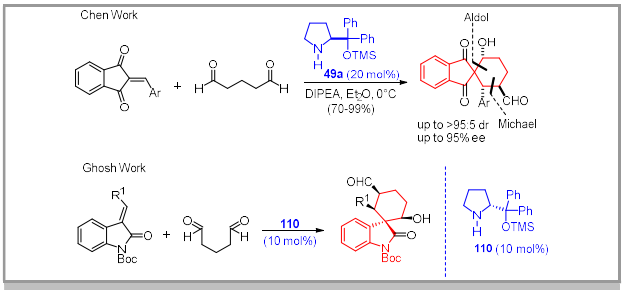


Scheme 22 Synthesis and mechanism of spirocyclohexaneoxindoles.

Notably, the Michael–Aldol reactions with substrates bearing electron-donating groups generally required longer reaction times (7–15 hours), providing the desired products in 71–88% yields with moderate diastereoselectivities and excellent enantioselectivities. In contrast, the substrates bearing halogen substituents on the oxindole backbones, performed very well in the corresponding domino reactions in less than two hours, resulting in the desired products in 74–83% yields with 5.2: 1 to 8.7 : 1 dr and over 97% ee.[40]

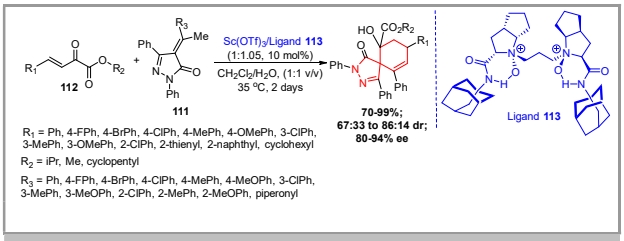
The spirocyclohexaneoxindoles structure was determined by single crystal X-ray diffraction analysis, which showed that the formyl and hydroxy groups are in *trans* configuration. In addition, electronic circular dichroism (ECD) spectroscopy and time-dependent density functional theory (TD-DFT) were used to investigate the rational structures of spirocyclohexaneoxindoles.

Similar studies were performed independently by Chen and Ghosh research groups (**Scheme 23**).[41]



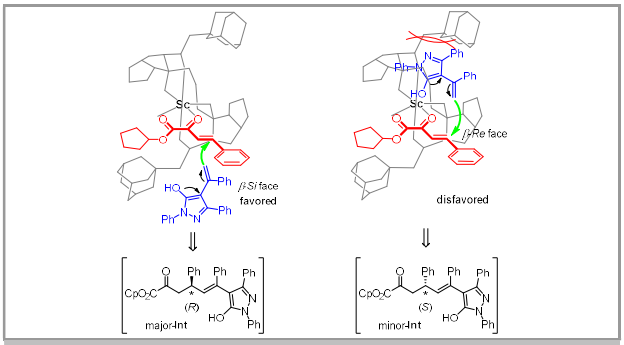
Scheme 23 Synthesis of spirocyclohexaneoxindoles by Michael/aldol domino reaction.

An efficient asymmetric vinylogous Michael–Aldol domino reaction between α-arylidene pyrazolinones **111** and β,γ-unsaturated-α-ketoesters **112** catalyzed by a chiral N,N′-dioxide-Sc^{III} complex **113** in aqueous media has been established by Feng research group.[42] Various spirocyclohexene pyrazolones with were obtained in excellent yields with good diastereoselectivities and enantioselectivities (**Scheme 24**). Pyrazole and pyrazolone derivatives represent a class of valuable five-membered nitrogen heterocyclic compounds, which contain unique structures found in some bioactive natural products and pharmaceuticals.[43]



Scheme 24 Synthesis of spirocyclohexene pyrazolones by Michael/aldol.

After optimization of the reaction conditions, the substrate scope of this domino reaction was examined. Ketoesters containing isopropyl, cyclopentyl, or methyl ester substituents, could deliver the related products with high enantioselectivity. Both electron-withdrawing and electron-donating groups on the β-aryl moiety of ketoesters were tolerated, yielding the products in excellent yields (95%–99%) with good diastereoselectivities (81:19–85:15) and high enantioselectivities (87%–90% ee). In addition, various α-arylidene pyrazolinones were evaluated. In R_1 position aromatic rings with electron-donating substituents give slightly higher enantioselectivities than those bearing electron-withdrawing ones. A plausible mechanism was proposed by the authors (**Scheme 25**).



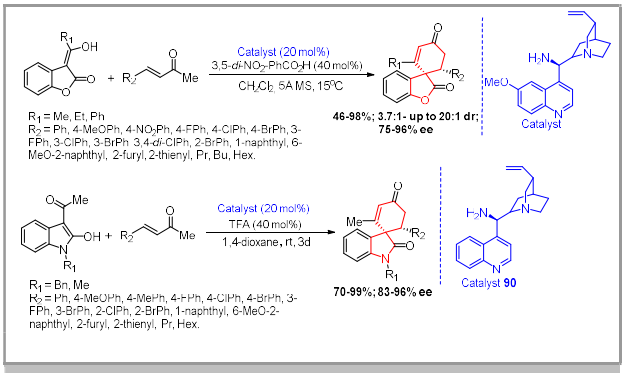
Scheme 25 Mechanism for synthesis of spirocyclohexene pyrazolones.

First, two carbonyl oxygens of β,γ-unsaturated-α-ketoester **112** can coordinate with the **113**/Sc^{III} complex to form a octahedral transition state. Because of the steric hindrance between the adamantyl group, of the ligand, and the active dienoate species of α-arylidene pyrazolinones **111**, the vinylogous Michael addition occurs preferentially from the *β-Si* face, followed by an intramolecular aldol addition to afford the corresponding spiropyrazolone.

The same ligand **113**, but now coordinate to a Ni^{II} atom, was used by Feng research group to catalyze the domino thia-Michael-Aldol reaction of 1,4-dithiane-2,5-diol with 3-alkenyloxindoles. A series of the desired spirocyclic oxindole-fused tetrahydrothiophenes was obtained in good yields, up to 97% with excellent enantioselectivities (98% ee) and diastereoselectivities (dr >19:1).[44]

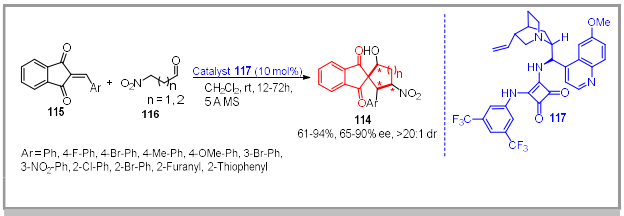
Spiro-pyrazolone scaffolds with five contiguous stereogenic centers, two quaternary and three tertiary, were also synthesized by Zhou and coworkers using 4-substituted 5-nitropentan-2-ones as chiral building blocks, in the presence of DBU. The Michael-Aldol domino methodology employed, provided the spiro-pyrazolone derivatives in acceptable to good yield with high levels of diastereo- and enantioselectivity. Moreover, the reaction could be scaled up without any loss in terms of yield and stereoselectivity.[45]

An efficient Michael–aldol–dehydration domino reaction has been developed by Wang and coworkers to construct spirocyclic benzofuranones[46a] and six-membered spirocyclic oxindoles.[46b] Both reactions used a Cinchona-based primary amine as a catalyst. A scheme of these reactions is presented below (**Scheme 26**). In the first example, the desired chiral spirocyclic benzofuranones were obtained in excellent stereoselectivities (dr > 20:1 and up to 96% ee) and moderate to excellent yields (up to 98%). In the other example, spiro[cyclohex-2-enone-oxindole] motifs were obtained with high yields and excellent stereoselective.



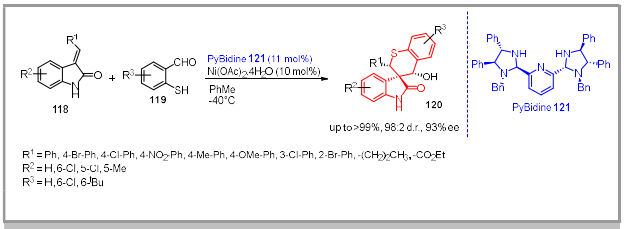
Scheme 26 Michael–aldol–dehydration domino reaction.

Enantioenriched spiro-1,3-indandione framework **114** with three stereocenters were prepared by means of an asymmetric Michael-Aldol domino reaction between 2-arylideneindane-1,3-diones **115** and nitro aldehydes **116**, in the presence of a squaramide-tertiary amine **117** (**Scheme 27**). Chiral spiro-1,3-indandione derivatives were obtained in good yields with high enantioselectivities and diastereoselectivities.[47]



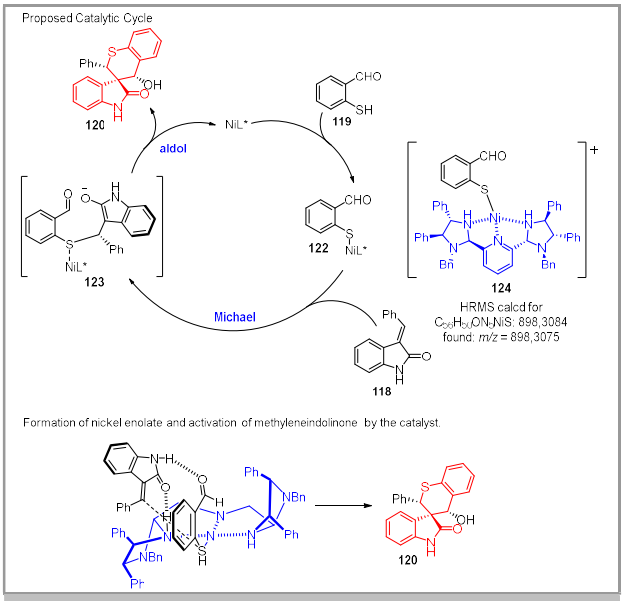
Scheme 27 Synthesis of spiro-1,3-indandione **114**.

An asymmetric Michael-aldol domino reaction of methyleneindolinones **118** and thiosalicylaldehydes 119 catalyzed by bis(imidazolidine)pyridine (PyBidine)–$Ni(OAc)_2$ was employed by Arai and coworkers to produce thiochromanyl-spirooxindoles **120** (**Scheme 28**), having three contiguous stereogenic centers, in good yields, diastereo- and enantioselectivities.[48]



Scheme 28 Synthesis of thiochromanyl-spirooxindoles **120.**

According to the proposed catalytic cycle brought by the authors (**Scheme 29**), the reaction started with formation of nickel-thiolate of thiosalicylaldehyde **122**. Then, the nickel-thiolate attacked methyleneindolinone **118** through a Michael addition, giving rise to the indolinone enolate **123**, which underwent an intramolecular aldol reaction, supplying the **120** and regenerating the catalyst..

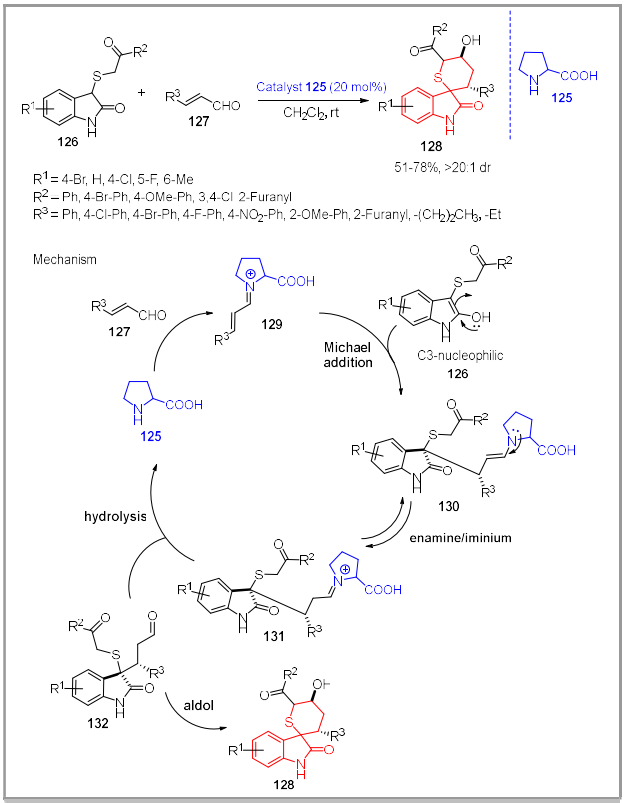


Scheme 29 Proposed catalytic cycle for the formation of thiochromanyl-spirooxindoles.

It is worth mentioning that the complex [PyBidine–Ni–$S(C_6H_4)CHO]^+$ **124** was identified through HRMS analysis, which provided the peak at m/z = 898.3075. In addition to generating

nickel enolate, the PyBidine–Ni(OAc)$_2$ catalyst also activated methyleneindolinone by hydrogen bonding with the NH of the imidazolidine ring, as shown in **Scheme 29**. Therefore, hydrogen bonding controlled the direction of methyleneindolinone for acceptance of nucleophilic addition of thiolate and guided the following aldol reaction.

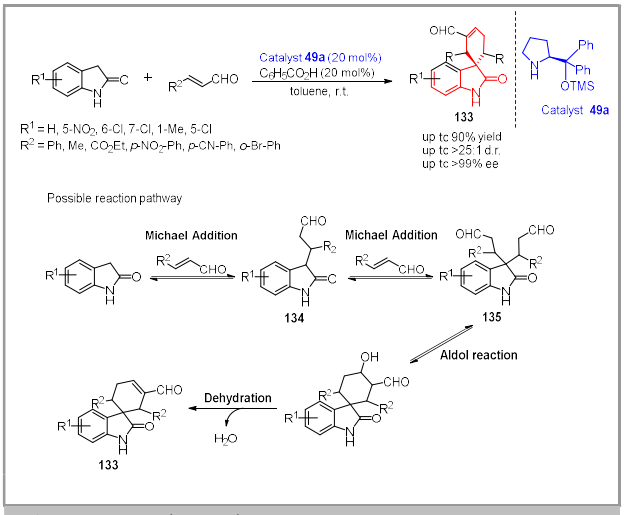
Ultimately, Sheng research group developed a Michael-aldol domino process, catalyzed by proline **125**, between 3-substituted indolin-2-one derivatives **126** with α,β-unsaturated aldehyde **127** to construct spiro-tetrahydrothiopyran oxindoles **128** scaffolds containing diverse functional groups (**Scheme 30**).[49] The compounds were obtained in moderate to good yields and excellent diastereoselectivities. In addition, they were found to be potent p53-MDM2 inhibitors with good antitumor activity. A plausible reaction mechanism is depicted in **Scheme 30**. Initially, the formation of the iminium ion **129** occurs from the reaction between **125** and **127**. Then, there is the addition of Michael of the C3-nucleophilic of **126** to the conjugated double bond of **129**, generating the intermediate **130**, which after tautomerism enamine/iminium, gives rise to intermediate **131**. This in turn undergoes hydrolysis generating **132** and regenerating catalyst **125**. Then, **132** undergoes an intramolecular aldol reaction providing the spiro compound **128** of interest.



Scheme 30 Synthesis of spiro-tetrahydrothiopyran oxindoles **128.**

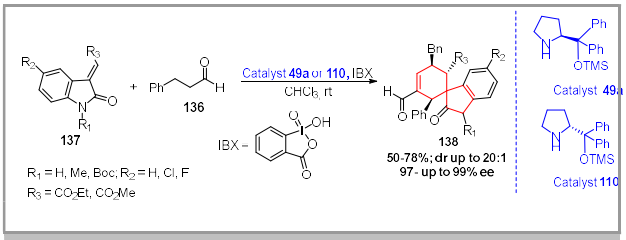
2.1.3 Double Michael/Aldol and triple Michael/Aldol domino reaction

In 2010, Rios and collaborators developed an organocatalytic methodology for the synthesis of spiro compounds via a Michael-Michael-aldol reaction. The reaction provided spirooxindole derivatives **133** with good yields and in almost diastereo- and enantiomerically pure forms (**Scheme 31**). In addition to oxindols, the methodology can also be applied to other heterocycles, such as benzofuranones, pyrazolones and azlactones, giving rise to spirocycles with good yields and excellent stereoselectivities.[50] A possible reaction pathway proposed by the authors is shown in **Scheme 31**, where the oxindole initially reacts with the unsaturated aldehyde leading to compounds **134** or **135**. However, the quaternary carbon formed in **135** is non-stereogenic, so this compound is desymmetrized in an irreversible dehydration after the aldolic reaction. The relative configuration of the compounds was determined by means of NOE and NOESY NMR experiments, and the absolute configuration was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.



Scheme 31 Michael/Michael/aldol domino reaction.

In 2013, Enders and coworkers have developed a "branched domino reaction" where, contrary to the traditional domino reaction, the starting material is used in two parallel reactions at the same time under identical conditions to generate two intermediates, which will then act as reactants in the next reaction step to form the desired product. In this work a two-component four step branched domino reaction of oxindole-derived spirocyclic compounds was developed through an asymmetric organocatalytic cascade of a double Michael addition with parallel oxidation, using 2-Iodoxybenzoic acid (IBX) as oxidant agent, and a final aldol condensation. Both the enamine nucleophile and the iminium electrophile are derived from the same aldehyde (**Scheme 32**).[51]

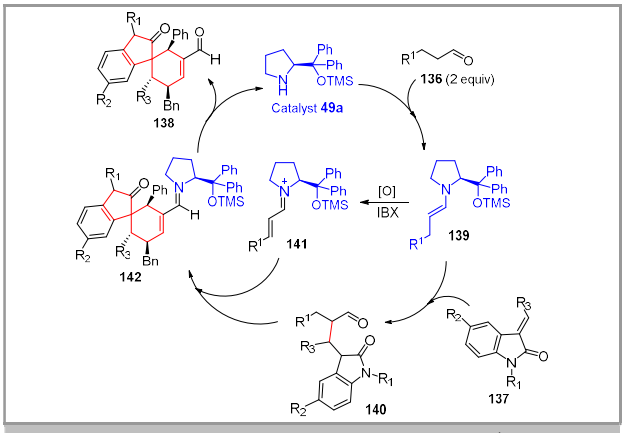


Scheme 32 Double Michael/aldol domino reaction.

The reaction of aldehyde **136** with 2-(2-oxoindolin-3-ylidene) acetate derivatives **137** afforded oxindole-derived spirocyclic

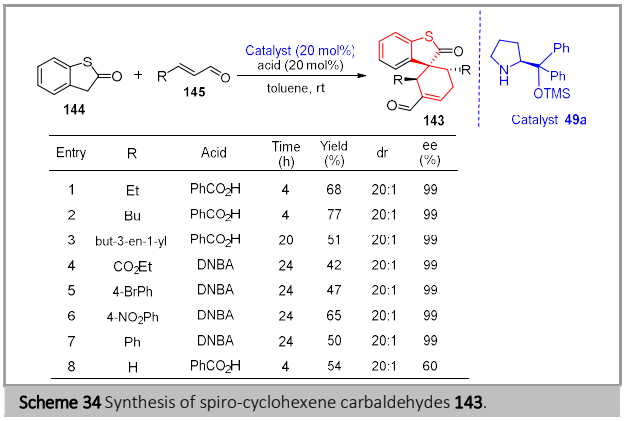
compounds **138** in good yields and with excellent diastereo- and enantioselectivities. The absolute configuration of the spiro compound **138** with R_1 = Me, R_2 = H and R_3 = CO_2Et was confirmed by crystallography.

The mechanisms suggest that aldehyde **136** first react with amine catalyst **49a** to form a correspondent enamine **139** as intermediate, which performs a Michael addition with 2-(2-oxoindolin-3-ylidene) acetate **137**, leading to adduct **140**. Simultaneously, enamine **139** is oxidized to the corresponding iminium ion **141**, which reacts as a Michael acceptor with **140** to form intermediate **142** through aldol condensation. Finally, hydrolysis leads to product **138** and release of the catalyst (**Scheme 33**).



Scheme 33 The proposed mechanisms to double Michael/aldol domino reaction.

In the same year, Veselý and coworkers described a double Michael-aldol domino reaction to afford the spiro-cyclohexene carbaldehydes **143** in good yields (up to 68%) and with excellent selectivities (dr 20:1, up to 99% ee) through reaction between benzothiophen-2-one **144** and enals **145** in the presence of a secondary amine catalyst **49a** (**Scheme 34**).[52]

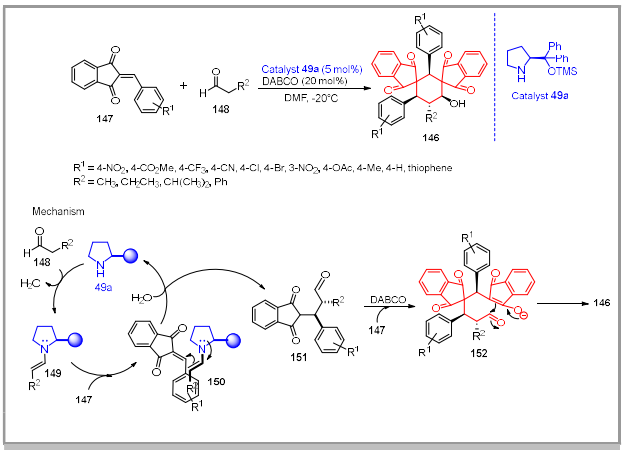


Entry	R	Acid	Time (h)	Yield (%)	dr	ee (%)
1	Et	$PhCO_2H$	4	68	20:1	99
2	Bu	$PhCO_2H$	4	77	20:1	99
3	but-3-en-1-yl	$PhCO_2H$	20	51	20:1	99
4	CO_2Et	DNBA	24	42	20:1	99
5	4-BrPh	DNBA	24	47	20:1	99
6	4-NO_2Ph	DNBA	24	65	20:1	99
7	Ph	DNBA	24	50	20:1	99
8	H	$PhCO_2H$	4	54	20:1	60

Scheme 34 Synthesis of spiro-cyclohexene carbaldehydes **143**.

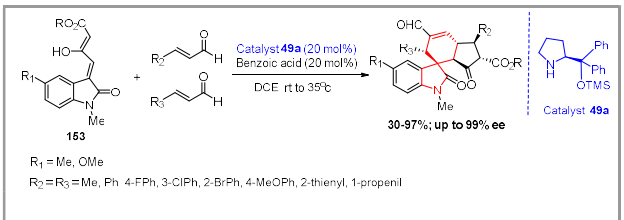
In almost all cases, the stereoselectivity of the reaction were excellent, only unsubstituted acrylaldehyde exhibited a lower selectivity with 60% ee. Aliphatic enals reacted quickly with moderate-to-good yields with benzoic acid as the acidic additive, but, with electron-withdrawing group (R = CO_2Et), benzoic acid appeared to be inefficient, and the use of a stronger acid additive (2,4-dinitrobenzoic acid, DNBA) was required.

An efficient Michael-Michael-aldol reaction was developed for the synthesis of dispirocyclohexanes **146** from 2-arylideneindane-1,3-diones **147** and aldehydes **148**. The spirocycles were obtained in reasonable-to-good chemical yields and with high stereoselectivities (>95: 5 dr and up to 99% ee) using α,α-l-diphenylprolinol trimethylsilyl ether **49a** as catalyst and DABCO in DMF at −20°C (**Scheme 35**).[53] According to the mechanism proposed by the authors and presented in **Scheme 35**, initially the formation of nucleophilic enamine **149** occurs through the reaction between the catalyst **49a** and the aldehyde **148**. Then, the enamine **149** undergoes the addition of Michael with the 2-arylideneindane-1,3-dione **147** from the *si*-face to give intermediate **150**, which in turn, in the presence of DABCO, is converted into the nucleophilic enolic species **151** and reacts with the second 2-arylidenoindane-1,3-dione **147** to provide diindane-1,3-dione aldehyde **152**. Finally, an intramolecular aldol reaction occurs, giving rise to the compound of interest.



Scheme 35 Synthesis of dispirocyclohexanes **146**.

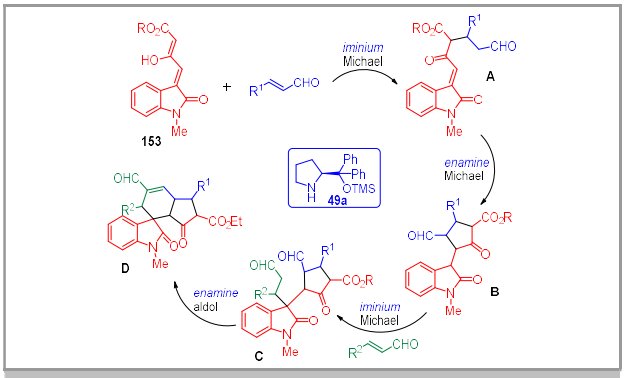
Still using catalyst **49a** the Chen research group developed quadruple aminocatalytic domino sequences to fused carbocycles, where the steps involved are three Michael-aldol reactions.[54] In this work the efficient assembly of hydroindane derivatives incorporating a spirooxindole motif, was realized via domino reaction between (E)-4-(1-methyl-2-oxoindolin-3-ylidene)-3-oxobutanoates **153** and two molecules of α,β-unsaturated aldehydes. The complex products bearing six contiguous stereogenic centers were obtained in excellent stereoselectivities (96->99% ee, >99% dr). After reaction conditions optimization, methodology scope was tested as shown in the **Scheme 36**.



Scheme 36 Triple Michael/aldol domino reaction.

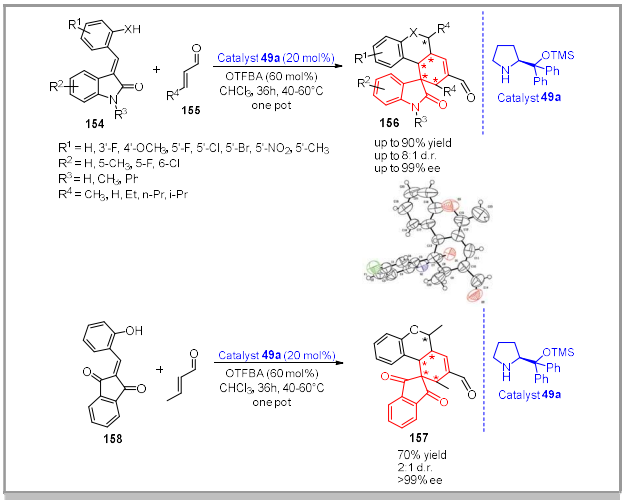
The mechanism, a quadruple iminium-enamine-iminium-enamine catalysis of chiral secondary amine is described in the **Scheme 37**. The authors further highlighted that intermediate B

could be applied in a highly diastereoselective Michael addition/Henry reaction with nitroolefins.



Scheme 37 Quadruple iminium-enamine-iminium-enamine mechanism.

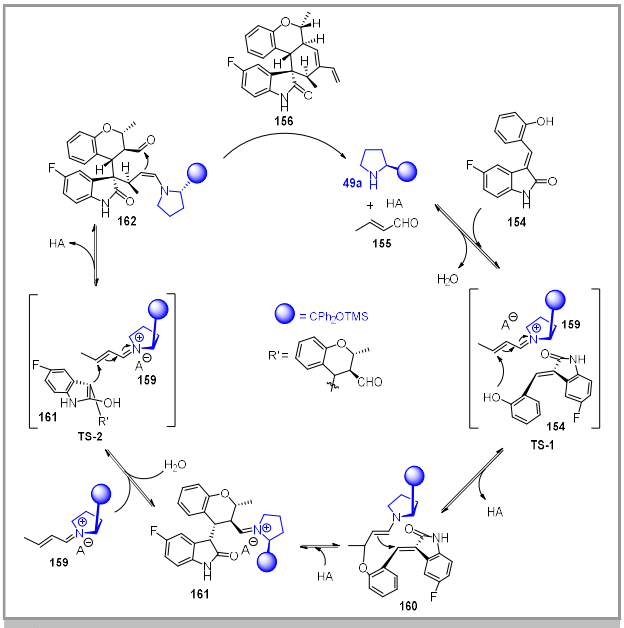
Wang research group also developed an asymmetric organocatalytic quadruple domino reaction of (*E*)-3-(2-hydroxybenzylidene)oxindole derivatives **154** and two molecules of α,β-unsaturated aldehyde **155** under quadruple iminium–enamine–iminium–enamine catalysis for the synthesis of highly functionalized polycyclic spiro-fused carbocyclicoxindoles **156** (**Scheme 38**).[55] The products bearing a spiro quaternary center and five contiguous stereocenters were obtained in moderate to high yields (up to 90%) with good diastereoselectivities (up to 8:1) and excellent ee values (up to 99% ee). In addition, expanding the scope of the substrate, it was possible to obtain spiro derivatives **157** from indanedione **158** (**Scheme 38**). These derivatives showed moderate antitumor activities in the micromolar range.[55]



Scheme 38 Synthesis of highly functionalized polycyclic spiro-fused carbocyclicoxindoles **156** and **157**.

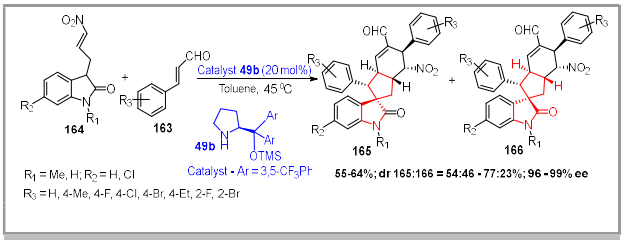
The structure and absolute configuration of the products were confirmed by NMR spectroscopy and single crystal X-ray analysis and a possible mechanism was proposed for understanding the stereochemistry observed (**Scheme 39**). In the first oxo-Michael addition step of the domino reaction, the activated iminium**159** is attacked on its *re*-face by the hydroxyl group of **154** (TS-1) generating intermediate enamine **160,** which, through an intramolecular Michael addition, provide the intermediate **161**.

This intermediate, act as nucleophile in a third Michael addition, attacking the *re*-face of another molecule of **159** (TS-2). The third Michael addition step leads to intermediate **162**, which reacts through an intramolecular aldol condensation providing product **156** and regenerating the catalyst.



Scheme 39 Plausible reaction mechanism.

In a similar work, Hong and coworkers demonstrated an organocatalyzed enantioselective triple Michael-aldol domino reaction for the construction of cyclopentane fused spirooxindoles with six contiguous stereocenters including a quaternary center, in good yields with excellent enantioselectivities (**Scheme 40**). [56]

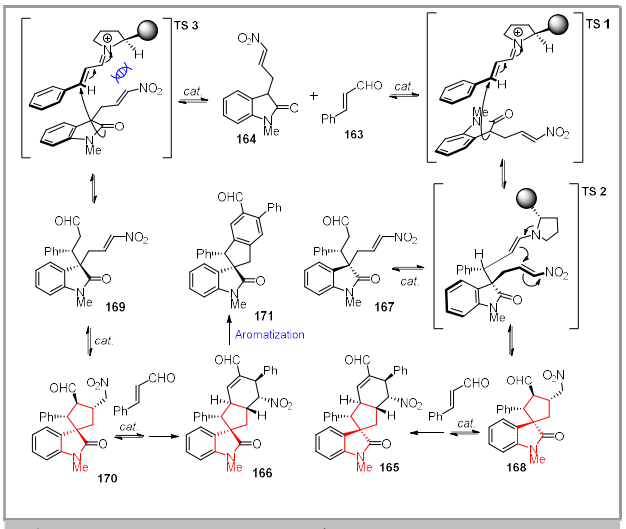


Scheme 40 Synthesis of cyclopentane fused spirooxindoles.

With the optimized conditions in hand, the domino reactions, between enal **163** and nitrooxindole **164**, were explored. It was observed that the reaction of enal with the halogen substituents and oxindole where R_1 = Me, required a slightly longer time for the reaction to be completed. It is noteworthy that this four-step cascade reaction would potentially generates six new chiral centers, but only two diastereomers, **165** and **166** in ca. 7:3 ratio with excellent enantiomeric excesses (96 to >99% ee), were observed in this domino reaction.[56]

The proposed mechanism for the reaction starts with conjugate addition of oxindole **164** to enal **163** through the iminium activation process (TS-1) to generate intermediate **167** (**Scheme 41**). Then, conjugate addition of enamine-activated aldehyde **167** to nitroalkene (TS-2), to afford the *trans*-substituted

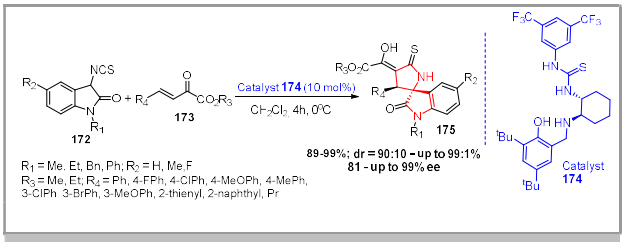
cyclopentane **168**. A later intermolecular conjugate addition of nitroalkane **168** to cinnamaldehyde, and the subsequent intramolecular aldol condensation, would provide product **165**. The concurrent path initiated by Michael addition of oxindole **164** to enal **163** via transition state TS-3, which is less favorable than TS-1 due to steric hindrance, would give intermediate **169**. Subsequent double Michael-aldol condensation reaction provides the corresponding product **166** as the minor product.[56]



Scheme 41 Mechanism of triple Michael/aldol in the synthesis of cyclopentane fused spirooxindoles.

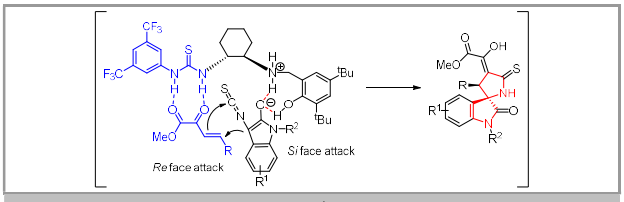
2.1.4 Domino Michael-Cyclization process

Recently Chen research group published a reaction between 3-isothiocyanato oxindoles **172** and β,γ-unsaturated α-keto esters **173** catalyzed by a chiral thiourea organocatalyst **174** via a domino Michael-cyclization process, to offer a range of 2'-thioxospiro[indoline-3,40-oxazolidin]-2-one compounds **175**, with anti-inflammatory activities in high yields and good stereoselectivities (**Scheme 42**).[57] Under the optimized reaction conditions, all of the reactions showed excellent reactivity and could complete within 4 h (**Scheme 42**), however, the reactivity and stereoselectivity were affected by the incorporation of various substituents on the aryl group of β,γ-unsaturated α-keto esters. Specifically, the presence of substituents at the meta positions of the aryl group brought about some decrease of enantioselectivity.



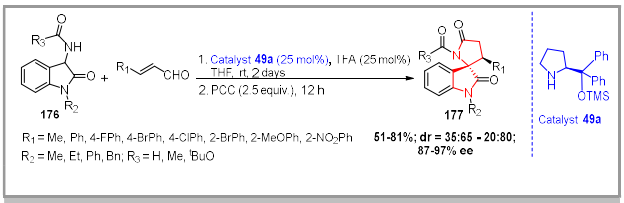
Scheme 42 Domino Michael-cyclization process in the synthesis of **175.**

A possible dual activation model to explain the stereochemistry of the domino Michael-cyclization reaction was proposed by the authors (**Scheme 43**).



Scheme 43 Mechanism of triple Michael/aldol in the synthesis of cyclopentane fused spirooxindoles.

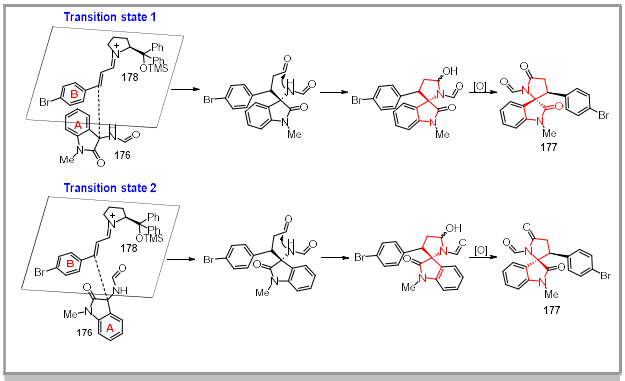
Another example of Michael-cyclization domino reaction, was described by Wang and coworkers where the first organocatalytic enantioselective Michael-cyclization domino reaction between 3-amideoxindoles **176** and α,β-unsaturated aldehydes was realized. After sequential oxidation, with pyridinium chlorochromate, highly sterically hindered spirocyclic oxindole-γ-lactams **177** in 51–81% yields with 87–97% ee and ≤80-20 dr (**Scheme 44**).[58] The acidity of additives had effects on yields and stereoselectivities, the best results were obtained with TFA. A lower temperature improves the stereoselectivities, while the yields significantly dropped. The evaluation of the effect of the substituents on aromatic rings of α,β-unsaturated aldehydes in different positions, show that electronic characteristics are indifferent and provided the desired products. Substituents on nitrogen atoms of oxindoles and the electronic properties of the substituents on amides also affect yields and stereoselectivity.



Scheme 44 Domino Michael-cyclization process in the synthesis of **177**.

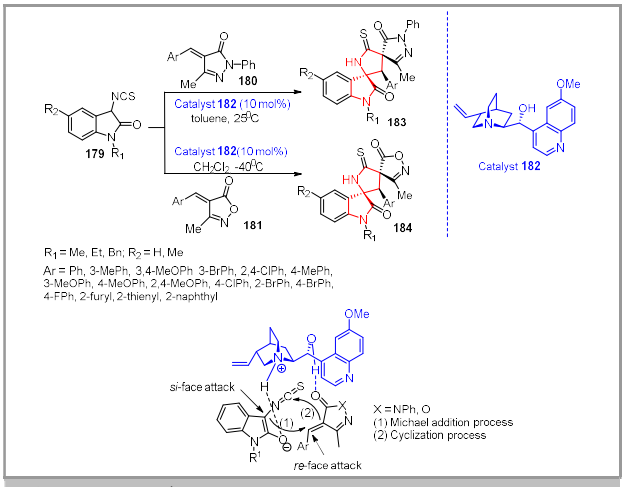
Based on experimental results, a plausible mechanism was proposed and is illustrated in **Scheme 45**. Cinnamaldehyde derivatives was first activated by catalyst **49a** in the presence of acid additives to form iminium ion **178** that reacted with 3-amideoxindole **176** via transition state 1, to afford major product **177**. However, it should be noted that in transition state 1 aromatic ring A expriences a considerable steric hindrance with aromatic ring B, while in transition state 2 aromatic ring A has some steric repulsion with the OTMS and the hindrance with aromatic ring B is released effectively. The comparable two TS account for the low diastereoselectivity.

An efficient organocatalytic diastereo- and enantioselective method for the construction of spirocyclic oxindole derivatives bearing two spiro quaternary centers and three consecutive stereocenters via a domino Michael-cyclization process has been developed by Yuan and coworkers.[59] The reactions of 3-isothiocyanato oxindoles **179** with unsaturated pyrazolones **180** and unsaturated isoxazolones **181**, was catalyzed by commercially available quinine **182** to form two classes of spirocyclic oxindole compounds **183** and **184.**



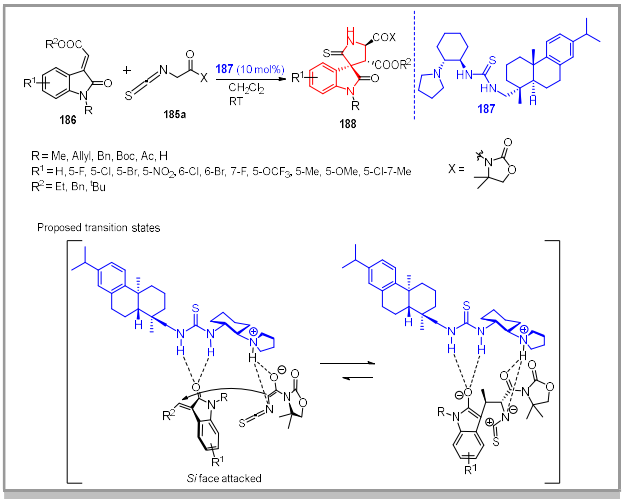
Scheme 45 Proposed transition state for synthesis of **177**.

A plausible dual activation working model was tentatively proposed to rationalize the stereochemistry of the domino Michael-cyclization process (**Scheme 46**).



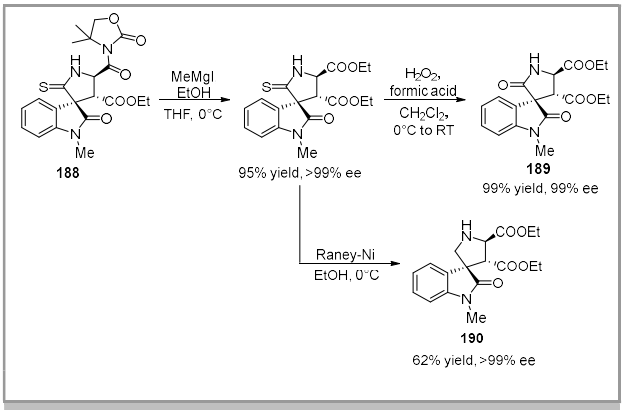
Scheme 46 Michael/cyclization process in the synthesis of **183** and **184**.

An efficient organocatalyzed asymmetric Michael-cyclization reaction sequence of α-isothiocyanato imides **185**, with various methyleneindolinones **186**, using **187** as the catalyst and mild reaction conditions, was developed by Wang research group for the synthesis of 3,3′-thiopyrrolidonyl spirooxindole compounds **188** (**Scheme 47**).[60] Generally, the products was obtained with excellent yield values (up to 99%), diastereoisomeric ratio (>20:1) and enantiomeric excess (>99%), however, the increase in stereo impedance by a bulkier ester group from methyleneindolinone, caused a decrease in the diastereoisomeric ratio of the products (16: 1 and 7: 1) and in the activity of the reactions, that required longer reaction times. The absolute and relative configurations of the spirooxindoles were determined by X-ray crystallography. The authors proposed a model to explain the stereochemistry of the reaction (**Scheme 47**). Methyleneindolinone is activated by hydrogen bonds between the carbonyl group in the indolinone and the thiourea hydrogen atoms of the catalyst; the α-isothiocyanato imide is enolized by deprotonation at its α-carbon atom by the tertiary amine. Thus, the *re*-face of the enolate nucleophilically attacks the *si*-face of the double bond of methyleneindolinone. Subsequently, the enolate generated in methyleneindolinone makes a C-nucleophilic attack on the electron deficient carbon of α-isothiocyanate imide, leading to the spiro compound with the 3*R*, 4′*R*, 5′*R* configuration obtained experimentally.



Scheme 47 Michael/cyclization process in the synthesis of **188**.

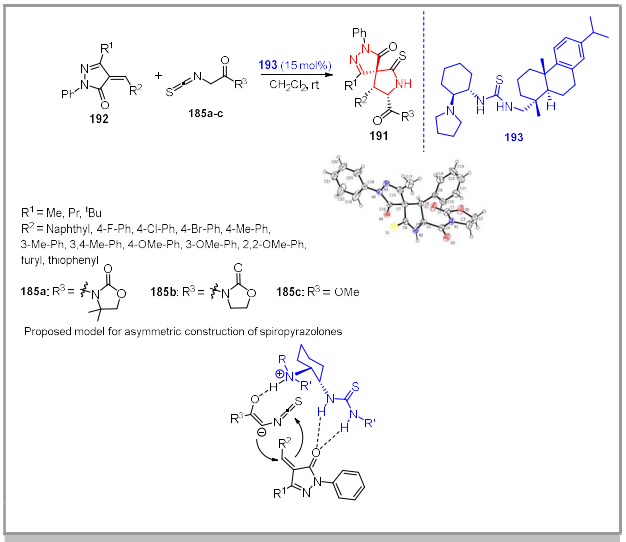
In addition, the authors also converted the 3,3′-thiopyrrolidonyl spirooxindoles **188** to 3,3′-pyrrolidonyl spirooxindoles **189**, in nearly quantitative yield without loss of diastereo- and enantioselectivity, and 3,3′-pyrrolidinyl spirooxindoles **190** in moderate yield without change in dr and ee values, as shown in **Scheme 48**.



Scheme 48 Transformation of the 3,3′-thiopyrrolidonyl spirooxindoles **188** into pyrrolidonyl **189** and pyrrolidinyl spirooxindoles **190**.

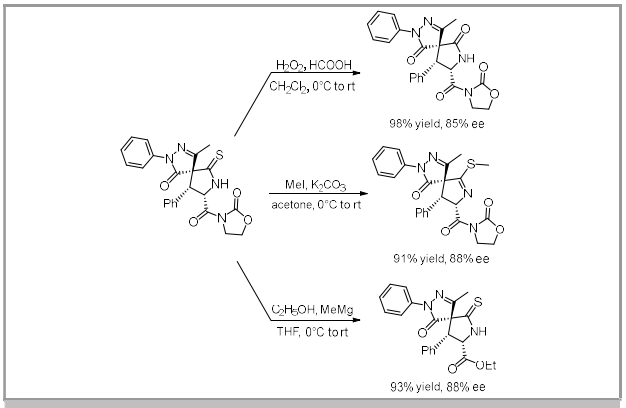
Wang and coworkers also disclosed the synthesis of highly optically active spiropyrazolones **191** through an organocatalyzed asymmetric Michael-cyclization sequence of α-isothiocyanato imides **185a-c** with various unsaturated pyrazolones **192** using **193** as catalyst (**Scheme 49**).[61] The spiro compounds were obtained with high levels of enantio- and diastereoselectivity (up to 20:1 dr and 99% ee), except when a bulkier 1-naphthyl group was introduced into R^2 (in this case only 4:1 dr, 72% yield and 81% ee were obtained). When 2-furyl-substituted pyrazolone was used, lower values of yield (71%), enantiomeric excess (73%) and diastereoisomeric ratio (4:1) were also obtained. In addition, the results suggested that the rigid skeleton of the isoxazolidinone functional group in R^3 is necessary for stereocontrol in this reaction, because when methyl isothiocyanate acetate was employed, the product was

obtained with only 71% ee and 3:1 dr. A model for asymmetric construction of spiropyrazolones is proposed in the **Scheme 49**. The absolute and relative configurations of this kind of spiropyrazolones were determined by X-ray crystallography of one of the synthesized compounds.



Scheme 49 Synthesis of spiropyrazolones **191.**

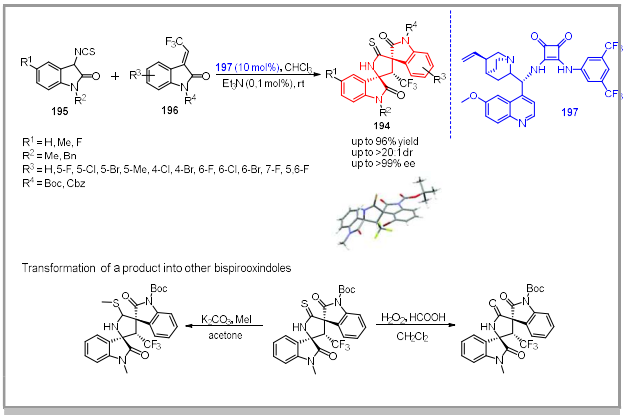
The transformation of the spiropyrazolone skeletons to a number of valuable compounds was performed, as illustrated in **Scheme 50**. Preliminary studies on the cytotoxicity of some of the synthesized compounds toward the human T-cell leukemia cell line (jurkat), human cervical cancer cell line (Hela), and human bladder cancer cell line (5637) proved to be promising.



Scheme 50 Construction of Other Chiral Spiropyrazolones Frameworks.

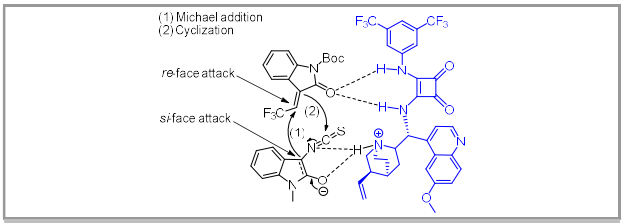
Bispirooxindoles **194** were synthesized by Lu and coworkers from an efficient asymmetric Michael-cyclization domino reaction of 3-isothiocyanato oxindoles **195** with 3-trifluoroethylidene oxindoles **196** (**Scheme 51**). The products were conveniently constructed in a highly stereoselective manner (up to 96% yield, >20 : 1 dr and >99% ee), under bifunctional organocatalysis with a cinchona alkaloid **197** derived squaramide catalyst.[62] An additional scaled-up experiment showed that this reaction could be performed on the gram scale, and although the yield decreased slightly, the diastereoselectivity and the enantioselectivity (86% yield, >20 : 1 dr and >99% ee) were maintained.

The synthetic utility of this domino reaction was illustrated by converting one of the products into others functionalized 3′-trifluoromethyl substituted 3,2′-pyrrolidinyl-bispirooxindoles, as shown in **Scheme 51**. The absolute configuration of the products were determined by analogy to X-ray crystallographic analysis of one of the compounds.



Scheme 51 Construction of bispirooxindoles **194** through a Michael/cyclization process.

Based on the experimental results and the literature, the authors have proposed a plausible bifunctional transition state, which is shown in **Scheme 52**. The squaramide moiety of the catalyst forms two hydrogen bonds with the carbonyl group of the 3-trifluoroethylidene oxindole. Meanwhile, the tertiary amine moiety deprotonates and activates the 3-isothiocyanato oxindole through a double hydrogen bonds. Thus, in the Michael addition step, the activated 3-isothiocyanato oxindole (*si*-face) attacks the β-position (*re*-face) of the 3-trifluoroethylidene. Subsequently, in the cyclization step, the α-position of the 3-trifluoroethylidene approaches the –NCS group of the 3-isothiocyanato oxindole resulting in the desired spirocyclic oxindole product with fixed stereochemistry.



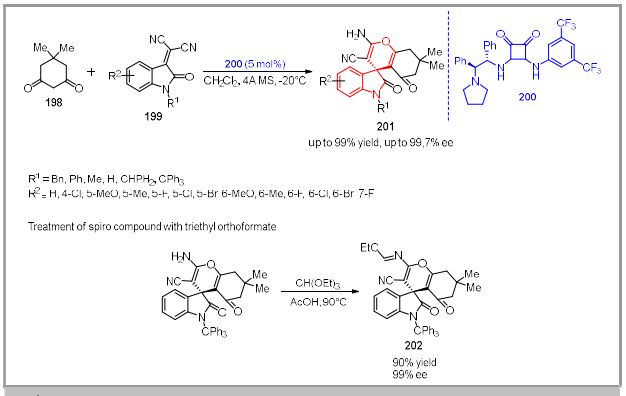
Scheme 52 Proposed transition state of the Michael/cyclization domino process.

Highly functionalized bispirooxindoles bearing three contiguous stereogenic centers with two quaternary stereocenters were also synthesized by Xiao and coworkers in almost quantitative yields (up to 99%) and with extremely high enantio- and diastereoselectivities (>99% ee, >95:5 dr, respectively), through an organocatalytic asymmetric Michael addition-cyclization domino reaction (formal [3+2] cycloaddition) of ylideneoxindoles with isothiocyanato oxindoles.[63]

A series of chiral multi-functionalized tetracyclic spiro[chromeno[3,4-*c*]pyrrole-1,3′-indoline] derivatives with four vicinal chiral carbon centers, including two quaternary stereocenters, were successfully prepared by Xie and coworkers also through an asymmetric Michael addition/cyclization sequence between 3-isothiocyanato oxindole and various 3-nitro-2H-chromene derivatives in moderate to good enantioselectivities (up to 84% ee), employing a bifunctional thiourea as organocatalyst.[64]

Isatylidene malononitriles have been widely used as starting material in the construction of spirooxindole derivatives through domino Michael-cyclization sequences. Wu and coworkers, for example, developed a highly enantioselective Michael/cyclization domino reaction between dimedone 198 and isatylidene malononitriles **199** organocatalyzed by a chiral tertiary amine-squaramide **200** for the synthesis of chiral spiro[2-amino-4H-pyran-oxindole] derivatives **201** (**Scheme 53**).[65] The products were obtained in excellent yields (97–99%) with excellent enantioselectivities (up to > 99% ee). The study of the substrate scope revealed that the substituents on the nitrogen atom of isatylidene malononitriles significantly influenced the enantioselectivity (6-98% ee) and the N-trityl substrate yielded the best result (98% ee). The different N-trityl isatylidene malononitriles were tolerated to the reaction, providing 94–99.7% ee values.

The synthetic utility of this work was demonstrated by a gram-scale construction of a spiro compound under the optimized reaction conditions. The reaction was achieved in 99% yield with 98% ee. Treatment of chiral product with triethyl orthoformate in the presence of acetic acid at 90 °C afforded imine **202** in 90% yield with 99% ee (**Scheme 53**).



Scheme 53 Synthesis of chiral spiro[2-amino-4H-pyran-oxindole] derivatives **201**.

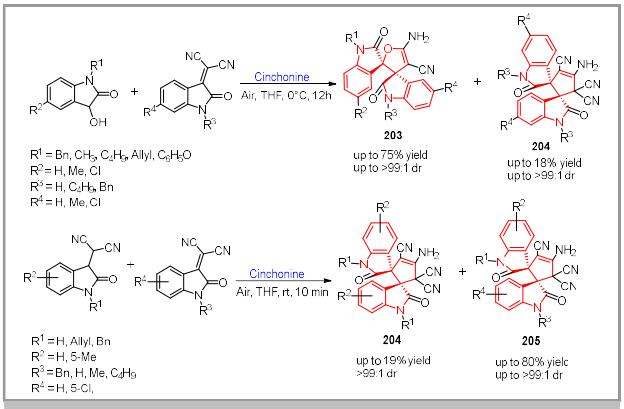
In addition, the one-pot three components reaction of dimedone, malononitrile and N-trityl isatin was carried out under the same reaction conditions, but using 10 mol% of the catalyst and increasing the temperature to 0°C. In this case, the reaction occurred through a Knoevenagel/Michael/cyclization domino sequence, providing the desired product with 96% yield and 95% ee.

Wu research group developed three other works also using isatylidene malononitriles in the construction of spirooxindole derivatives through organocatalyzed domino Michael cyclization reactions with acyclic β,γ-unsaturated amides,[66a] pyrazolones[66b] and α-cyano ketones.[66c] Good yields and stereoselectivities were achieved in all of them.[66]

Similarly, Wang and coworkers reported an organocatalytic asymmetric domino Michael/cyclization sequence of 2-hydroxynaphthalene-1,4-diones to isatylidene malononitriles, which provided the spiro[4H-benzo[g]chromene-indoline] derivatives in up to 99% yield with up to 99% ee. To verify the utility of these products, a transformation was performed generating a spiropolyheterocyclic compound in moderate yield without loss of enantioselectivity (> 99% ee). The evaluation of the biological activity of the spiro [benzo[g]chromene-indoline] derivatives showed excellent antiproliferative activity against cancer cell lines, with an inhibition rate ranging from 93% to 99% at a concentration of 50 μM.[67]

Chiral spirooxindole-pyranopyrimidines was synthetized by Wang and coworkers through an asymmetric strategy *via* organocatalyzed Michael cyclization reaction using isatylidene malononitriles as substrate. Several of the new spiro alkaloids obtained showed significant antiproliferative activity of various cancer cells, which suggested that such compounds can serve as a potential chemotherapeutic agents.[68]

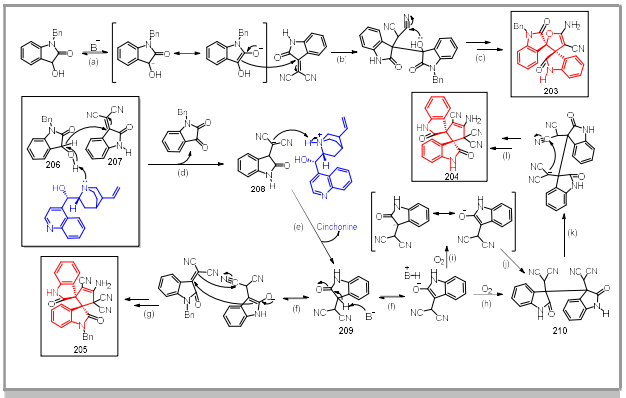
Xie and collaborators developed a facile and mild synthesis of bi-spirooxindole frameworks, including 2,3-dihydrofuranyl bi-spirooxindoles **203** and 1,5-cyclopent[2]ene bispirooxindoles 204, *via* a Michael addition-cyclization and an unexpected redox-oxidative coupling-cyclization to afford 1,5-cyclopent[2]ene bispirooxindoles **205** (**Figure 54**).[69] Both domino reactions used simple and available starting materials, in addition they presented good tolerance to a range of functional groups for the production of substituted bispirooxindole frameworks in moderate to good yields with excellent diastereoselectivities.



Scheme 54 Synthesis of 2,3-dihydrofuranyl bispirooxindoles **203** and 1,5-cyclopent[2]ene bispirooxindoles **204** and **205**.

A possible mechanism for the Michael addition-cyclization reaction and for the unexpected oxidative coupling-cyclization is shown in **Scheme 55**. The deprotonation of **206** by cinchonine catalyst followed by a domino Michael intramolecular cyclization-proton transfer, formed the 2,3-dihydrofuranyl bi-spirooxindole **203** (a-c). On the other hand, for the formation of compound **205**, initially compound **206** was deprotonated by cinchonine and then a hydride was transferred to compound **207**, generating the intermediate **208** (d), which in turn was protonated giving rise to **209** (e). After that, the deprotonative

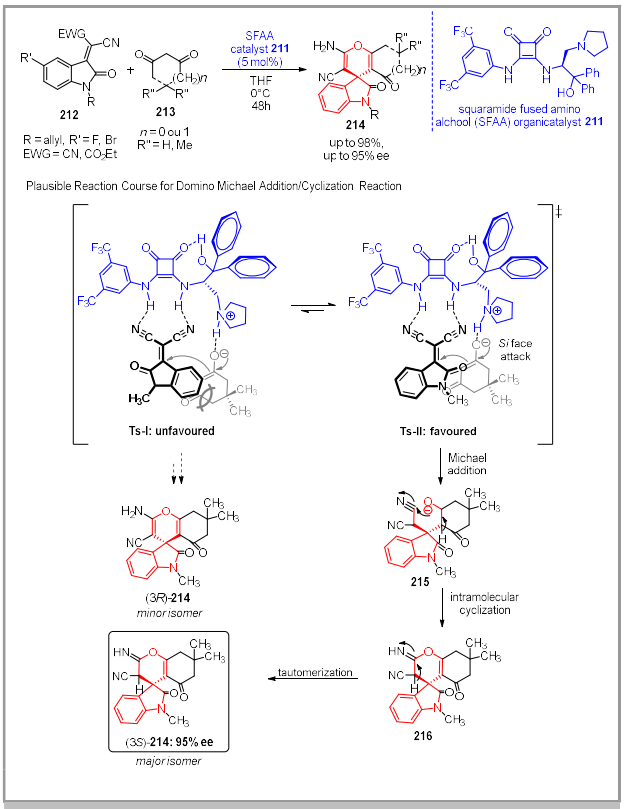
activation of **209** under basic conditions followed by a domino Michael intramolecular cyclization proton transfer, formed compound **205** (f-g). Simultaneously, an unexpected oxidative coupling (through oxidative dimerization or a radical process) gave rise to intermediate **210** (h-j), which after an intramolecular cyclization proton transfer (k-l) provided compound **204** under basic conditions.



Scheme 55 Proposed mechanisms.

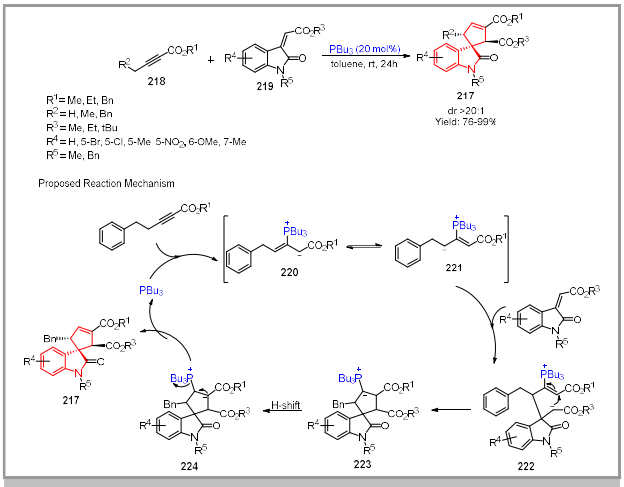
A hybrid-type squaramide-fused amino alcohol **211** containing both a Brønsted basic site and hydrogen-bonding sites in the molecule was used by Nakano and coworkers as organocatalyst in the enantioselective domino Michael addition-cyclization reaction of oxoindolines **212** with cyclic 1,3-diketones **213** to afford the chiral spiro-conjugated oxindoles featuring 2-aminopyrans fusing with carbo-heterocyclic ring systems **214** with excellent chemical yields (up to 98%) and enantioselectivities (up to 95% ee) (**Scheme 56**).[70]

The reaction of N-methyl-oxoindoline with acyclic 1,3-diketones provided the products as racemates in good chemical yields (72-81%). The products of the reactions between dimedone and 2-(5-bromo-1- methyl-2-oxoindolin-3-ylidene) malononitrile or ethyl (*E*)-2-cyano-2-(1-methyl-2-oxoindolin-3-ylidene) acetate were also obtained as racemates with yields of 92% and 81%, respectively. The reasons for these observations were not clear to the authors, however the plausible course for the reaction was proposed as shown in **Figure 56**. The active methylene proton of dimedone is abstracted by basic tertiary nitrogen in the pyrrolidine ring of **211**, and the generated enolate species forms hydrogen bond with ammonium site of **211**. In turn, the oxoindoline is fixed to catalyst through two hydrogen-bonding interactions of cyano groups with two amino hydrogen atoms of the squaramide part of the catalyst. Among the two possible transition states (TS-I and TS-II), the Michael addition can occur through TS-II, which has less steric interactions between the substrate and the enolate. Therefore, enolate attacks the electrophilic olefin site of oxoindoline on the *si* face, providing the chiral Michael adduct **215**. Posteriorly, an intramolecular cyclization leads to the formation of intermediate **216**, whose tautomerization might afford the formation of (3*S*)-**214** as the major enantiomer.



Scheme 56 Synthesis of chiral spiro-conjugated oxindoles **214**.

Spiro-(cyclopentene) oxindoles **217** containing three contiguous stereocenters, including the quaternary stereogenic center joining the two rings have been synthesized by Miao and coworkers through a phosphine-catalyzed [3 + 2] annulation of isatin-derived α,β-unsaturated ketones **218** with alkynoates **219** (**Scheme 57**).[71] This reaction afforded the desired products in high to excellent yields (up to 99%) with high regioselectivity and from moderate to high diastereoselectivities (up to 20:1).

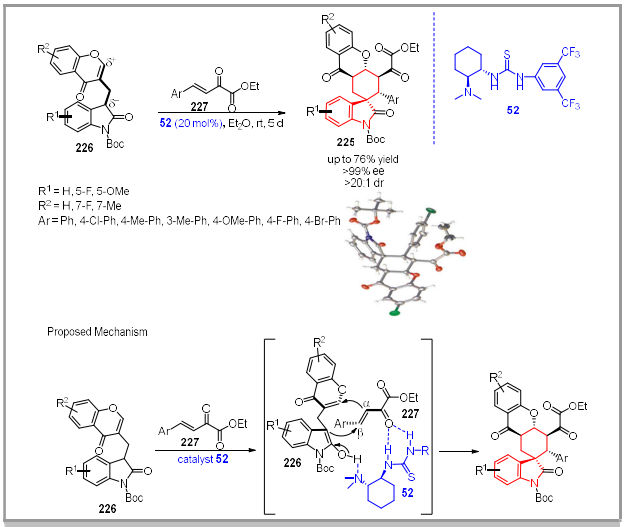


Scheme 57 Synthesis of Spiro-(cyclopentene) oxindoles **217**.

According to the authors the catalyst phosphine reacts with alkynoate to produce the zwitterionic intermediate **220**, which can isomerize to intermediate **221**. In turn, intermediate **221** undergoes a Michael addition to generate the intermediate **222**,

which further undergoes an intramolecular cyclization to furnish the phosphorene **223**. Then, **223** can be converted to intermediate **224** *via* an H-shift. Releasing the phosphine, the products **217** are finally furnished.

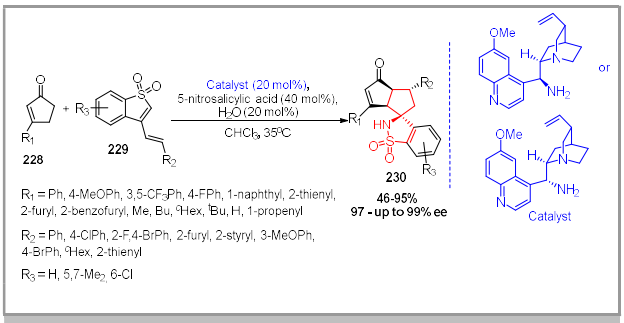
An asymmetric Michael annulation process was recently employed by Zhou and coworkers for the synthesis of structurally diverse polysubstituted hexahydroxanthones **225** with five contiguous stereogenic centers including one spiro quaternary center in acceptable yields and diastereo- and enantioselectivities (up to 76% yield, >20:1 dr, and >99% ee). The reaction, catalyzed by the thiourea **52**, was carried out between bifunctional oxindole-chromones **226** as C_4 synthons and β,γ-unsaturated α-keto esters **227** as C_2 synthons under mild conditions (**Scheme 58**).[72] The absolute configurations of the products were assigned by analogy to the configuration determined for one of the compounds by single-crystal X-ray analysis. A plausible reaction mechanism was proposed by the authors based on the experimental results obtained (**Scheme 58**). The substrate **226** is activated by protonation from the chiral tertiary amine moiety of the catalyst. Meanwhile, the carbonyl bond of substrate **227** is activated by hydrogen-bonding interaction with the thiourea group of the catalyst. Then, the γ-position of the electrophilic substrate **227** is attacked at the *Re* face by the activated enolated substrate **226** from the *Si* face. Finally, the *Si* face of the electron-deficient chromone moiety is attacked by the *Si* face of the carbon anion intermediate, to afford the expected product. In addition, scale-up demonstrated the applicability of this protocol.



Scheme 58 Synthesis of polysubstituted hexahydroxanthones **225**.

2.1.5 Domino Michael-Mannich reaction

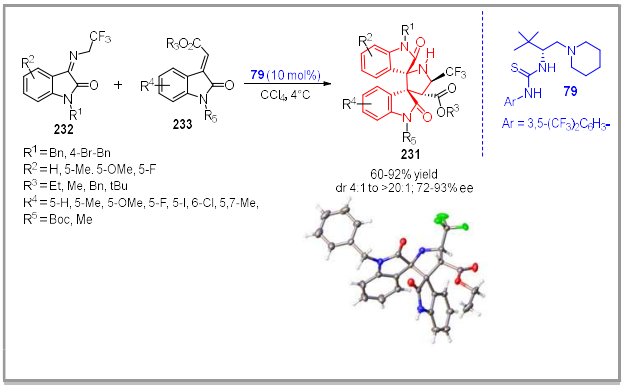
In the first example, a domino α'-regioselective Michael addition γ-regioselective Mannich reaction to give fused or bridged architectures with a spirocyclic skeleton was provided by Chen and coworkers.[73] With the optimal reaction conditions, a variety of 2-cyclopentenones **228** and 3-vinyl-1,2-benzoisothiazole-1,1-dioxides **229** were tested in reactions promoted by 9-amino-9-deoxyepiquinine or 9-amino-9-deoxyepiquinidine in combination with 5-nitrosalicylic acid as additive (**Scheme 59**). The spiro compounds **230** were obtained in good yield, excellent enantiomeric excess and exhibited promising anticancer activity in A549 lung adenocarcinoma epithelial, DU145 prostate cancer, Eca109 esophageal squamous carcinoma, MDA-MB-231 breast cancer and U937 leukemic monocyte lymphoma.



Scheme 59 Domino Michael-Mannich reaction in the synthesis of **230**.

Chen research group also developed a domino Michael addition–Mannich reaction between diversely structured aliphatic ketones and electron-deficient cyclic 1-azadienes, bearing a 1,2-benzoisothiazole-1,1-dioxide or 1,2,3-benzoxathiazine-2,2-dioxide motif, to afford spirocyclic architectures in excellent diastereo- and enantioselectivity. These reactions were catalyzed by a cinchona-based amine.[74]

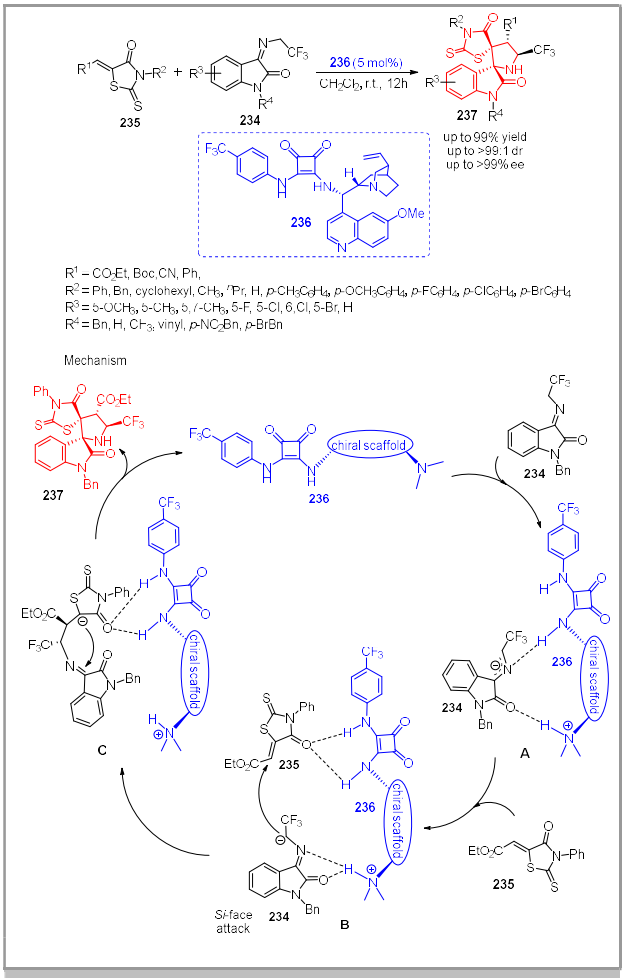
A strategy for the asymmetric synthesis of trifluoromethylated 3,3'-pyrrolidinyl-dispirooxindole derivatives **231** with four contiguous stereogenic centers, including two vicinal spiro-stereocenters, was described by Enders and coworkers.[75] Isatin ketimines **232** and isatin-derived enoates **233** was employed in the domino Michael–Mannich [3+2] cycloaddition catalyzed by a bifunctional thiourea **79** to provide the products with good yields and very high stereoselectivities (**Scheme 60**). The gram-scale reaction demonstrated the practical utility and robustness of the methodology, making it possible to obtain the desired product, whose absolute configuration was determined by X-ray crystallography. The configuration of other products were assigned by analogy.



Scheme 60 Domino Michael-Mannich reaction in the synthesis of **231**.

A highly diastereo- and enantioselective domino Michael-Mannich [3+2] cycloaddition reaction of N-(2,2,2-trifluoroethyl)isatin ketimines **234** with rhodanine derivatives **235**, in the presence of a squaramide tertiary amine catalyst **236**, was developed by Du and coworkers for the synthesis of a wide range of CF_3-containing bispiro[oxindole-pyrrolidine-

rhodanine]s **237**, as promising drug candidates for chemical biology and drug discovery (**Scheme 61**).[76] The applicability of the methodology was demonstrated from a large-scale experiment and subsequent product transformation. In mechanistic terms, initially catalyst **236** promotes the formation of transition state A, through deprotonation of the N-(2,2,2-trifluoroethyl)isatin ketamine **234**. Afterward, both **234** and **235** are simultaneously activated via hydrogen-bonding with **236**. Rhodamine **235** then undergoes Michael addition on the *Si* face by deprotonated N-(2,2,2-trifluoroethyl) isatine ketamine via transition state B. The resulting nucleophilic rhodanine anion attacks the C═N of the imine in a Mannich cyclization reaction via intermediate C, providing the desired product and regenerating the catalyst.



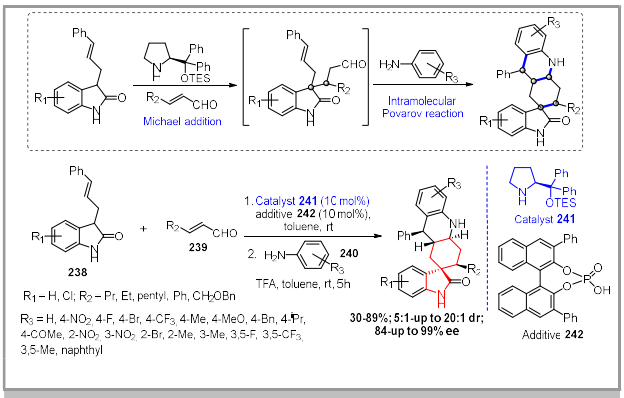
Scheme 61 Domino Michael-Mannich reaction in the synthesis of **237**.

Du's research group also developed a similar methodology for the enantioselective synthesis of biologically important CF_3-containing 3,2'-pyrrolidinyl spirooxindole dispirooxindole derivatives via a organocatalytic asymmetric domino Michael-Mannich [3+2] cycloaddition of N-2,2,2-trifluoroethylisatin ketimines and arylidene azlactones by using a hydroquinine-derived thiourea as the catalyst. The products were obtained in high yields (up to 99% yield) with excellent diastereoselectivities (>20:1 dr, in all case) and enantioselectivities (up to >99% ee).[77] A bifunctional squaramide-catalyzed one-pot three-component Michael-Mannich-Michael cyclization sequential cascade reaction was another interesting methodology recently disclosed by Du's research group for the enantioselective construction of bispirooxindole-spirooxindoles with seven stereocenters in good yields with excellent stereoselectivities (up to >20:1 dr, 99% ee).[78]

2.1.6 Miscellaneous reactions initiated by Michael

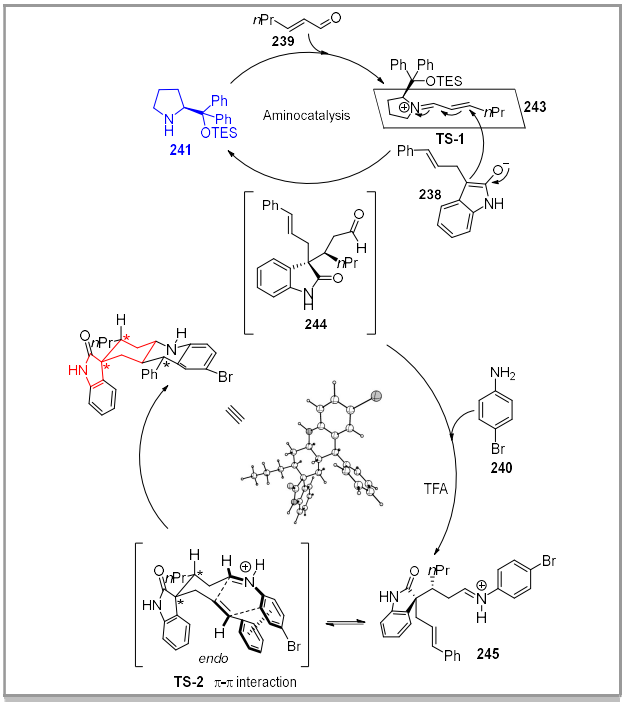
In this section examples of domino reactions that start with a Michael reaction followed by some different transformations, such as Povarov, Mannich, alkylation, acylation etc. will be presented.

An asymmetric organocatalytic one-pot procedure for the construction of spirooctahydroacridine-3,3'-oxindole scaffolds was successfully developed through domino Michael-Povarov reaction.[79] Chiral octahydroacridine (OHA) can act as gastric acid secretion inhibitors.[80] In this reaction some challenges had to be overcome: creation of four new chemical bonds and five stereocenters including a spiro quaternary center; styrene-type substrate as the dienophile component in Povarov reaction and the control of diastereo- and enantioselectivity of the products. The authors performed a study to probe the generality of domino strategy in substituted spirooctahydroacridine-3,3'-oxindole derivatives synthesis with variation of 3-substituted oxindoles 238, α,β-unsaturated aldehydes 239, and aniline derivatives **240**. The best results were obtained through organocatalysis supported by chiral secondary amines – diphenyl prolinol triethylsilyl ether (O-TES) **241** in combination with 10 mol% of additive **242** (**Scheme 62**).



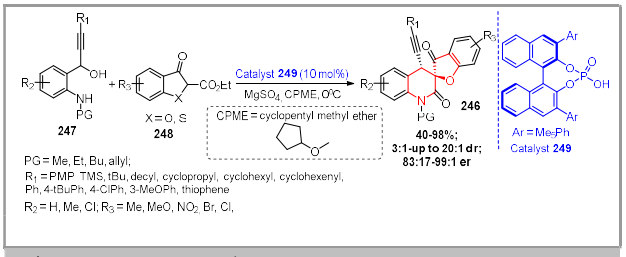
Scheme 62 Domino Michael-Povarov reaction.

The stereochemical outcome and mechanism proposed by authors is demonstrated in the **Scheme 63**. The reaction start with the nucleophilic attack of 3-substituted oxindole **238** on the iminium-activated α,β-unsaturated aldehyde **243** via TS-1. The *Re*-face under the catalyst control, by efficient shielding of the *Si*-face afforded the Michael addition adduct **244**, which then reacted with 4-bromoaniline **240** and TFA through condensation to provide iminium intermediate **245**. This intermediate underwent the intramolecular Povarov reaction through an endo transition state (TS-2), preferring the stabilized π-π stacking and chairlike conformation, to provide the spiro compound with the observed diastereoselectivity.



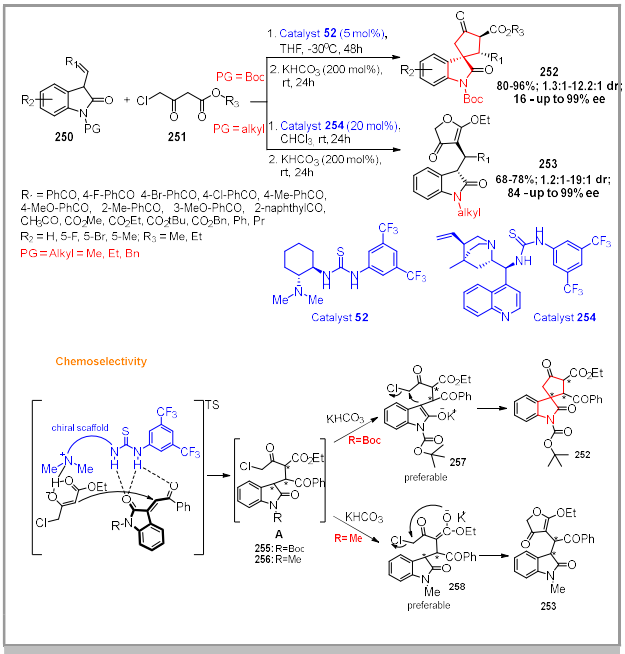
Scheme 63 Stereochemical outcome and mechanism of the domino Michael/Povarov reaction. Adapted to reference **78**.

Schneider and coworkers recently published the spirocyclic dihydroquinolones **246** synthesis from in situ generated ortho-quinone methide imines, using propargylic alcohol derivatives **247** and cyclic β-oxoesters **248** as nucleophile, through one-step domino Michael addition–lactamization. This reaction was catalyzed by chiral phosphoric acid **249** (**Scheme 64**). Mechanistic studies revealed the in situ generated chiral magnesium phosphate salt acts as the catalyst. [81]



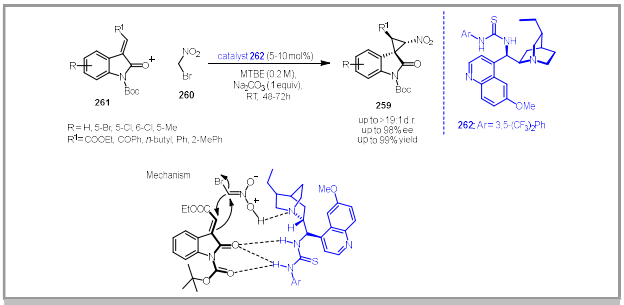
Scheme 64 Domino Michael/lactamization reaction.

Examples of a domino reaction using alkylation and acylation will be shown below. Wang research group developed an organocatalytic asymmetric domino Michael-alkylation process of methyleneindolinones **250** and γ-halogenated-β-ketoesters **251**, for the preparation of a variety of spiro-cyclopentanone oxindoles **252** in high yields, good diastereoselectivities and excellent enantioselectivities via α-alkylation (**Scheme 65**).[82] For this transformation the catalyst **52**, a tertiary-amine based on chiral thiourea, was used. Interestingly the reaction of N-alkyl protected methyleneindolinone with ethyl 4-chloroacetoacetate afforded an O-alkylated product with a tetronic acid scaffold **253**. The mechanism for different chemoselectivities is depicted in the same scheme.



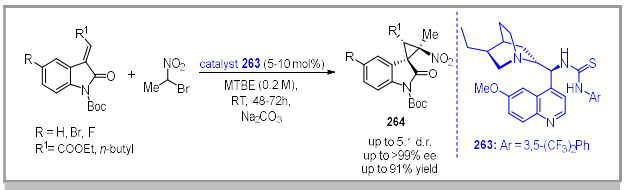
Scheme 65 Domino Michael/Alkylation reaction.

Bencivenni and coworkers developed the first enantioselective synthesis of spiro nitrocyclopropyl oxindoles **259** through a Michael addition–alkylation sequence between bromonitroalkyl derivatives **260** and *N-tert*-butoxycarbonyl (Boc)-protected 3-alkylidene oxindoles **261**. A bifunctional thiourea derivative **262** as catalyst was able to simultaneously activate the electrophilic oxindole and Michael donor halonitroalkane (**Scheme 66**).[83] According to the authors mechanistic proposal, the hydrogen bond interactions between the N-H bonds of the thiourea moiety and the imidic carbonyl groups of the oxindole place it in the proper position for nucleophilic attack on the *Si* face of the double bond, so the reaction follows the alkylation route shown in **Scheme 66**, providing the desired spiro compound with high diastereo- and enantioselectivity.



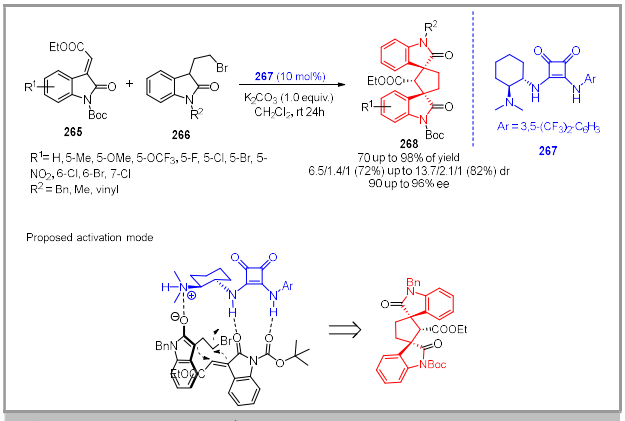
Scheme 66 Synthesis of spiro nitrocyclopropyl oxindoles **259**.

Using catalyst **263**, a diastereoismer of catalyst **262** acting as its "pseudo enantiomer", the opposite enantiomers of the spirooxindoles was obtained, as expected, with an improvement of both the diastereo- and enantiocontrol, plus a series of highly substituted spiro cyclopropyl oxindoles with two quaternary stereogenic centers **264** in an almost enantiomerically pure form in high yields, with good diastereocontrol (**Scheme 67**).



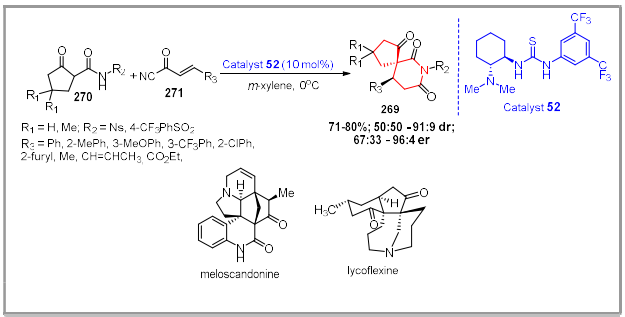
Scheme 67 Synthesis of spiro cyclopropyl oxindoles **264**.

Also using a Michael-Alkylation domino sequence between methyleneindolinones **265** and 3-substituted oxindoles **266**, catalyzed by a chiral squaramide **267** in the presence of a base. Hong and coworkers, with this method, built spirocyclopentane bioxindoles **268**, biologically important,[84] in high enantioselectivities, as shown in the **Scheme 68**. The proposed activation mode of the substrates by the catalyst is shown in the same scheme.[84]



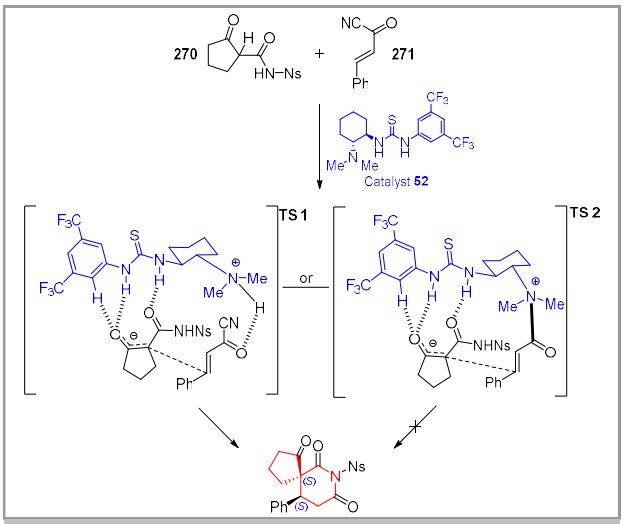
Scheme 68 Domino Michael/Alkylation reaction.

In the next example, azaspiro[4,5]decanone ring systems **269** was synthetized via a domino enantioselective organocatalysed Michael-intramolecular acylation domino sequences using ketoamide **270** α,β-unsaturated acyl cyanides **271** as bis-electrophile substrates, and Takemoto's thiourea catalyst **52** (**Scheme 69**).[85] This is one of the rare examples of direct enantioselective synthesis of glutarimide derivatives, a spirocyclic substructure found in several natural products, such as meloscandonine and lycoflexine alkaloids (see **Scheme 69**). In this reaction, the use of acryloyl cyanide (R_3=H) was not successful, and the starting ketoamide was recovered.



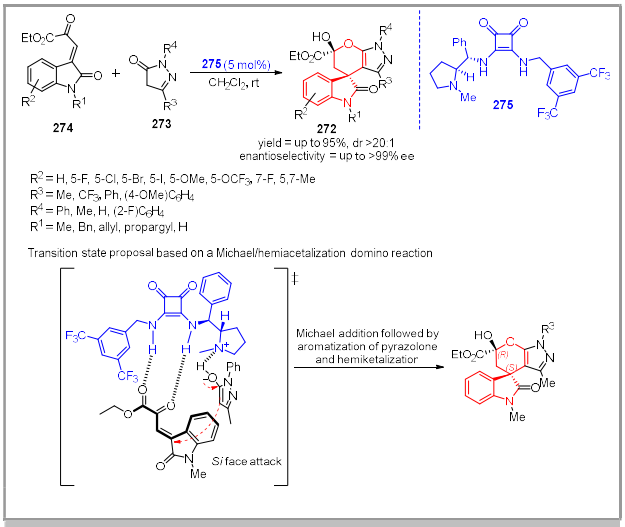
Scheme 69 Domino Michael-Acylation reaction.

Two possible activation modes could explain the observed stereochemical outcome (**Scheme 70**). The enolate of the ketoamide **270** is coordinated to the thiourea moiety in a perpendicular fashion in both transition state (TS1 and Ts2), exposing the *Re* face of the enolate to the electrophile **271**. In TS1, an activation of the α,β-unsaturated acyl cyanide **271** through hydrogen bonding with the ammonium part of the organocatalyst is proposed. In TS2, the catalyst could form a covalent bond with **271** by nucleophilic displacement of the cyanide ion. In both cases, the nucleophile would react on the *Re* face of the electrophile explaining the stereoselectivity. ^{1}H NMR studies have led the authors to propose that TS1 should be the preferred path of reaction.



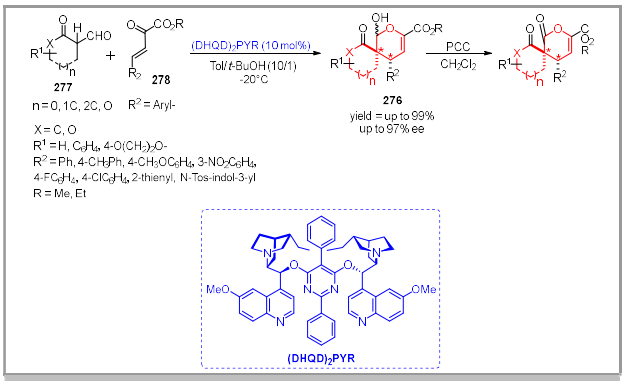
Scheme 70 Stereochemical outcome of domino Michael/Acylation reaction.

Kumarswamyreddy and Kesavan developed the first enantioselective synthesis of dihydrospiro-[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives **272** by reacting pyrazolones **273** with isatylidine β,γ-unsaturated α-ketoester **274** (**Scheme 71**).[86a] A new bifunctional squaramide organocatalyst **275** derived from L-proline was used, surpassing the widely used thioureas and squaramides in yield and stereoselectivity. The stereochemical result of the reaction was explained by a transition state proposal based on a Michael-hemiacetalization domino reaction (**Scheme 71**), in which activation of both starting materials facilitates the *Si* face attack of pyrazolone **273** to the oxindole ketoester **274** followed by aromatization of pyrazolone and hemiketalization leading to the desired product. The synthetic application of the products was explored by fluorination using fluorinating agent DAST in good diastereoselectivit and excellent enantioselectivity.



Scheme 71 Michael/hemiacetalization domino reaction.

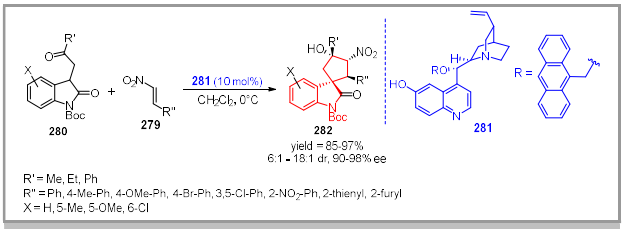
Spiro-3,4-dihydropyran structures **276** were synthesized by Ma and coworkers by a cinchona alkaloid-catalyzed domino Michael/hemiacetalization reaction of cyclic β-oxo aldehydes **277** and aromatic β,γ-unsaturated γ-keto esters **278** with high levels of diastereoselectivities and enantioselectivities (**Figure 72**).[86b]



Scheme 72 Spiro-3,4-dihydropyran structures **276** synthesized by Ma and coworkers.

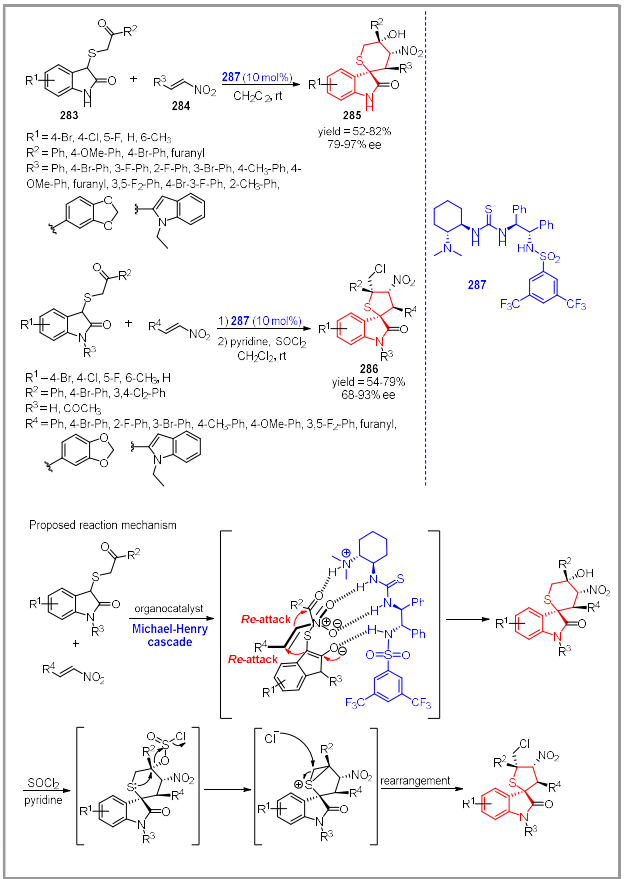
Similarly a quinidine-derived squaramide catalyzed domino Michael-hemiacetalization reaction of β-oxo aldehydes and aliphatic or aromatic β,γ-unsaturated α-keto ester was developed by the same research group also for the synthesis of Spiro-3,4-dihydropyran structures.[86c]

Starting from a Michael-Henry domino reaction between nitrostyrenes **279** and 3-substituted oxindoles **280**, organocatalyzed by a cinchona alkaloid **281**, Albertshofer, Tan and Barbas III synthesized highly substituted spirocyclopentaneoxindoles **282** in high yield and excellent enantioselectivity in a single step (**Scheme 73**).[87a]



Scheme 73 Spirocyclopentaneoxindoles **282** synthesized by Albertshofer, Tan and Barbas III.

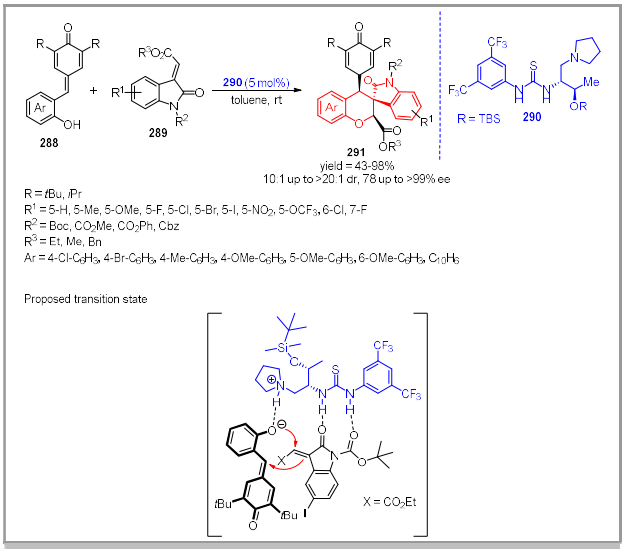
Wang and coworkers also developed a one-pot Michael–Henry domino reaction between 3-substituted indolin-2-one derivatives **283** with nitroalkenes **284** for the synthesis of highly functionalized tetrahydrothiopyran-fused spirooxindole scaffolds **285** in good yields, diastereo- and enantio-selectivities (**Scheme 74**).[87b] Spiro-tetrahydrothiophene oxindoles **286** could be efficiently obtained through the same reaction, including a sulfonium-mediated rearrangement step. The plausible mechanism proposed by the authors to explain the stereochemical result is shown in **Scheme 74**.



Scheme 74 Michael/Henry domino reaction.

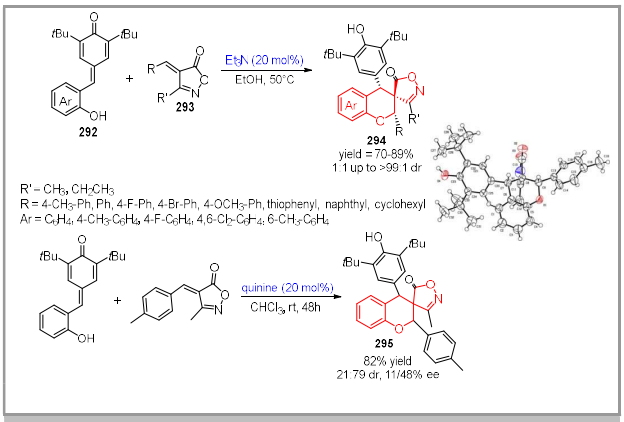
Both starting materials are activated by the catalyst **287**. The intermolecular Michael reaction between the nucleophilic oxindole-C3 and the β-carbon atom of nitroalkenes proceeds through *Re*-face attack. Then, the carbanion generated attacks the *Re*-face of the carbonyl group of **283** to afford the Henry products **285**, which treated with $SOCl_2$ and pyridine, undergo rearrangement.

A domino oxa-Michael 1,6-addition reaction of *ortho*-hydroxyphenyl-substituted *para*-quinone methides **288** and isatin-derived enoates **289**, organocatalyzed by 5 mol% of a bifunctional thiourea **290**, was developed by Enders and coworkers for the synthesis of 4-phenyl-substituted chromans bearing spiro-connected oxindole scaffolds **291** in good to excellent yields and with very high stereoselectivities (**Figure 75**).[88a] In the transition state proposed to explain the stereochemical of the reaction, the catalyst **290** activates the olefinic oxindole **289** through hydrogen-bonding interactions and its tertiary amino group activates **288**. Then, the *Si* face of **289** is attacked by the phenolic oxygen atom in an oxa-Michael addition and a subsequent intramolecular 1,6-addition provide the desired product **291** (**Figura 75**).



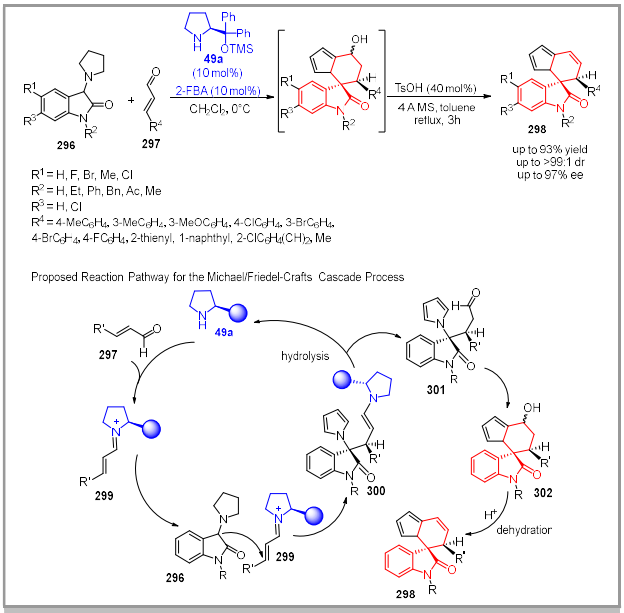
Scheme 75 Domino oxa-Michael 1,6-addition reaction.

Also starting from a domino oxa-Michael 1,6-addition methodology between *ortho*-hydroxyphenylsubstituted *para*-quinone methides **292** and unsaturated isoxazolones **293**, catalyzed by Et_3N, Zhou and coworkers synthesized new spiro-isoxazolonechromans **294** in good yields and with excellent diastereoselectivities (**Scheme 76**).[88b] The structure of one of the compounds was determined by single crystal X-ray analysis and the other compounds had their structures determined by analogy. This methodology was extended to asymmetric organocatalysis, using a quinine as a chiral catalyst. The product **295** was obtained with moderate diastereoselectivity and enantioselectivity (**Scheme 76**).



Scheme 76 New spiro-isoxazolonechromans **294** and **295** synthesized by Zhou and coworkers.

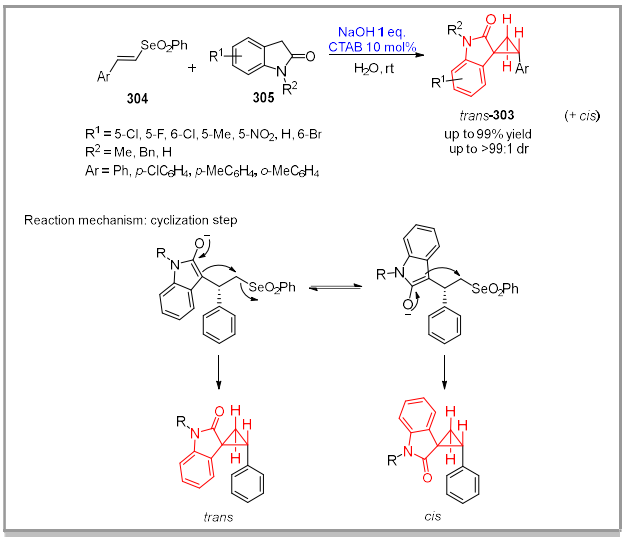
Yuan's research group demonstrated an asymmetric Michael Friedel–Crafts domino process of 3-pyrrolyl-oxindoles **296** with α,β-unsaturated aldehydes **297**, catalyzed by diphenylprolinol silyl ether 49a and 2-fluorobenzoic acid, followed by dehydration with *p*-toluenesulfonic acid to afford spiro[5,6-dihydropyrido[1,2-a]pyrrole-3,3′-oxindole]derivatives **298** in high yields, diastereo- and enantioselectivities (**Scheme 77**).[89] According to the mechanism proposed by authors (in the same scheme), the catalyst **49a** reacts with aldehyde **297** giving rise to the iminium **299**. Then, Michael addition between **299** and **296** provides intermediate **300**, which after hydrolysis results in adduct **301** and regenerates the catalyst. Finally, the intramolecular Friedel-Crafts reaction of **301** generates the spirocycle **302**, which after dehydration generates the desired spiro oxindole **298**. The synthetic usefulness of the spiro compounds **298** was proven from the reduction by Pd-catalyzed hydrogenation. The product of this reaction was obtained with good yield and without decreasing ee or dr.



Scheme 77 Asymmetric Michael/Friedel–Crafts domino process.

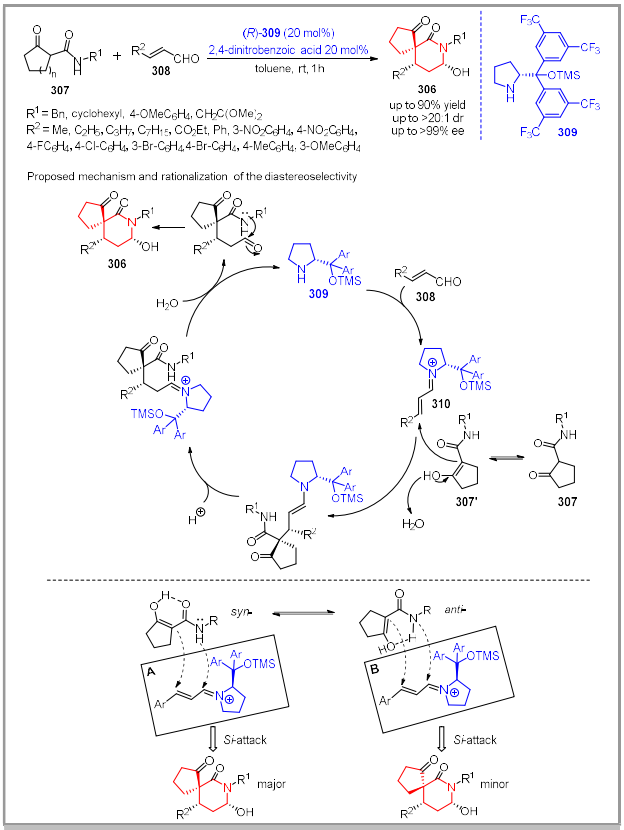
Spirocyclopropyl oxindoles 303 were accessed by Marini and coworkers, with excellent diastereoselectivity, through a domino

Michael intramolecular nucleophilic substitution reaction with variously substituted vinyl selenones **304** and enolizable oxindoles **305** in aqueous sodium hydroxide solution, using CTAB as catalyst (**Scheme 78**).[90] Based on the proposed mechanism, the stereochemistry of the cyclization reaction is independent of the relative configuration of the initially formed Michael adduct, due to the formation of an oxindole enolate by proton transfer. This intermediate allows the formation of both diastereoisomers (*cis* and *trans*) by rotation around a single C-C bond. However, π–π stacking interactions between oxindole and the neighboring aromatic ring in the transition state may be responsible for the high diastereoselectivity (*trans*) observed in the presence of aryl groups (**Scheme 78**). Some of the synthesized compounds were selected for biological evaluation and showed anti-HIV-1 activity.



Scheme 78 Domino Michael intramolecular nucleophilic substitution reaction.

As the last example, α-spiro-δ-lactams **306** were obtained by Rios and coworkers through a domino Michael/hemiaminal annulation reaction of β-ketoamide **307** and α,β-unsaturated aldehyde **308** (**Scheme 79**).[91] The combination of trifluoromethyl-substituted Jørgensen-Hayashi catalyst **309** and 2,3-dinitrobenzoic acid enabled excellent enantioselectivities with both aromatic and aliphatic α,β-unsaturated aldehydes, while lower diastereoselectivities were obtained with aromatic enals. The mechanism proposed (**Scheme 79**) starts with a Michael addition of the ketoamide, in it is enol form **307'**, to the iminium ion **310**. Then, the intramolecular hemiacetalization generates the spiro compound **306**. The enantioselectivity of the reaction is controlled by the catalyst in the Michael addition step. The bulky group on the catalyst, blocks the bottom face of the iminium intermediate, allowing nucleophilic attack only on the *Si* face. The nucleophile **307'** can attack the iminium ion in different trajectories. In trajectory A, the bulky ketoamide stays away from the catalyst, giving rise to the major diastereoisomer. In the case of aliphatic enals, the steric hindrance between the enal and the ketoamide is small, which increases diastereoselectivity. On the other hand, in the case of aromatic enals, which have greater volume, the steric hindrance of both trajectories A and B have similar energies, explaining the lower diastereoselectivity. Since the control of the reaction is thermodynamic, the R and OH substituents are in the equatorial position on the formed six-membered ring.



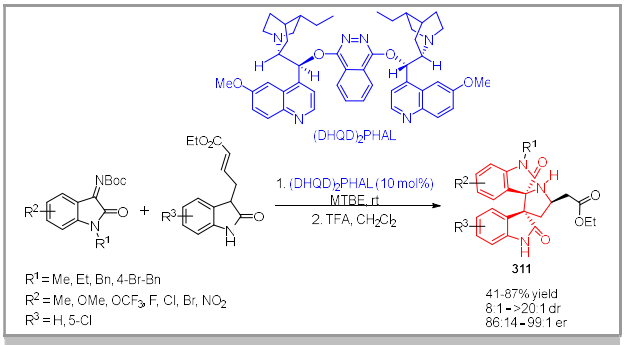
Scheme 79 Domino Michael-hemiaminal annulation reaction.

2.2 Domino reaction initiated by Mannich reaction

The intermolecular Mannich reaction became a classic method for preparing β-amino carbonyl compounds,[92] is one of the most important and applicable carbon-carbon bonds forming reactions in organic syntheses and it is the key step in the synthesis of numerous pharmaceuticals and natural products.[92]

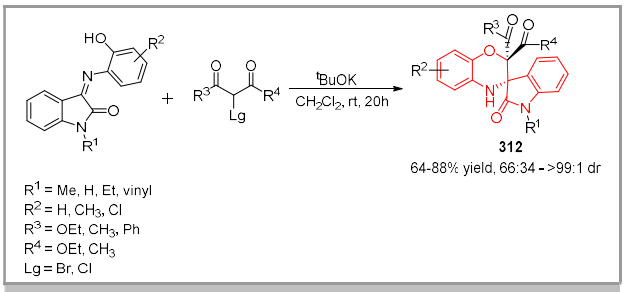
The domino reaction initiated by Mannich reaction can be an interesting strategy in forging ring systems, although it is not much explored in the literature. As example, we can highlight a highly stereoselective synthesis of functionalized 3,3'-pyrrolidinyl-dispirooxindole derivatives **311** with three stereogenic centers achieved through an organocatalytic Mannich Boc-deprotection aza-Michael sequence (**Scheme 80**).[93]

This new protocol proposed by the authors proved effective with a variety of 3,3'-pyrrolidinyl-dispirooxindole derivatives **311**, bearing two vicinal spiro-stereocenters. The products could be easily accessed in good yields (41-87%) with good to excellent diastereo- and enantioselectivities. This one pot sequence could be scaled up without any loss of its efficiency and stereoselectivity.



Scheme 80 Synthesis of 3,3'-pyrrolidinyl-dispirooxindole derivatives **311** *via* an organocatalytic Mannich/Boc-deprotection/aza-Michael sequence.

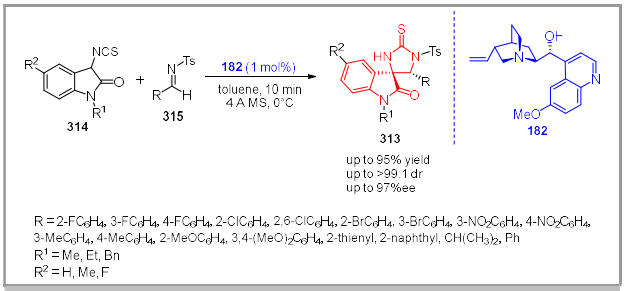
In the same year, Huang and co-workers construction a series of functionalized spiro 1,4-benzoxazine oxindole derivatives **312** were obtained in moderate to good yields via a domino Mannich-alkylation of α-halocarbonyl compounds with imines under mild conditions (**Scheme 81**).[94]



Scheme 81 Synthesis of spiro 1,4-benzoxazine oxindole derivatives **312** *via* a domino Mannich-alkylation.

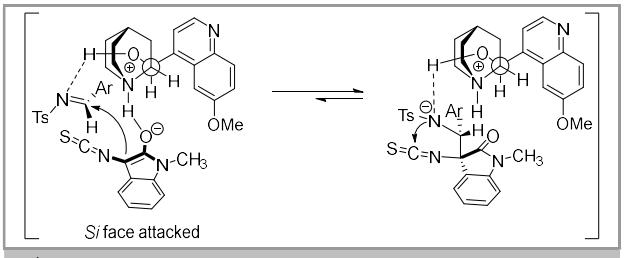
The authors attested of the Mannich reaction could be applied with a broad substrate scope, with a facile methodology access to various new analogues of bioactive heterocyclic spiro 1,4-benzoxazine oxindole derivatives which contain two new heterocyclic rings and up to two quaternary carbon centers.

Thereafter, Bai and collaborators provided a range of structurally diverse chiral spiro[imidazolidine-2-thione-4,3'-oxindole] compounds **313** *via* a domino Mannich-cyclization reaction of 3-isothiocyanato oxindoles **314** and imines **315** with quinine **182** as catalyst under mild conditions (**Scheme 82**).[95] The authors highlight a protocol significantly characterized by simple process, easily available catalyst, high reactivity, low catalyst loading (1 mol %), and good to excellent diastereo- and enantioselectivity (up to>99:1 dr and 97% ee).



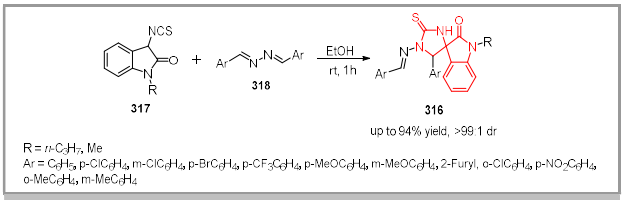
Scheme 82 Spiro[imidazolidine-2-thione-4,3'-oxindole] compounds **313** *via* a domino Mannich-cyclization reaction.

On the basis of experimental results and previous related work regarding to a-isothiocyanato compounds with imines a plausible dual activation working model was proposed to account for the stereochemistry of the domino Mannich-cyclization process. The authors proposed that the imine was activated by hydrogen bond involving the hydrogen atom of quinine and the nitrogen atom of tosyl-protected imine. Then, the 3-isothiocyanato oxindole was synchronously enolized by deprotonation at its 3-position carbon atom by the tertiary amine of quinine. The *Si* face of the imine is attacked by the *Si* face of the enolate of the incoming nucleophile. Next, nucleophilic attack of the nitrogen anion onto the electron-deficient carbon atom of the isothiocyanato group in the 3-isothiocyanato oxindole leads to the optically active spirocyclic oxindole product (**Scheme 83**).



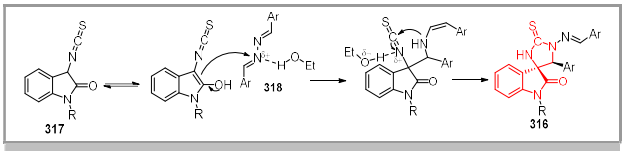
Scheme 83 Proposed transition state for the asymmetric domino Mannich-cyclization of 3-isothiocyanato oxindoles **314** with tosyl-protected imines **315**.

Alternatively, Ping et al. developed an efficient protocol for the synthesis of spiro[imidazolidine-2-thioneoxindole] derivatives **316** with multi-functionalized groups via catalyst-free domino reaction of by domino Mannich cyclization of 3-isothiocyanato oxindoles **317** and bis(arylmethylidene)hydrazines **318** (**Scheme 84**).[96] The domino reaction could proceed smoothly in an environmentally benign conditions and provides pure functionalized spiro[imidazolidine-2-thione-oxindole] derivatives with excellent diastereoselectivity in moderate to excellent yield.



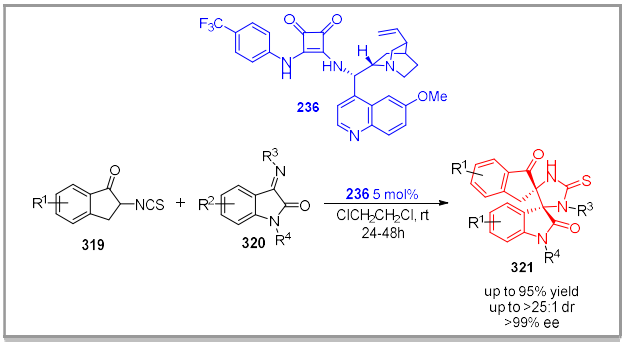
Scheme 84 Synthesis of spiro[imidazolidine-2-thioneoxindole] derivatives **316** developed by Ping et al.

A plausible mechanistic were proposed by the authors with the reaction proceeds faster in ethanol than that in other organic solvents without catalyst, since hydrogen atom of ethanol could activate bis(arylmethylidene)hydrazines **318** by the hydrogen bond between ethanol and nitrogen atom of the bis(arylmethylidene)hydrazines **318**, increasing electrophilic property of the α-carbon. In addition, the hydrogen bond between ethanol and nitrogen atom of the 3-isothiocyanato oxindoles **317** increases the electrophilic property of 3-isothiocyanato oxindoles **317**. Thus, a domino Mannich-cyclization between 3-isothiocyanato oxindoles **317** and bis(arylmethylidene)hydrazines **318** proceeded smoothly using ethanol as solvent (**Scheme 85**).



Scheme 85 Proposed mechanism of domino Mannich-cyclization of 3-isothiocyanato oxindoles **317** and bis(arylmethylidene)hydrazines **318**.

More recently, Zhao and Du demonstrates that novel isothiocyanates derived from 1-indanones **319** are useful building blocks in heteroannulation reactions with isatinimines **320**. The authors showed that the Mannich cyclization domino reaction serves as a powerful tool for the enantioselective construction of bispirocyclic indanone–thioimidazolidine–oxindoles **321** (**Scheme 86**) bearing two adjacent spiro-quaternary stereocenters in good to excellent yields (up to 95%) with excellent diastereo- and enantioselectivities (up to >25:1 dr, > 99% ee).[97]

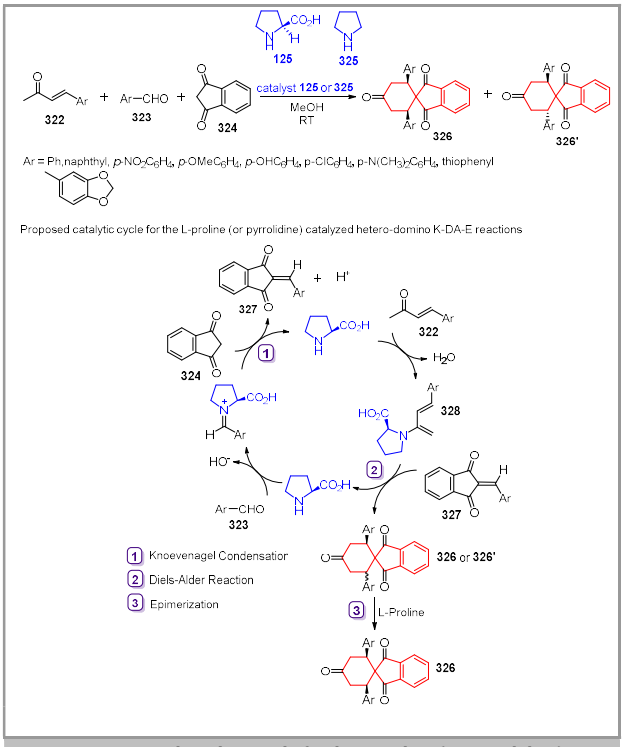


Scheme 86 Enantioselective construction of bispirocyclic indanone–thioimidazolidine–oxindoles **321** *via* Mannich/cyclization domino reaction.

2.3 Domino reaction initiated by Knoevenagel reaction

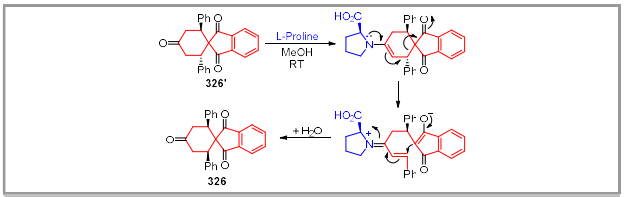
Knoevenagel condensation is one of the most useful reactions for C-C double bond formation. The electron-deficient alkenes resulting from this reaction can be used in subsequent reactions as optimal Michael acceptors, dienes, dipolarophiles and so on. Thus, Knoevenagel reactions are an excellent tool for developing domino and multicomponent reactions.[98]

A hetero-domino Knoevenagel-Diels-Alder-Epimerization reaction of enones **322**, arylaldehydes **323** and 1,3-indandione **324**, catalyzed by L-proline **125** or pyrrolidine **325**, was developed by Barbas III and coworkers to furnish highly substituted symmetric prochiral spiro[cyclohexane-1,2'-indan]-1',3',4-triones **326** and **326'** in a highly diastereoselective fashion with excellent yields (**Scheme 87**).[99] According to the proposed catalytic cycle, L-proline (or pyrrolidine) would catalyze the domino Knoevenagel condensation of aldehyde **323** with 1,3-indandione **322** to provide arylidene indandione **327**. It would then undergo a concerted [4+2] cycloaddition with a 2-amino-1,3-butadiene **328** generated *in situ* from enone **322** and proline or pyrrolidine to form substituted spiro[cyclohexane-1,2'-indan]-1',3',4-triones **326** and **326'** in a diastereoselective manner.



Scheme 87 Proposed catalytic cycle for the L-proline (or pyrrolidine) catalyzed hetero-domino K–DA–E reactions.

Epimerization of the minor diastereomer *trans*-spirane **326'** to the more stable *cis*-spirane **326** could occur under the same reaction conditions, via deprotonation/reprotonation or retro-Michael/Michael reactions also catalyzed by L-proline and pyrrolidine, as shown in **Scheme 88**.

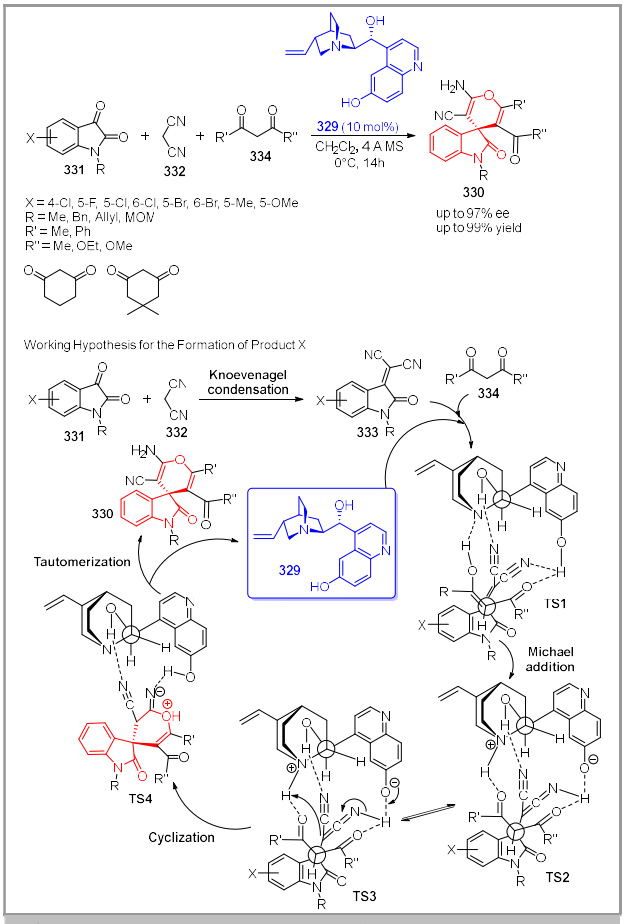


Scheme 88 Epimerization of the trans-spirane **326'** to cis-spirane **326**.

The prochiral spiranes **326** were applied as excellent starting materials for the synthesis of benzoannelated centropolyquinanes. In a complementary work, Barbas III and coworkers used different amino acids and amines in the synthesis of symmetrical and nonsymmetrical spiro[cyclohexane-1,2'-indan]-1',3',4-triones *via* hetero-domino Knoevenagel Diels–Alder epimerization reactions. These compounds were also used as starting materials in the synthesis of benzoannelated centropolyquinanes.[100]

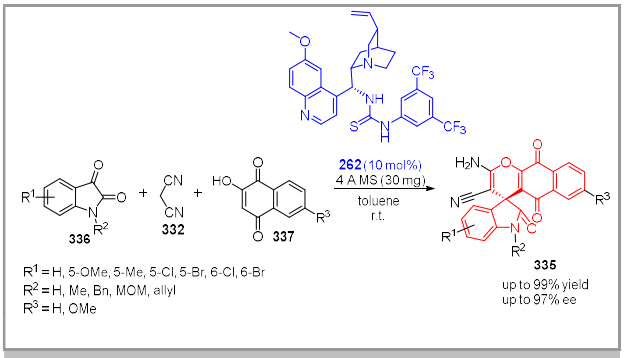
Yuan research group reported the first asymmetric organocatalytic two- and three-component reactions *via* a domino Knoevenagel-Michael cyclization sequence, catalyzed by cupreine **329**, that provided a series of spiro[4H-pyran-3,3'-oxindoles] **330** in excellent yield, with good to excellent ee values, from simple and readily available starting materials (**Scheme 89**).[101] According to the mechanism proposed by the

authors, first, isatin **331** reacts with malononitrile **332** via Knoevenagel condensation generating the **333** structure. Subsequently, the Michael addition of **333** to **334** catalyzed by cupreine proceeds via transition-state TS1 to generate TS2. TS2 and TS3 coexist as a keto–enol tautomerism equilibrium in the reaction system. Then, the intramolecular cycloaddition, involving the CN group activated by the phenolic OH as the electrophile, occurs via TS3 to form TS4. Finally, molecular tautomerization leads to the formation of the desired product **330** and concurrently releases catalyst cupreine back into the catalytic cycle.



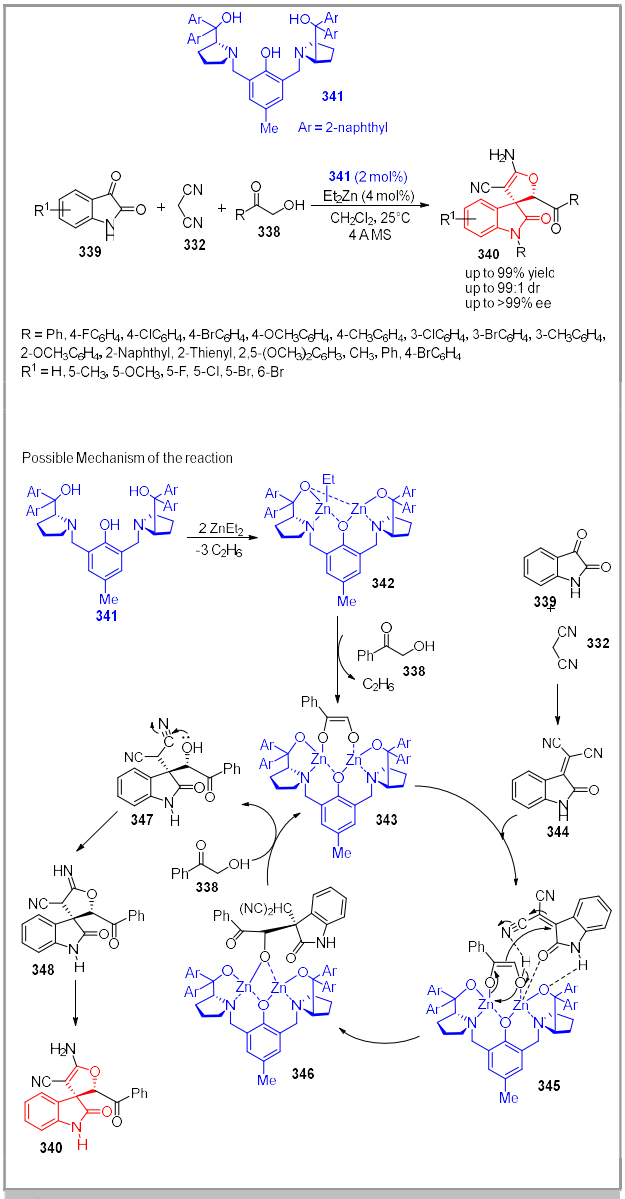
Scheme 89 Synthesis of spiro[4H-pyran-3,3′-oxindoles] **330** *via* a domino Knoevenagel-Michael cyclization sequence.

Similarly, Zhao and coworkers developed a highly enantioselective synthesis of chiral pyranonaphthoquinone-fused spirooxindoles **335** through organocatalytic three-component domino Knoevenagel-Michael cyclization reactions between isatins **336**, malononitrile **332** and 2-hydroxynaphthalene-1,4-diones 337, using a cinchona-thiourea **262** as catalyst (**Scheme 90**).[102] The products were obtained with excellent chemical yields and and high enantioselectivities.



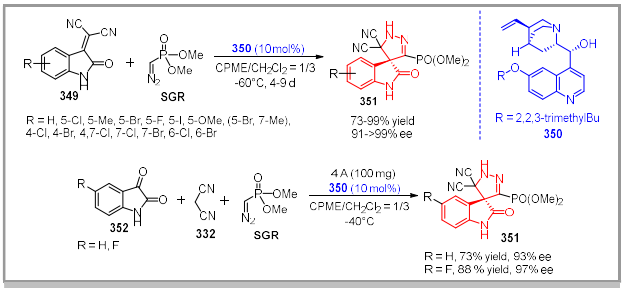
Scheme 90 Synthesis of pyranonaphthoquinone-fused spirooxindoles **335** through organocatalytic three-component domino Knoevenagel-Michael cyclization reactions.

A dinuclear zinc cooperative catalytic asymmetric three-component reaction of α-hydroxy ketones **338**, isatins **339** and malononitrile **332**, also involving a domino Knoevenagel-Michael cyclization sequence, was developed by Wang and coworkers for the synthesis of a series of chiral 3,3′-dihydrofuran spirooxindoles **340** in excellent enantioselectivities and yields under mild conditions (**Scheme 91**).[103] It is noteworthy that this protocol has been reproduced on a large scale without any loss in reactivity and stereoselectivity. And a possible mechanism of the reaction was proposed starting with the reaction of ligand **341** with $ZnEt_2$ giving rise to the dinuclear Zn catalytic species **342**. Next, α-hydroxy acetophenone **338** was deprotonated by ethylzinc to form the bidentate bridging enolate **343**. Then the Knoevenagel condensation product **344** coordinated to the less hindered zinc atom of **343** to afford intermediate **345**, wich after asymmetric Michael addition and tautomerization resulted in intermediate **346**. Finally, the proton transfer with another α-hydroxy acetophenone nucleophile 338 liberated the unstable product **347**, completing the catalytic cycle. This unstable product **347** underwent a Pinner reaction-isomerization, affording the final product **340**.



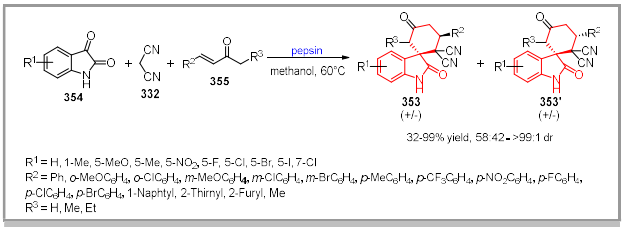
Scheme 91 Synthesis of 3,3'-dihydrofuran spirooxindoles **340** through a domino Knoevenagel/Michael/cyclization sequence.

A method for the catalytic enantioselective 1,3-dipolar cycloaddition of the Seyferth–Gilbert reagent (SGR) to isatylidene malononitriles **349** using a cinchona alkaloid derivative **350** as a catalyst was developed by Peng and coworkers.[104] This method allowed for the synthesis of a series of chiral spiro-phosphonylpyrazoline-oxindoles **351** in good yields with excellent enantioselectivities. The synthetic utility of this method was demonstrated by its use in a three-component domino reaction involving isatina **352**, malononitrile **332**, and SGR based on sequential Knoevenagel condensation and 1,3-dipolar cycloaddition reactions no decrease in yields or enantioselectivities (**Scheme 92**).



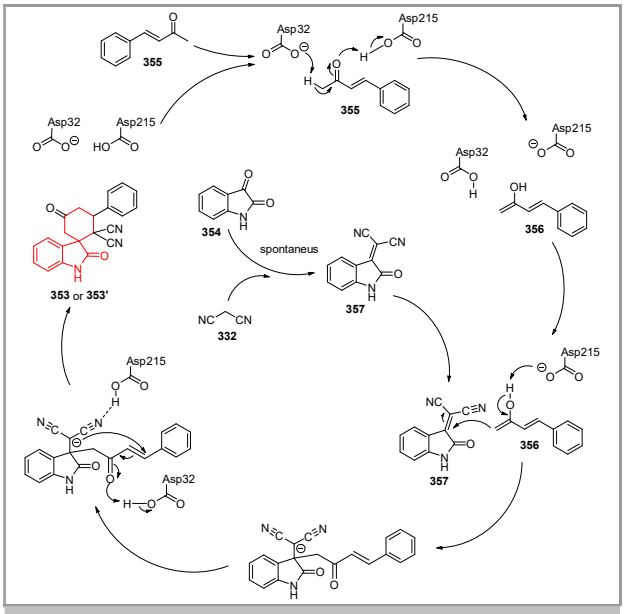
Scheme 92 Synthesis of chiral spiro-phosphonylpyrazoline-oxindoles **351**.

Guan and coworkers developed a domino Knoevenagel-Michael-Michael reaction for the synthesis of spirooxindole derivatives **353** and **353'** in methanol, biocatalyzed by pepsin from porcine gastric mucosa as a sustainable and environmentally friendly biocatalyst.[105] A wide range of isatins **354** and α,β-unsaturated ketones **355** reacting with malononitrile **332** provided the corresponding products in high yields and diastereoselectivities (**Scheme 93**).



Scheme 93 Synthesis of spirooxindole derivatives **353** and **353'** via a domino Knoevenagel-Michael-Michael reaction.

According to the literature,[106,107] the active site of pepsin from porcine gastric mucosa contains Asp32 and Asp215 residues. The function of aspartic acid (32nd residue) has been confirmed to act as a base. Thus, based on the literature, in control experiments and kinetic experiments, the authors proposed a mechanism for the pepsin-catalyzed domino reaction of isatina **354**, malononitrile **332** and benzalacetone **355** (**Scheme 94**). First, the carbonyl of benzalacetone is stabilized *via* a hydrogen bond with Asp215 in pepsin, and Asp32 acts as a base to take away a proton from the benzalacetone forming the enol **356**, which in turn reacts by intermolecular Michael addition with the intermediate isatilidene malononitrile **357** spontaneously formed by Knoevenagel condensation. Finally, the intramolecular Michael addition occurs forming the spirocyclic oxindole skeleton **353** or **353'**.

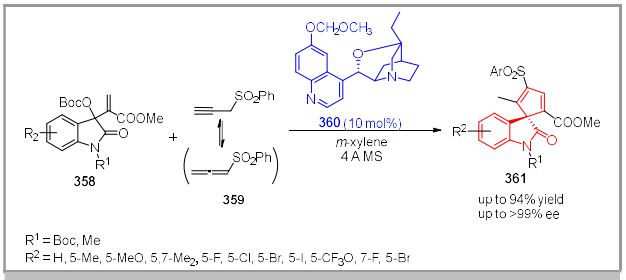


Scheme 94 Proposed a mechanism for the pepsin-catalyzed domino reaction.

2.4 Domino reaction initiated by Cycloaddition reaction

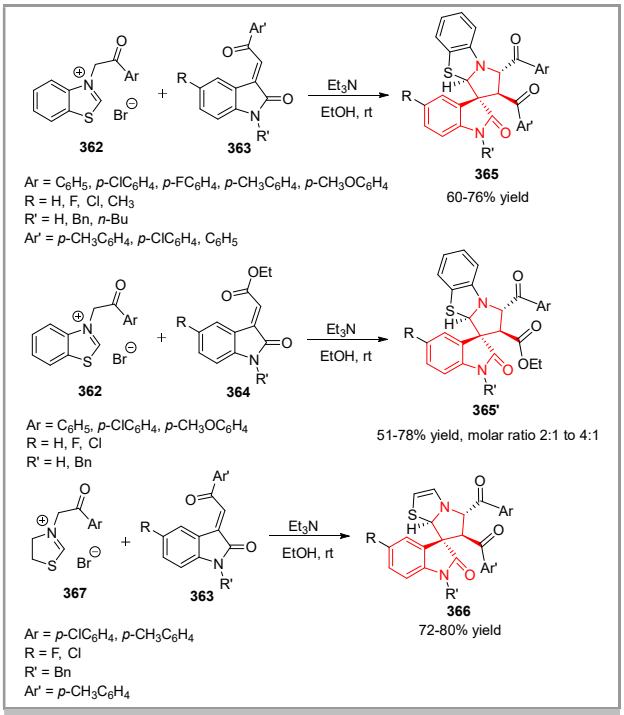
Cycloadditions are reactions in which two π bonded molecules come together to make a new cyclic molecule with the formation of two new σ bonds. These reactions are one of the main strategies employed in the synthesis of spiro compounds.[1,3,13a]

A chemo- and enantioselective [3+2] annulation between Morita-Baylis-Hillman carbonates of isatines **358** and propargyl sulfones **359**, catalyzed by a chiral tertiary amine **360**, was developed by Chen and coworkers for the synthesis of spirocyclic 2-oxindoles **361** incorporating an unusual cyclopentadiene motif in good yields and excellent enantiomeric excesses (**Scheme 95**).[108] The reaction takes place through a dipolar cycloaddition of *in situ* generated allylic N-ylide and allenyl sulfone, followed by a C=C bond domino isomerization sequence.



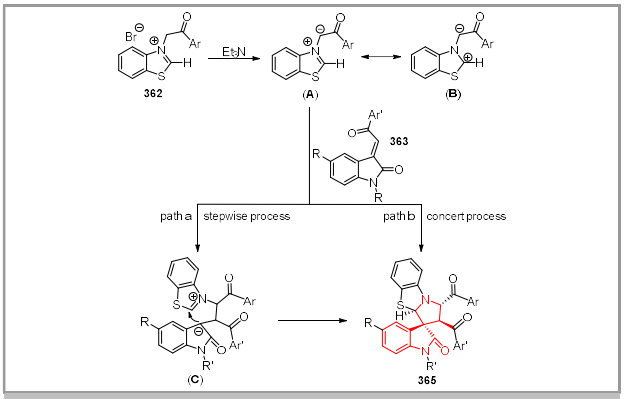
Scheme 95 Synthesis of spirocyclic 2-oxindoles **361.**

Yan research group developed domino cycloaddition of N-phenacylbenzothiazolium bromides **362** with 3-phenacylideneoxindoles **363** or ethyl 2-(2-oxoindolin-3-ylidene)acetates **364** in ethanol at room temperature in the presence of trimethylamine for the synthesis of functionalized spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,3′-indolines] 365 and **365'** in good yields and high diastereoselectivity. Moreover, spiro[indoline-3,7′-pyrrolo[2,1-b]thiazoles] **366** could be obtained, with satisfactory yields and also with high diastereoselectivity, through reactions of N-phenacylthiazolium bromides **367** with 3-phenacylideneoxindoles **363** (**Scheme 96**).[109]



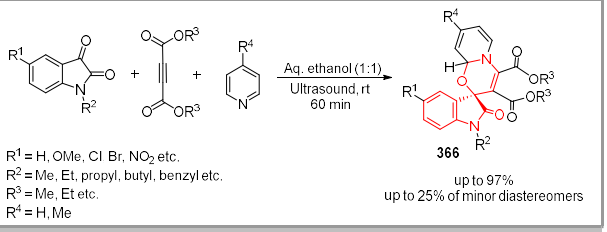
Scheme 96 Synthesis of spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,3′-indolines] **365**, **365'** and **366** *via* domino cycloaddition reactions.

According to the proposed formation mechanism of spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,3′-indolines], TEA deprotonated N-phenacylbenzothiazolium bromides **362** to give a nitrogen ylide **A**, which has a canonical form **B**. Then, the reaction of the nitrogen ylide could proceed with a stepwise process (path a) or a concerted process (path b). In the path a, a Michael addition of nitrogen ylide **A** to 3-phenacylideneoxindole **363** resulted in intermediate **C**, which underwent an intramolecular addition, providing the spiro[benzo[d]pyrrolo[2,1-b]thiazole-3,3′-indoline] derivatives. On the other hand, in the path b, the addition of nitrogen ylide **A** to the C=C double bond of 3-phenacylideneoxindole **363** directly resulted in the desired product (**Scheme 97**).



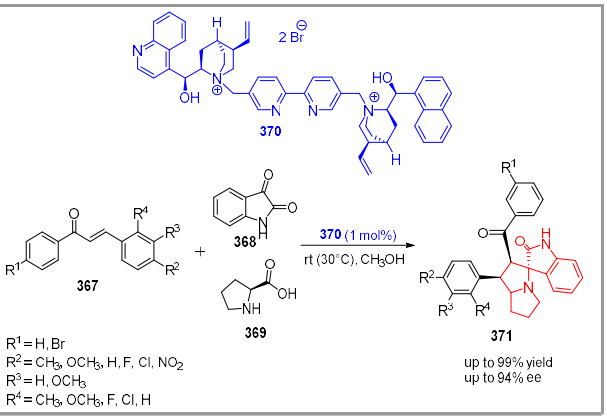
Scheme 97 Proposed formation mechanism of spiro[benzo[d]pyrrolo [2,1-b]thiazole-3,3′-indolines] **365**.

Similarly, Mukhopadhyay and coworkers developed an ultrasound assisted methodology to obtain spiropyrido[2,1-b][1,3]oxazino compounds 366, in good yields and diastereoselectivity, based on three component reactions approach via domino 1,4-dipolar cycloaddition in aq. ethanol medium at room temperature (**Scheme 98**).[110]



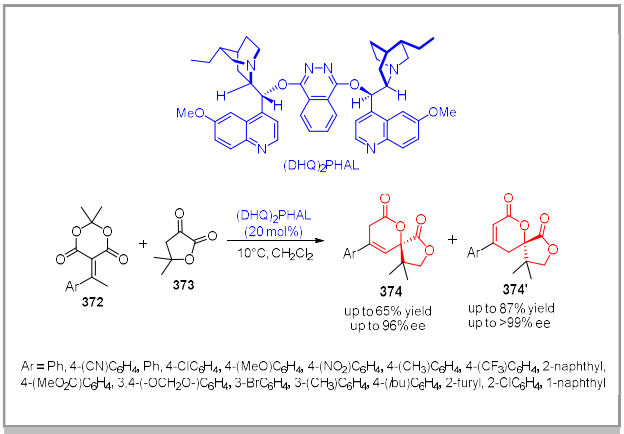
Scheme 98 Synthesis of spiropyrido[2,1-b][1,3]oxazino compounds **366.**

Recently, Siva research group also developed an asymmetric one-pot 1,3-dipolar cycloaddition domino sequence of chalcones **367**, isatin **368** and proline **369**, organocatalyzed by a bipyridine-based chiral quaternary ammonium bromide **370** for the synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives **371** in excellent yields and with excellent ee's (**Scheme 99**).[111]



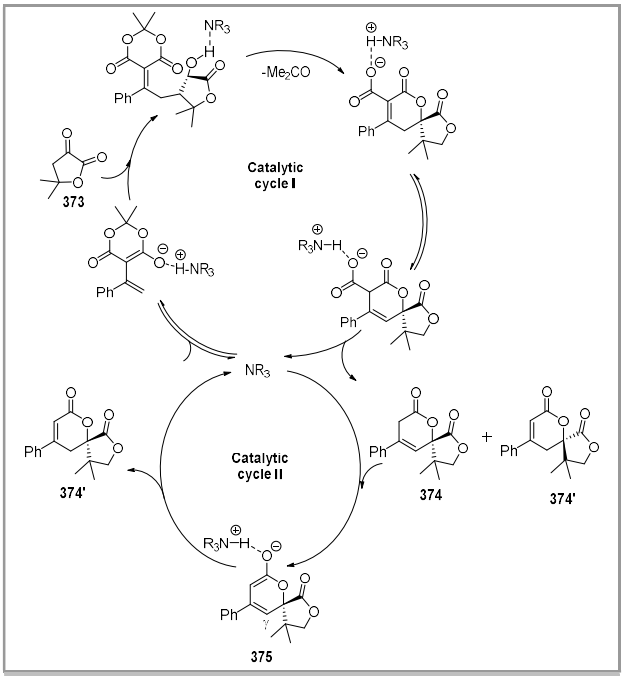
Scheme 99 Synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives **371.**

Toffano and coworkers described for the first time an Auto Tandem Catalysis (ATC) process including an enantioselective vinylogous formal (4+2) cycloaddition followed by a kinetic resolution (KR). The reaction pass through a 1,3-prototropic shift, between ketone-derived benzylidene Meldrum's acid **372** and α-ketolactones **373** to provide enantioenriched spirolactone dihydropyranones **374** and **374'** (**Scheme 100**).[112] This process resulting from dual and complementary role of $(DHQ)_2PHAL$ organocatalyst.



Scheme 100 Synthesis of spirolactone dihydropyranones **374** and **374'.**

The proposed catalytic sequence is shown in **Scheme 101**. The catalytic cycle I is related to the asymmetric formation of the spiro stereogenic center leading to the non-conjugated lactone **374** and **374'** as an enantioenriched mixture. The second cycle (catalytic cycle II) consists in the isomerization of **374** a to conjugated lactone **374'** via a kinetic resolution process, that proceeds through a 1,3-prototropic shift, on which basic catalyst deprotonates the weakly acidic α-position of **374** to form the intermediate **375**. A regioselective reprotonation of the enolate **375** would then occur preferentially at the γ-position to afford the product **374'**.



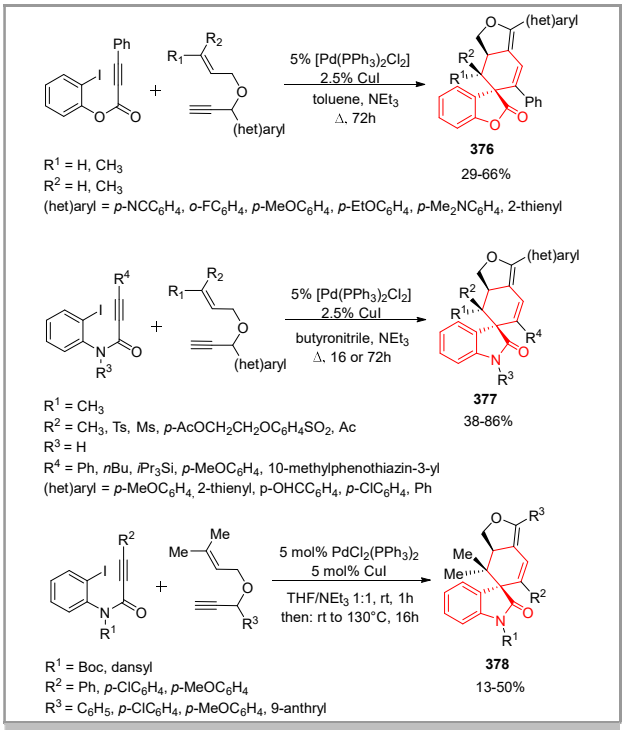
Scheme 101 Proposed catalytic sequence for the synthesis of spirolactone dihydropyranones **374** and **374'.**

2.5 Domino reaction initiated by metal insertion

Enantioselective metal catalysis is a powerful tool for many types of reactions. In particular, the combination of enantioselective metallic catalysis with the concept of domino reactions allowed

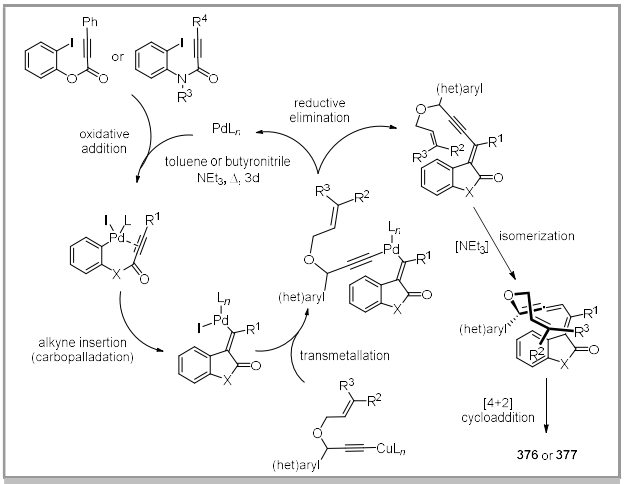
high molecular complexity to be achieved with remarkable levels of stereocontrol based on simple and economical one pot procedures. In the last decade, many enantioselective domino processes have been successfully catalyzed by a wide variety of chiral metal complexes. Especially, the considerable impact of the advent of asymmetric transition metal catalysis has allowed the immense development of many highly efficient enantioselective metal-catalyzed domino reactions. The wide variety of these processes well reflects the variety of metals used to promote them.[113,114]

In this scenery Müller and coworkers developed a new insertion–coupling–isomerization–Diels–Alder domino reaction that furnishes spirocyclic benzofuranones **376**, dihydroindolones **377** and bichromophoric spirocyclic indolones **378** (**Scheme 102**) in moderate to excellent yields under Sonogashira coupling conditions. The compounds could be crystallized and single crystal structure analyses display steric and electronic substituent effects. Compounds of this new class of spirocyclic compounds possess large Stokes shifts and fluoresce intensively with blue over green to orange colors. As a consequence of the spirocyclic rigidity fluorescence lifetimes and quantum yields are rather high in some cases.[115, 116]



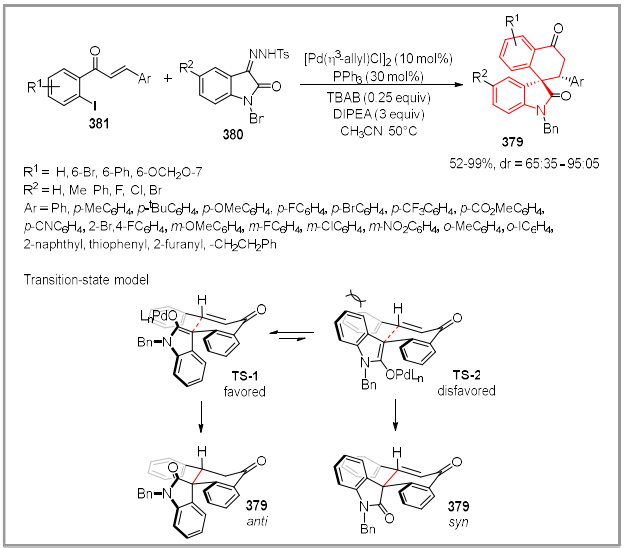
Scheme 102 Synthesis of spiro compounds **376**, **377** and **378.**

Based upon the product analysis the hetero domino sequence can be interpreted as a combination of a transition-metal-catalyzed insertion cascade that concludes in a pericyclic final step. Hence, the hetero domino sequence can be rationalized (**Scheme 103**) as an insertion alkynylation, followed by a base-catalyzed isomerization of an electron poor vinyl propargyl allyl ether, to give an electron poor vinyl allene that reacts in an intramolecular [4+2] cycloaddition through an *anti–exo* transition state. To conclude the sequence, by formation of spirocycles **376** or **377**. The authors highlight DFT computations, and reveal that in the final pericyclic step the Diels–Alder termination is by far thermodynamically and kinetically favored over a possible Claisen rearrangement.[115]



Scheme 103 Hetero domino sequence for the construction of **376** or **377**.

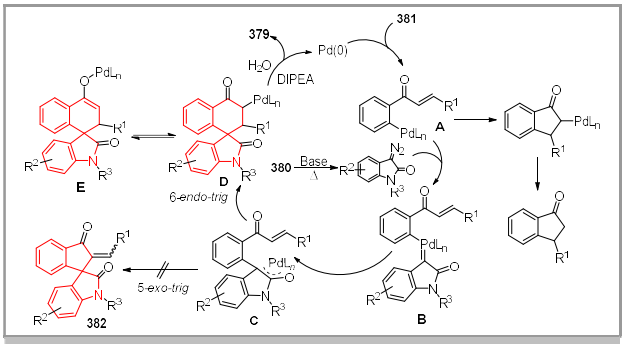
Arunprasath et al. also reported a Pd-catalyzed in an efficient diastereoselective synthesis of α-tetralone-fused spirooxindoles **379**. The authors developed a novel Pd-catalyzed carbene migratory insertion/conjugate addition strategy to access spirooxindoles with contiguous quaternary and tertiary carbon centers in a diastereoselective fashion. This operationally simple protocol represents the first example of isatin-derived N-tosylhydrazones **380** being utilized in a metal-carbenoid involving domino process, thus opening a new way to construct novel complex molecular spirocycles from readily accessible starting materials with a broad scope. In addition, a transition-state model has been proposed to understand the observed stereoselectivity (**Scheme 104**).[117]



Scheme 104 Synthesis of α-tetralone-fused spirooxindoles **379.**

Notwithstanding, NMR reaction profiling and deuterium-labeling investigations provide insight into the mechanistic pathway. Thus, the authors suggested a plausible mechanism outlined in

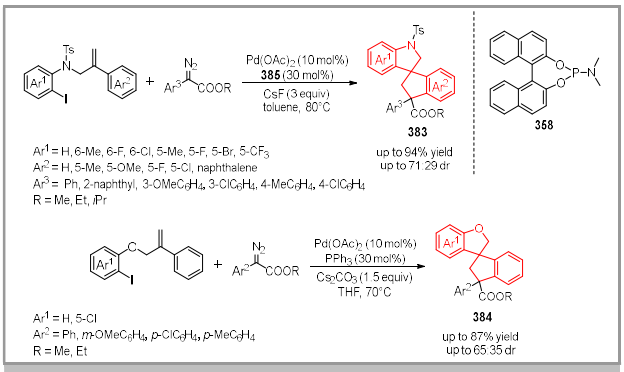
Scheme 105. Initially, oxidative addition of **381** to Pd(0) generates ArPd(II) species **A**, which would react with in situ formed diazo compound to give the Pd–carbenoid complex **B**. The intermediate **B** then, may evolve through the migratory insertion of the aryl group into the carbenic carbon atom to generate the C- or O-bound Pd-enolate which would exist as π-oxoallyl Pd-intermediate **C**. Then, the Pd-enolate undergoes an intramolecular 6-*endo-trig* mode of conjugate addition to form intermediate **D**. Since syn-β-H elimination precluded by the conformationally rigid nature, intermediate **D** or its corresponding O-bound tautomer **E** undergoes protonolysis to furnish the product. The resultant Pd(II) reduced to active Pd(0) with the aid of DIPEA. The formation of **382** via a 5-*exo-trig* mode of closure is disfavored presumably due to increased steric hindrance involved in the approach of the Pd to α-position of the double bond.[117]



Scheme 105 Proposed reaction pathway.

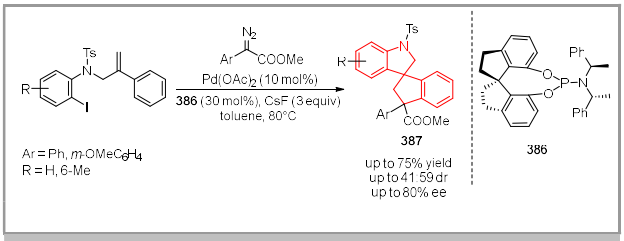
More recently a new palladium-catalyzed domino approach for the synthesis of attractive spirocyclic indolines and dihydrobenzofurans was developed by Xu and coworkers. The reaction proceeds through a sequential intramolecular Heck spirocyclization, remote C–H activation, and diazocarbonyl carbene insertion. The authors optimized a methodology enables efficient access to a broad range of spiroindolines **383** and spirodihydrobenzofurans **384** containing two quartenary stereogenic centers in good to excellent yields. An investigation reveals that $Pd(OAc)_2$ exhibited the best catalytic activity, very gratifyingly, monophosphoramidite ligand **385** could display unique catalytic activity and furnish the spiroindoline product **383** in excellent yield (up to 94%) with up to 71:29 dr.[118]

After careful investigation, the reaction in **Scheme 106** proceed smoothly in the presence of PPh_3 as ligand, Cs_2CO_3 as the base and THF as the solvent, enabling access to the expected spirocyclic dihydrobenzofurans **384** in good yields.[118]



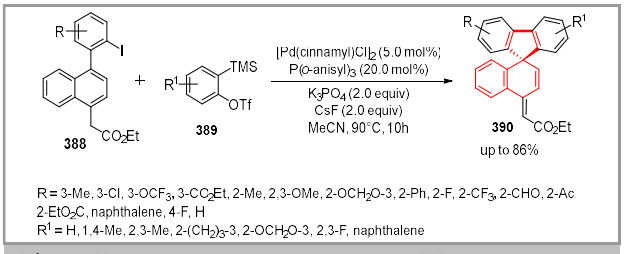
Scheme 106 Synthesis of spiroindolines **383** and spirodihydrobenzofurans **384.**

Nevertheless, the authors also conducted a study of asymmetric spirocyclization using chiral monophosphoramidite **386** as a ligand, enabling access to highly valuable chiral spiroindolines **387** with up to 80% ee.[118]



Scheme 107 Synthesis of spiroindolines **387.**

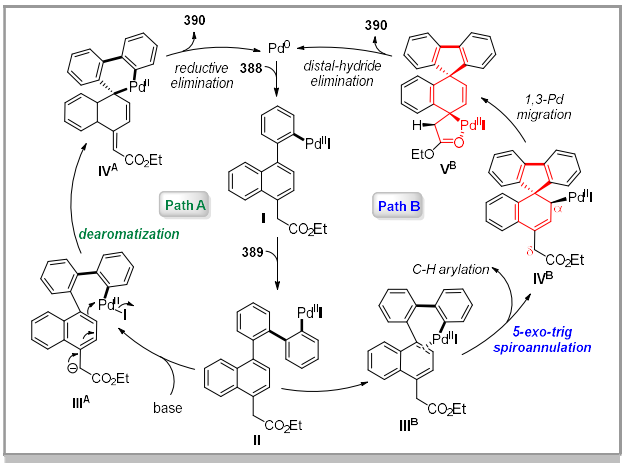
Alternatively, a palladium(0)-catalyzed dearomatizing [3+2] spiroannulation of naphthalene-based biaryls **388** with arynes **389** has been developed for the rapid construction of spirofluorene architectures **390** in good yields with excellent chemoselectivities, by Luan and coworkers. This reaction was realized by carbopalladation of aryne to generate an arylpalladium species, followed by termination with naphthalene dearomatization, which is a sharp contrast to the conventional C–H functionalization approach. The authors highlighted this reaction represents the first example of transition-metal-catalyzed dearomatization reactions by involving a highly reactive aryne coupling partner.[119]



Scheme 108 Synthesis of spirofluorene architectures **390.**

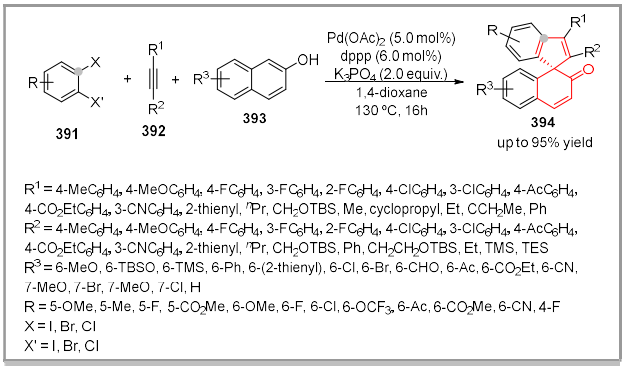
Furthermore, two plausible reaction pathways for the formation of **390** were depicted in **Scheme 109**. The key intermediate **II** is formed through carbopalladation of aryne **389** with a catalytically generated arylpalladium species **I**. Then, two divergent pathways could be considered by the authors: (a) base-assisted deprotonation leads to a [6,6] spirocyclic palladacycle **IV^A**, which consecutively undergoes direct reductive elimination

to generate product **390** (path A); (b) an intramolecular 5-*exo-trig* Heck-type cyclization takes place to construct a [5,6] spirocarbocyclic **IV^B**, followed by carbonyl-facilitated 1,3-Pd migration (**IV^B** → **V^B**) and distal-hydride elimination to give rise to **390** (path B). Mechanistic studies revealed that the arene dearomatization might take place through a 5-*exo-trig* spiroannulation and distal-hydride elimination Heck-type pathway.[119]



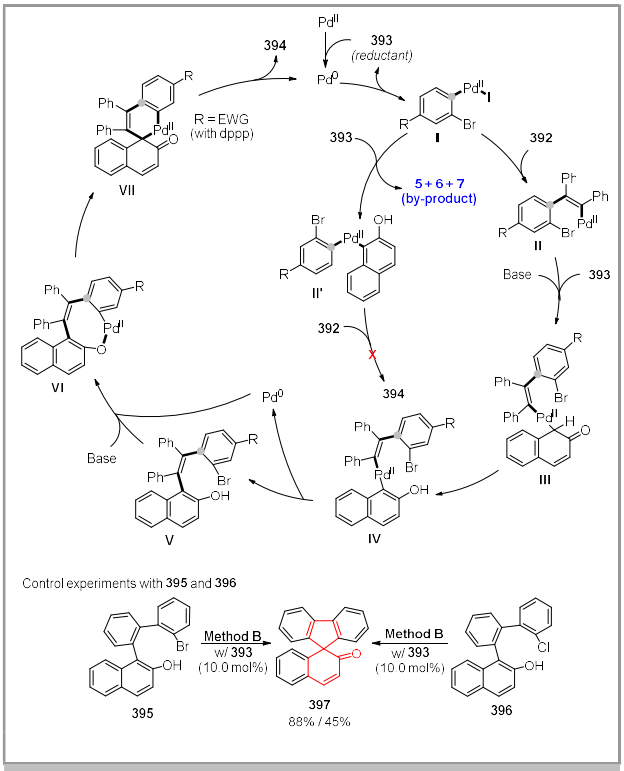
Scheme 109 Proposed mechanisms.

Very recently, Luan and co-workers successfully developed a chemo- and regioselective Pd(0)-catalyzed dearomative [2+2+1] spiroannulation reaction. Interesting to note of this method is the use of readily available 1,2-dihaloarenes **391**, alkynes **392** and 2-naphthols **393** for the rapid assembly of spirocarbocyclic molecules **394** (**Scheme 110**). Remarkably, the regiochemistry of this domino transformation, with respect to both 1,2-dihaloarene and alkyne coupling partners, could be selectively controlled by the precise variation of their structures.[120]



Scheme 110 Synthesis of spirocarbocyclic molecules **394.**

Mechanistic studies revealed that this domino reaction proceeded through a cascade of oxidative addition to Pd(0), alkyne migratory insertion, and 2-naphthol-facilitated dearomatizing [4+1] spiroannulation. The authors proposed a plausible reaction pathway for the formation of product **394** in **Scheme 111**. First, an active Pd(0)-catalyst is generated by the reduction of $Pd(OAc)_2$ with naphthol **393**. Afterwards, oxidative addition occurs at the more active iodo-site of 1-bromo-2-iodobenzene **391** to afford arylpalladium species **I**. The coordination and migratory insertion of alkyne **392** provides intermediate **II** according to the regiochemistry of **391**. Subsequently, intermediate **II** undergoes electrophilic palladation with naphthol **393**, followed by tautomerization and reductive elimination to deliver V. At the same time, the active Pd(0)-catalyst is regenerated. Next, it is assumed that the hydroxyl group would direct the Pd(0)-species to facilitate regioselective oxidative addition of aryl halide **V**. The intermediate **VI** then undergoes dearomative ring-contraction to afford spirocyclic **VII**. Finally, reductive elimination takes place to form product **394**. Although plausible intermediate **V** was not isolated, control runs with analogue **395** and its Cl-counterpart **396** were able to afford dearomative spiroannulation product **397** in reasonable yields (**Scheme 111**).[120]



Scheme 111 Proposed mechanism.

2.6 Others mechanisms

Some examples of domino reactions for the asymmetric synthesis of spiro compounds where several different reactions initiate the domino processes are presented in this section.

Wu and coworkers developed the first enantioselective vinylogous aldol–cyclization domino reaction of allyl pyrazoleamides with isatins for the asymmetric construction of spirocyclic oxindole–dihydropyranones in excellent yields and good-to-excellent enantioselectivities, in the presence of only 1 mol% of Takemoto catalyst.[121] Similarly, Han and Chang also synthesized a series of spirooxindole dihydropyranones *via* a vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles to isatins, using cinchona alkaloid-squaramide bifunctional organocatalysts.[122]

A stereoselective synthetic approach to spirooxindole 4H-pyran-2-one derivatives was developed by Du research group *via* a NHC-catalyzed three-component domino reaction of alkynyl aldehydes with oxindoles in good yields and with good to high diastereoselectivities.[123] Gravel and coworkers also described two novel domino NHC-catalyzed spirocyclizations, *via* Stetter–aldol–Michael (SAM) and Stetter–aldol–aldol (SAA) reactions, for the synthesis of a variety of spiro bis-indane structures, with high diastereoselectivity, from simple o-phthaldialdehyde derivatives.[124]

Recently, Samanta and co-workers reported an efficient, organocatalytic, environmentally friendly and stereoselective [3+3] one-pot allylic alkylation oxa-Michael reaction by involving a wide range of Morita–Baylis–Hillman (MBH) carbonates of isatins, cyclic carbonyl compounds in a biomass-derived 2-MeTHF as green solvent catalyzed by DABCO as a solid Lewis-base catalyst. This protocol delivers a unique class of medicinally promising spirooxindole-fused-dihydropyran scaffolds.[125]

A outstanding work of Hajra and collaborators in 2019 developed an highly efficient regio- and stereoselective domino aziridine ring opening and lactamization reaction between aziridines and 3-carboxy oxindole esters for the one pot asymmetric synthesis of 4-aryl-3,3'-spiropyrrolidonyl oxindoles with excellent selectivity (dr >99 : 1 and ee up to >99%).[126]

More recently, differently to the catalytic asymmetric dearomative reactions of indole substrates, the analogous benzofuran derivatives have been less explored. Chen and co-workers reported the stereoselective domino Rauhut–Currier-Michael addition process of 3-benzofuranyl vinyl ketones and 3-olefinic (7-aza)oxindoles realised via catalysis by a chiral bifunctional phosphine, furnishing the previously unreported direct asymmetric dearomative reaction of benzofuran substrates tethered to a carbonyl group in a formal [4+2] cycloaddition manner. The authors obtained an array of hydrodibenzofuran derivatives with dense substitutions is generally constructed with excellent diastereoselectivity and enantioselectivity (up to >19 : 1 dr, >99% ee).[127]

In this way, explored alternatvly reactions could be a new view in the world of spirocycles. The work of Zheng and You summarized systematic studies of the chemistry of spiroindolenines, including their enantioselective syntheses, their relationship with catalytic asymmetric Pictet–Spengler-type reactions, and their diverse transformations beyond classic asymmetric Pictet–Spengler reactions.[128]

3 Conclusion

Spiro compounds are promising structures for drug development, in addition to being used in organic optoelectronics and asymmetric synthesis. The synthesis of spiro compounds is quite challenging, especially with regard to the control of the absolute stereochemistry. However, domino reactions have emerged as an interesting and versatile methodology of wide applicability for the asymmetric synthesis of these compounds.

Funding Information

MB thanks MUR for the project PRIN 2017 "NATURECHEM".FM thanks MUR project PRIN 2017 "NATURECHEM" for a postdoctoral fellowship.

Acknowledgment

Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.

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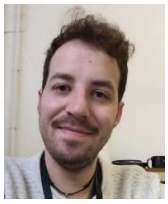
Biosketches

	Dr. Fabrizio Medici obtained his Master's degree in organometallic chemistry at the University of Insubria in Como. He then moved to Paris and joined the group of Pr. Louis Fensterbank at Sorbonne University, where he obtained his PhD in 2017 with a thesis on silicon complexes-based Lewis acids. After a postdoctoral fellowship at ICSN under the supervision of Dr. Voituriez and Dr. Marinetti working on photoswitchable bis Au(I) complexes, he returned to Italy and he is currently working under the supervision of Prof. Benaglia on the development of stereoselective photochemical and electrochemical organic reactions.
	Maurizio Benaglia was born in Bergamo in 1966; after completing his doctoral studies at the University of Milano with prof. M. Cinquini and F. Cozz,i and two years as postdoctoral fellow with prof. Jay Siegel, at UCSD, University of California, San Diego, he was appointed in 2006 as Associate professor and in 2015 as Full Professor of Organic Chemistry at the Department of Chemistry of the Università degli Studi di Milano. His research focuses on the development of novel sustainable synthetic methodologies and of new chiral organocatalysts, the study of stereoselective reactions in flow and with catalytic reactors, the synthesis of pharmaceutical products, taking advantage also of 3D-printing technologies, (organo)photoredox catalysis, organic electrochemistry and alternative, biodegradable reaction media.

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