

# Asymmetric organocatalytic synthesis of aza-spirocyclic compounds from isothiocyanates and isocyanides

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**Abstract:** The spirocyclic motif is present in natural products, chiral ligands and compounds of pharmacological interest. Isothiocyanates as well as isocyanides bearing electron-withdrawing groups in the  $\alpha$ -position can be deprotonated and react as formal dipoles on account of the presence of a nucleophilic carbanion and an electrophilic atom in the isothiocyanate or isocyanide functional groups. In the last years a number of procedures involving the formal [3+2] cycloaddition reaction of isothiocyanates or isocyanides with cyclic compounds bearing electrophilic exocyclic double bonds have been developed for the enantioselective synthesis of aza-spirocyclic compounds. Among them, organocatalysis has played a predominant role in the development of asymmetric versions for these reactions. The synthesis of spirooxindoles by using this methodology has received especial attention, although other spirocyclic scaffolds are available depending on the structure of the dipolarophiles and the formal isothiocyanate and isocyanide dipoles.

Carlos Vila received his degree in chemistry (2005) and his Ph.D. (2010) from the University of Valencia. In 2010, he joined the group of Prof. Rueping at RWTH Aachen University, Germany, for two years as a postdoctoral researcher where he focused on photoredox catalysis. In 2012, he commenced a two-year postdoctoral stay with Prof. Feringa at Groningen University as a Marie Curie Fellow, working on cross-coupling reactions with organolithium reagents and asymmetric catalysis. In 2018, he was appointed as a 'Ramón y Cajal' researcher at the Organic Chemistry Department, University of Valencia. His current research interests are asymmetric catalysis and photocatalysis.



Gonzalo Blay received his degree in chemistry (1987) and his Ph.D. (1992) from the University of Valencia. He has been a Marie Curie postdoctoral fellow at the Agricultural University of Wageningen, The Netherlands, with Prof. A. de Groot (1993–94) and visiting researcher at Aarhus University, Denmark, with Prof. K. A. Jørgensen (2005). In 1996, he became Associate Professor and was appointed Full Professor in 2012 at the Department of Organic Chemistry of the University of Valencia. His research interest includes organic synthesis and the development of catalytic methodologies, in particular asymmetric catalysis.



Adrián Laviós received his degree in Chemistry (2018) and his Master's degree in Organic Chemistry (2019) from the University of Valencia. Since then, he has continued his Ph.D. program at the same university, focusing on enantioselective reactions of isocynoacetates with diverse dipolarophiles, under the supervision of Prof. Dr. Gonzalo Blay Llinares and Amparo Sanz-Marco.



Amparo Sanz-Marco received her BSc (2009) and her PhD degree in organic chemistry (2015) under the supervision of Prof. José Ramón Pedro and Prof. Gonzalo Blay at the University of Valencia. She has been post-doctoral researcher at the University of Stockholm (2015-2019) with Prof. Belén Martín-Matute and Juan de la Cierva Researcher (2020) at the University of Valencia. She is currently assistant professor (Prof. Ayudante Doctor) at this University. Her current research interests focus on organocatalysis and organometallic chemistry.



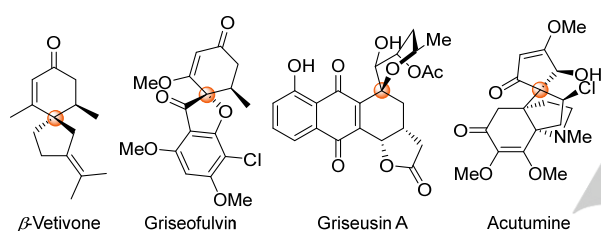
José R. Pedro graduated in chemistry from Valencia University, Spain, in 1974. He obtained his Ph.D. from the same university in 1977, and in the same year he became Assistant Professor, starting his independent research on natural product synthesis. In 1985, he was promoted to Associate Professor, and in 1998 to Full Professor in Organic Chemistry at Valencia University. His current research interests are in the field of asymmetric catalysis. He is the Director of the Research Group on asymmetric catalysis with metal complexes and organocatalysts at Valencia University (AsymCat, GIUV2013-125).



## 1. Introduction

Spiro compounds have one atom (the spiro atom) as the only common member of two rings.<sup>[1]</sup> This structural feature is present in a significant number of natural products that can be isolated from plants or animals.<sup>[2,3]</sup> Furthermore, spiro compounds have recently acquired relevance in the development of pharmaceuticals, owing to the conformational restriction that is imposed by the spiro atom, which allows the reduction of the entropic penalty associated with the binding to an active site of a protein target, a process that requires the adoption of a determined conformation.<sup>[4]</sup>

Figure 1 displays some examples of spirocyclic natural products, as well as spiro compounds of pharmaceutical interest, such as  $\beta$ -vetivone, extracted from vetiver oil; griseofulvin, an antifungal agent; griseusin A, an antibiotic produced by *Streptomyces griseus*;<sup>[5]</sup> and acutumine, extracted from the medicinal herb *Sinomenium acutum*, which has potential memory-enhancing properties.<sup>[6,7]</sup>



**Figure 1.** Selected examples of natural products and compounds of pharmaceutical interest which contain spiro rings.

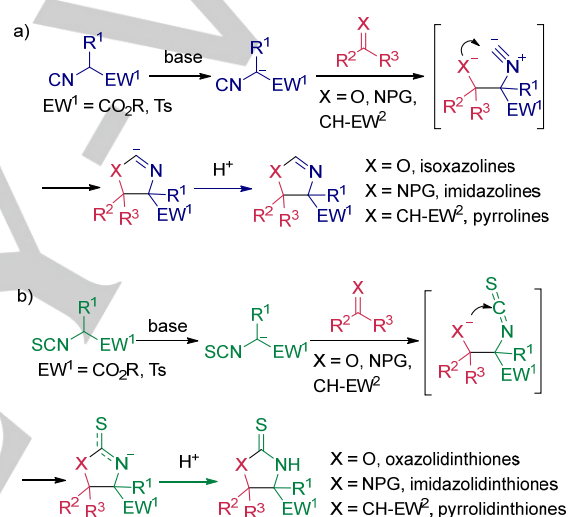
The importance of these kind of compounds has brought up interest in the development of synthetic methods for their preparation, particularly in an enantioselective fashion.<sup>[8]</sup> Among these, cycloaddition reactions with cyclic compounds bearing an exocyclic double bond result especially appealing because of its simplicity and the vast variety of reaction partners that can participate in this kind of reactions. In this context, cycloadditions based on the use of isothiocyanate and isocyano derived compounds have recently emerged as an excellent methodology for the preparation of *aza*-spirocycles. Organocatalysis,<sup>[9]</sup> particularly hydrogen-bonding catalysis,<sup>[10]</sup> has proved especially successful in the development of enantioselective versions for these reactions, which are reviewed herein.

## 2. Isocyanide and isothiocyanate derivatives as formal 1,3-dipoles

Isocyanides are compounds that contain the isonitrile group (-NC). This functional group is associated with highly special properties that highlight its uniqueness among the field of organic chemistry.<sup>[11]</sup> Namely, isocyanides can act both as nucleophiles and electrophiles, thus being able to react with a myriad of different nucleophilic or electrophilic species, as well as with radicals, to give rise to a variety of primary imine adducts.<sup>[12]</sup> Isocyanides also feature a significant  $\alpha$ -acidity, which can be further increased by placing electron-withdrawing groups

at this position, such as carboxylic or phosphoric esters, nitriles and sulfonyl groups.<sup>[13]</sup> The deprotonation of the  $\alpha$  position results in a carbanion which can perform addition reactions to electrophilic double bonds, such as carbonyl groups, imines, or C=C double bonds conjugated with an electron-withdrawing group. This addition results in a new anion that can intramolecularly attack the terminal carbon atom of the isocyanide moiety, which has electrophilic properties, bringing about the transformation of the formal divalent carbon atom into a tetravalent state, a process which is relatively uncommon in typical organic reactions.<sup>[14]</sup> The global procedure can be formally considered a [3+2] cycloaddition where the isocyanide acts like a 1,3-dipolar compound (Scheme 1.a). Oxazolines, imidazolines or pyrrolines are obtained depending on the reaction partner.

Similarly, isothiocyanates bearing an electron-withdrawing group in the  $\alpha$  position can react as formal 1,3-dipoles and provide oxazolidin- imidazolidin- or pyrrolidin- thiones when reacting with electrophilically-activated unsaturated bonds (Scheme 1.b).<sup>[15,16]</sup>

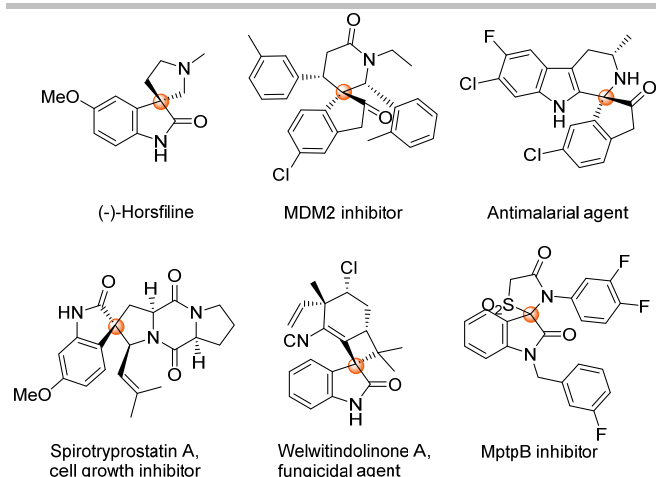


**Scheme 1.** Generic formal [3+2] cycloaddition of isocyanides (a) or isothiocyanates (b) with electrophilically-activated double bonds.

## 3. Spirocycle synthesis from isothiocyanates

### 3.1. Enantioselective synthesis of 3-spirooxindoles

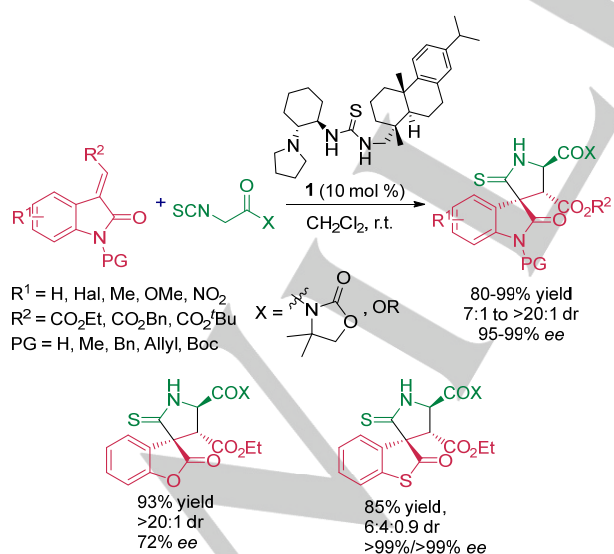
Spirooxindoles have emerged as privileged structures, that can be found in natural alkaloids such as horsfieldine, isolated from Malaysian tree *Horsfieldia superba*,<sup>[17,18]</sup> as well as in products of pharmaceutical interest.<sup>[19]</sup> Examples include promising actors in targeted cancer therapy,<sup>[20]</sup> antimalarial agents,<sup>[21]</sup> cell growth inhibitors such as spirotryprostatin A,<sup>[22]</sup> fungicidal agents such as welwitindolinone A,<sup>[23]</sup> or compounds with potential application in MtpB-inhibitor-based treatments for tuberculosis (Figure 2).<sup>[24]</sup> Consequently, a diversity of synthetic methods targeting these compounds have been developed.<sup>[25]</sup> Among them, a good number feature the use of isothiocyanates as formal dipoles. Two situations can be considered, depending on whether the isothiocyanate group is located on the oxindole framework or on the other reaction partner.



**Figure 2.** Selected natural and bioactive compounds featuring a spirooxindole motif.

### Oxindoles as dipolarophiles

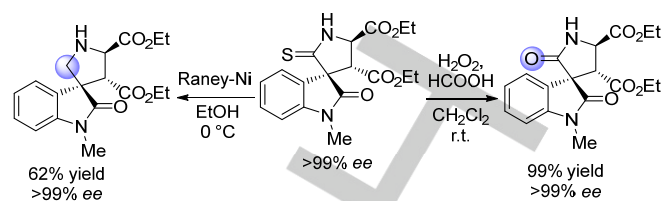
The first asymmetric synthesis of a spiro compound from isothiocyanates, was reported in 2011 by the group of Wang. The reaction of  $\alpha$ -isothiocyanato imides and 3-methyleneindolin-2-ones furnished optically active spirooxindoles with good to excellent yields, and excellent diastereo- and enantioselectivities (Scheme 2).<sup>[26]</sup> The process was catalyzed by a rosin-derived tertiary amine thiourea **1** and involved a Michael addition/cyclization sequence. The reaction proved to be robust, allowing the presence of substituents of varied electronic character at different positions of the aromatic ring. The procedure also tolerated several protecting groups on the oxindole nitrogen atom with similar results. In addition, the reaction conditions were compatible with the benzofuran or benzothiophene analogues with a small impact on the stereoselectivity.



**Scheme 2.** Synthesis of 3,3'-thiopyrrolidonyl spirooxindoles catalyzed by a rosin-derived thiourea **1**.

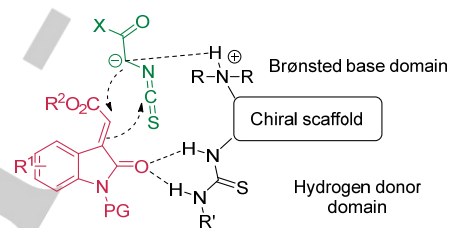
Furthermore, the thiopyrrolidonyl spirooxindoles can be readily transformed into pyrrolidonyl and pyrrolidinyl spirooxindoles

(Scheme 3), which highlights the synthetic potential of isothiocyanates.



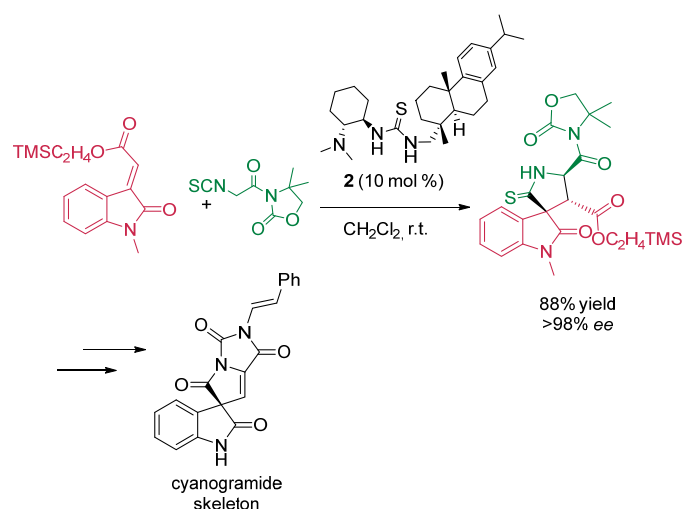
**Scheme 3.** Transformation of thiopyrrolidonyl spirooxindoles into pyrrolidonyl and pyrrolidinyl spirooxindoles.

In this work, the authors propose a catalytic mechanism where the chiral thiourea acts as a hydrogen-bonding donor towards the carbonyl group of the indolinone, the tertiary amine deprotonates the isothiocyanate for nucleophilic activation, while the chiral scaffold is responsible for the chiral induction (Figure 3).



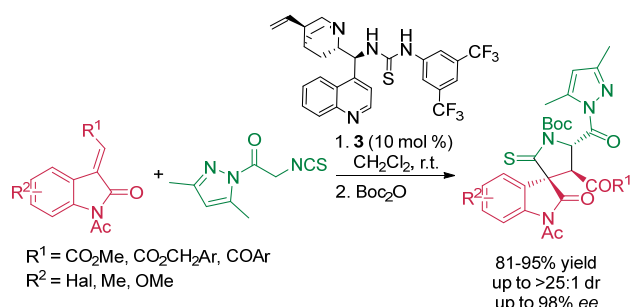
**Figure 3.** Proposed catalytic model for the formal [3+2] cycloaddition reaction of isothiocyanates and methylene indolinones catalyzed by a chiral thiourea.

A modification of the above procedure was applied by Monecke and Lindel in 2018 as the key step in the synthesis of an analog of the marine natural product cyanogramide (Scheme 4).<sup>[27]</sup> A rosin-derived tertiary amine thiourea **2**, similar to that employed by Wang was used as the catalyst.



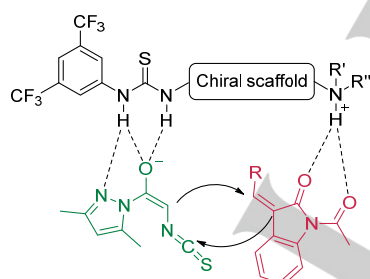
**Scheme 4** Formation of the spiro ring in a synthetic key step toward an analog of cyanogramide.

In 2012, Barbas and Zhong described another asymmetric synthesis of 3,3'-thiopyrrolidonyl spirooxindoles from 3-methyleneindolin-2-ones. Isothiocyanates featuring a dimethylpyrazolone instead of an oxazolidinone were used since this latter moiety provided reduced diastereoselectivity (Scheme 5).<sup>[28]</sup> This change allowed the use of a cinchonidine-based thiourea **3** as the catalyst providing excellent results in terms of yield, diastereo- and enantioselectivity for substituents with distinct properties on the oxindole ring or on the exocyclic double bond. Limitations were observed for spirooxindoles substituted with bulky groups such as phenyl, which was unreactive, or substituted with strong electron-withdrawing groups such as the cyano (CN) group, which provided low diastereoselectivity.



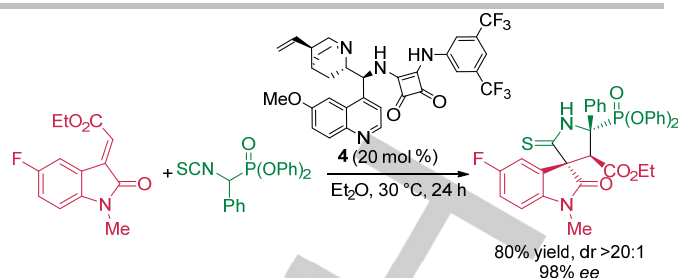
**Scheme 5.** Synthesis of thiopyrrolidonyl spirooxindoles from methylene oxindoles and dimethylpyrazoyl isothiocyanates.

Owing to the differences observed with the use of the dimethylpyrazolone-derived isothiocyanate, the authors suggested a mechanism with one of the pyrazolone nitrogen atoms participating in an additional hydrogen bond (Figure 4).



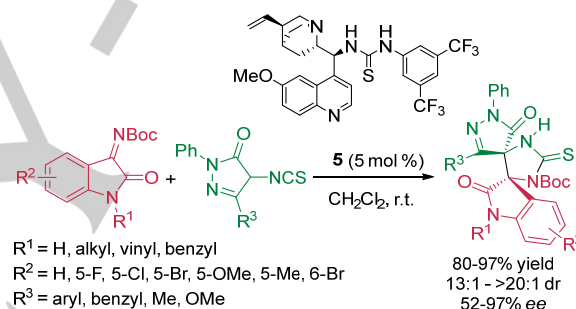
**Figure 4.** Mechanistic proposal for the reaction of dimethylpyrazolone-derived isothiocyanate and methylenide indolinones catalyzed by a chiral thiourea.

In 2014, Wang and coworkers described the reaction of  $\alpha$ -isothiocyanato phosphonates and dipolarophiles using a chiral squaramide **4** derived from quinine as bifunctional catalyst.<sup>[29]</sup> Although the major part of the work comprised direct 1,2-additions to carbonyl or imine groups, in one of the examples, a methylenide indolinone was used, and the result was a chiral  $\alpha$ -aminophosphonate spirooxindole, which was obtained with excellent diastereo- and enantioselectivity (Scheme 6).



**Scheme 6.** Squaramide catalyzed synthesis of an optically active phosphonate-substituted spirooxindole.

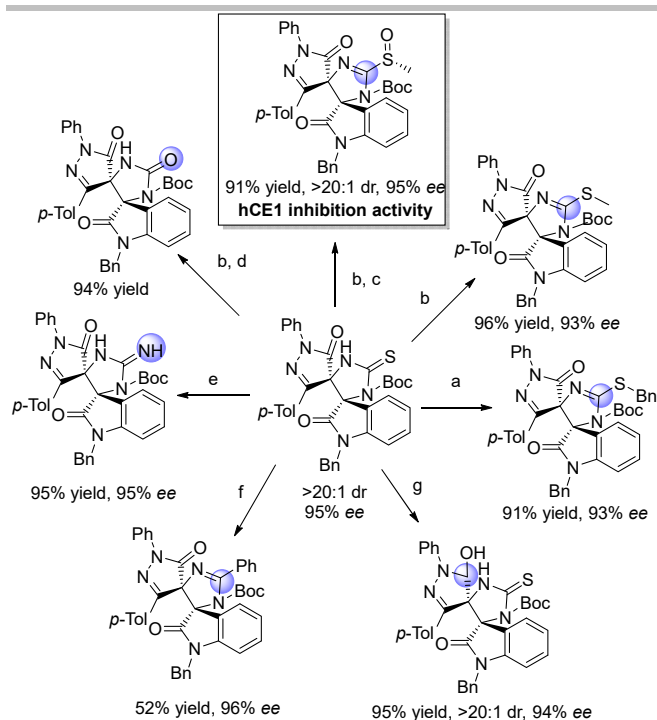
In 2018, the group of Qu and Wang introduced new 4-isothiocyanato pyrazolone synthons, which were used in the enantioselective formal [3+2] cycloaddition with isatin ketimines to give oxindoles bearing a dispirotriheterocyclic scaffold. The reaction was catalyzed by a bifunctional thiourea **5** derived from quinine. Unlike in the previous examples, the resulting spirocenters are attached to a nitrogen atom instead of to all carbon atoms (Scheme 7).<sup>[30]</sup>



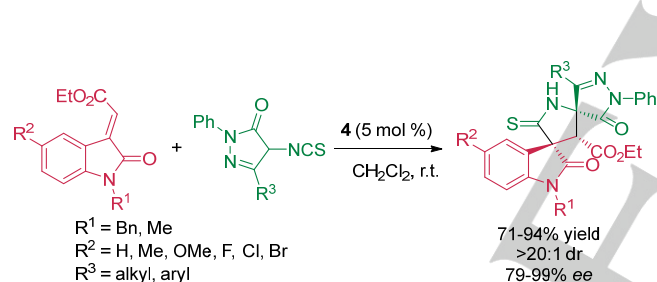
**Scheme 7.** Synthesis of dispirooxindoles from 4-isothiocyanato pyrazolones.

The developed protocol was shown to be compatible with either *N*-unsubstituted or substituted isatins, providing excellent yield, diastereo- and enantioselectivity. However, a drastic reduction of diastereo- and enantioselectivity was observed when the C3 carbon of the pyrazolone features an alkyl substituent. The reaction products showed great synthetic potential, and multiple transformations on the thiourea moiety and in the pyrazolone moiety were successful (Scheme 8). The chiral sulfoxide highlighted in this scheme showed significant inhibitory activity towards human carboxylesterase 1 (hCE1), a key target in the modulation of cholesterol and lipid metabolism.

Later in 2020, the same research group reported a modification of this reaction using this time 3-ylideneoxindoles as dipolarophiles (Scheme 9).<sup>[31]</sup> In this case, the squaramide derived from quinine **4** was used as the catalyst, which provided the best combined results of enantio- and diastereoselectivity and short reaction times. This protocol afforded products with excellent yield, diastereo- and enantioselectivity for a number of 3-ylideneoxindoles. The isothiocyanato pyrazolone partner tolerated alkyl and polycyclic aromatic substituents, however a decreased enantiomeric excess was observed when this was a 2-thiophenyl group.



**Scheme 8.** Transformations of the trispirocyclic oxindoles. Reaction conditions: (a) BnBr, K<sub>2</sub>CO<sub>3</sub>, acetone; (b) MeI, K<sub>2</sub>CO<sub>3</sub>, acetone (c) *m*CPBA CHCl<sub>3</sub>, 0 °C; (d) *m*CPBA, CHCl<sub>3</sub>, 0 °C; (e) NH<sub>4</sub>OH, TBHP, MeOH; (f) PhB(OH)<sub>2</sub>, CuTC, Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, 50 °C; (g) NaBH<sub>4</sub>, THF.

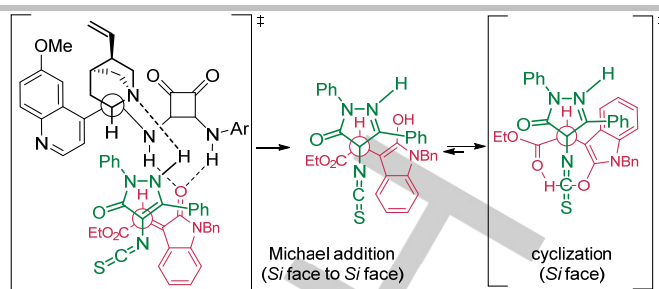


**Scheme 9.** Synthesis of 4-pyrazolone-derived trispirocycles via a Michael addition and tandem cyclization of 4-isothiocyanato pyrazolones and 3-ylidene oxindoles.

The authors proposed a working model in which the enamine tautomer of 4-isothiocyanato pyrazolone rather than the enol form and the 3-ylideneoxindole were engaged by the bifunctional squaramide catalyst via hydrogen bonding interactions to give an ordered transition structure where the *Si* face of the nucleophilic enamine tautomer approaches the *Si* face of the 3-ylideneoxindole to deliver the Michael adduct. Then, an intramolecular hydrogen bonding-driven C–C bond rotation of the Michael adduct enabled the addition of the indole moiety to the *Si* face isothiocyanate to give the final product with the observed stereochemistry (Figure 5).

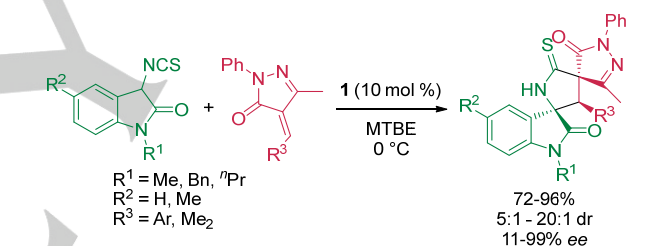
### 3-Isothiocyanato oxindoles as formal dipoles

Oxindoles bearing an isothiocyanate group at position 3 have been extensively used as formal dipoles in enantioselective reactions providing spirooxindoles. This strategy permits the preparation of 3,2'-pyrrolidonyl spirooxindoles, featuring the nitrogen atom next to the spiro carbon center.



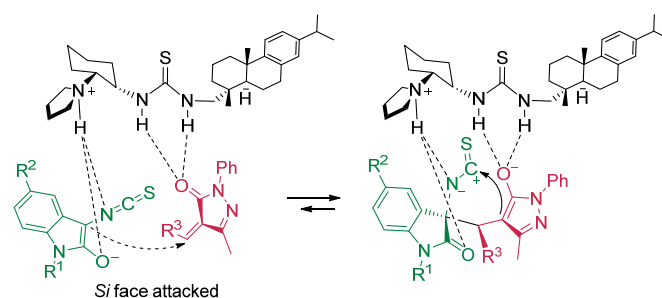
**Figure 5.** Proposed working model for the Michael addition/cyclization process of 4-isothiocyanato pyrazolones and 3-ylidene oxindoles catalyzed by squaramide **4**.

Many examples were reported as earlier as the year 2013. Rui Wang and coworkers published the synthesis of optically active bi-spirocycles from isothiocyanato oxindoles and alkylidene pyrazolones catalyzed by their rosin-derived thiourea **1** (Scheme 10).<sup>[32]</sup> The reaction, avoids the use of environmentally harmful halogenated solvents and provided multicyclic structures containing three contiguous stereogenic centers, including two spiro quaternary centers, with good to excellent yields and enantiomeric excess, except for pyrazolones disubstituted at the exocyclic double bond.



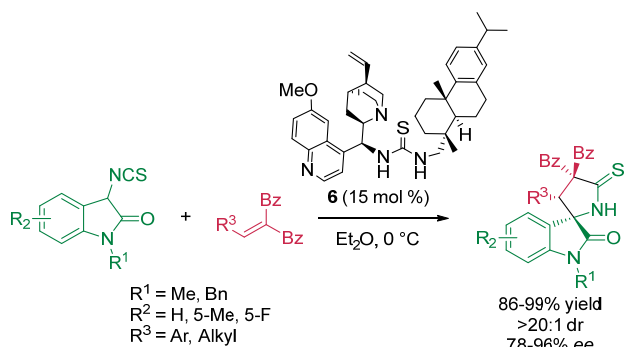
**Scheme 10.** Rosin-thiourea catalyzed formal [3+2] cycloaddition of isothiocyanato oxindoles and unsaturated pyrazolones.

To explain the observed stereochemistry the authors proposed a dual activation model with the pyrazolone activated by hydrogen bonding with the thiourea moiety and the protonated tertiary amine forming another hydrogen bond with the isothiocyanato oxindole enolate (Figure 6).



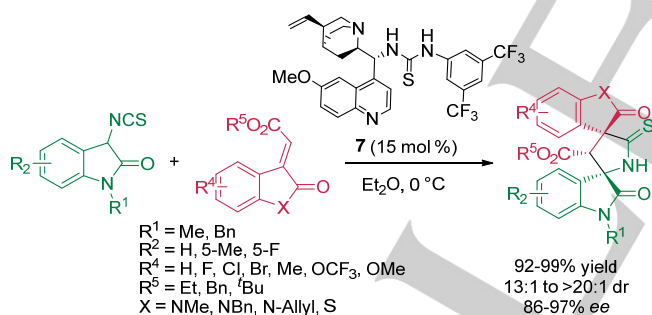
**Figure 6.** Proposed model for the asymmetric reaction of isothiocyanato oxindoles and unsaturated pyrazolones catalyzed by thiourea **1**.

The same group also reported a similar reaction using 2-alkylidene-1,3-diketones as dipolarophiles (Scheme 11).<sup>[33]</sup> The Michael addition and cyclization reactions were enabled by the use of a chiral bifunctional thiourea **6** derived from quinidine and rosin, leading to 3,3'-pyrrolidinyl spirooxindoles. The reaction tolerated the presence of aromatic groups of diverse electronic character on the olefin partner, as well as heteroaromatic groups. Substitution at the aromatic ring of the isothiocyanato oxindole was also tolerated with excellent results.



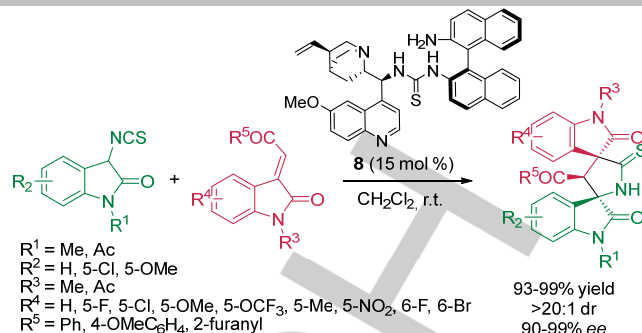
**Scheme 11.** Asymmetric synthesis of 3,2'-pyrrolidinyl spirooxindoles from 3-isothiocyanato oxindoles and 2-alkylidene-1,3-diketones.

The authors also explored the reaction of isothiocyanato oxindoles with methylene indolinone dienophiles in order to obtain complex bi-spirooxindoles with three contiguous stereocenters, including two spiro-quaternary chiral carbon atoms (Scheme 12). Again, a quinidine-derived thiourea but with lower steric hindrance **7** was needed.



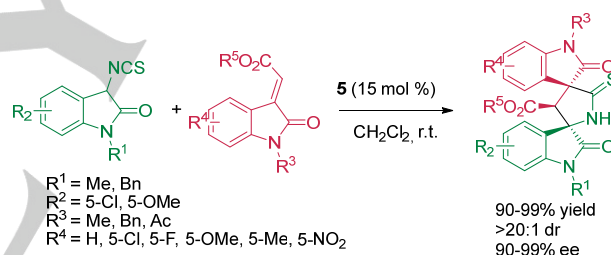
**Scheme 12.** Wang's approach to bi-spirooxindole derivatives.

Simultaneously, the group of Huang and Wang described another Michael addition/cyclization of isothiocyanato oxindoles and 3-(2-acylmethylidene) indolinones to afford 3,2'-pyrrolidinyl bi-spirooxindoles, this time catalyzed by a thiourea **8** derived from (*R*)-BINAM and quinine (Scheme 13).<sup>[34]</sup> This catalyst allows for the reaction to be carried out at room temperature with excellent results. The enantiomeric products can also be obtained with similar enantioselectivity and excellent diastereoselectivity by employing a pseudoenantiomer catalyst based on quinidine and (*S*)-BINAM.



**Scheme 13.** Bi-spirooxindole synthesis catalyzed by a thiourea derived from (*R*)-BINAM and quinine.

Extension to methylenedioxy oxindoles bearing an ester group attached to the exocyclic double bond required a change of organocatalyst (Scheme 14). Thiourea **5**, based on quinine, allowed the synthesis of the bi-spirooxindoles with excellent diastereoselectivity and good to excellent enantioselectivity, irrespectively of the electronic character of the substituents present in the isothiocyanato oxindole or in the alkylidene indolinone. This catalyst delivered the opposite enantiomers to those obtained with catalyst **7** (Scheme 12). Excellent results were also observed when attempting the reaction at a gram scale.

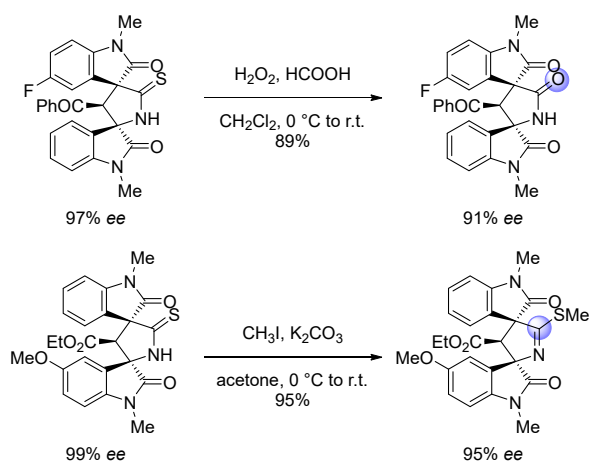


**Scheme 14.** Bi-spirooxindole synthesis catalyzed by a thiourea derived from quinine.

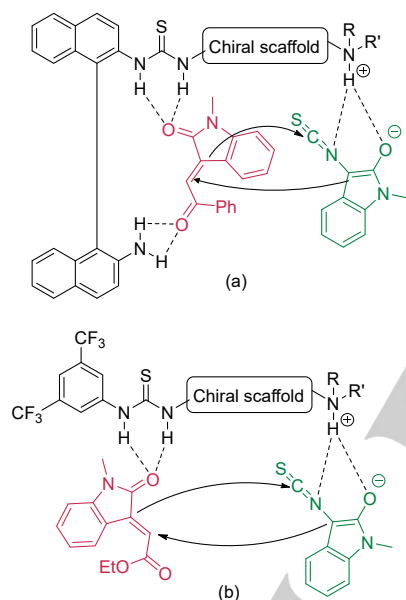
Interestingly, all reactions proceeded in very short periods of less than one minute. Conversion of the thiolactam into a lactam could be achieved by oxidation with hydrogen peroxide while reaction with MeI provided the methylated thiolactam (Scheme 15).

Mechanistic studies carried out with the reaction catalyzed by the BINAM/quinine-derived catalyst **8** (Scheme 13) using ESI-MS methods revealed a strong interaction between the catalyst with the isothiocyanato oxindole reaction partner. According to this and the low reactivity observed with substrates lacking a carbonyl group on the alkylidene oxindole double bond, the authors suggested a combined activation model in which there is hydrogen-bond interaction between the catalyst and the electron-deficient olefin, and a strong interaction, probably with certain ionic character between the catalyst and the isothiocyanato oxindole (Figure 7a). On the other hand, when catalyst **5** was used for the reaction between methylene indolinone esters and isothiocyanato oxindoles (Scheme 14), the electron-deficient methylene indolinone was activated by hydrogen bonds involving the carbonyl group in the indolinone and the thiourea moiety, while simultaneously the isocyanato

oxindole was enolized and activated by the tertiary amine (Figure 7b).

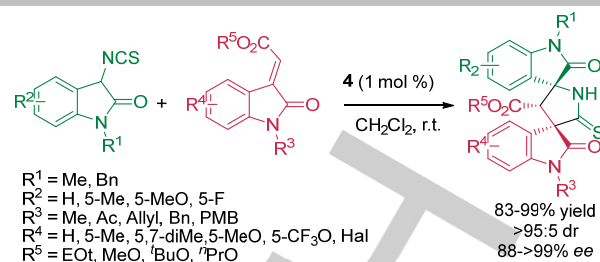


**Scheme 15.** Transformation of the thioamide moiety in bi-spirooxindoles.



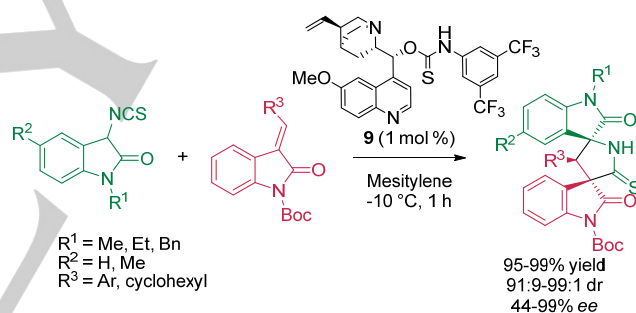
**Figure 7.** Mechanistic proposal for the interaction of the BINAP/quinine-derived thiourea **8** (a) or thiourea **5** (b) and the reacting species.

Squaramide **4**, derived from quinine, has been shown also effective in the enantioselective reaction of isothiocyanato oxindoles and ylidene oxindoles as reported by the group of Chen and Xiao (Scheme 16).<sup>[35]</sup> The amount of catalyst could be reduced to just 1 mol%, implying significantly lower catalyst loading compared with previous examples, still allowing to obtain the corresponding bi-spirooxindole products with excellent stereoselectivity, despite the increased reaction times.



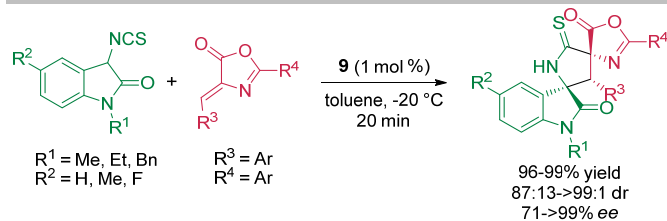
**Scheme 16.** Bi-spirooxindole synthesis catalyzed by a squaramide derived from quinine.

Later in 2013, another alternative for the previous synthesis of bi-spirocycles with two oxindole units was presented by the group of Yuan.<sup>[36]</sup> A novelty of this work was the use of thiocarbamate organocatalyst **9** derived from quinine, featuring a different hydrogen donor/acceptor unit compared with previous examples. The procedure requires a low catalyst load and delivers the expected products with overall excellent yields, diastereo- and enantioselectivities (Scheme 17), although with the requirement of cooling to much lower reaction temperatures. The reaction demonstrated high dependence on the protecting group of the isothiocyanato oxindole nitrogen, with the enantioselectivity being reduced as the volume of the protecting group progressively increased from methyl to ethyl and benzyl.



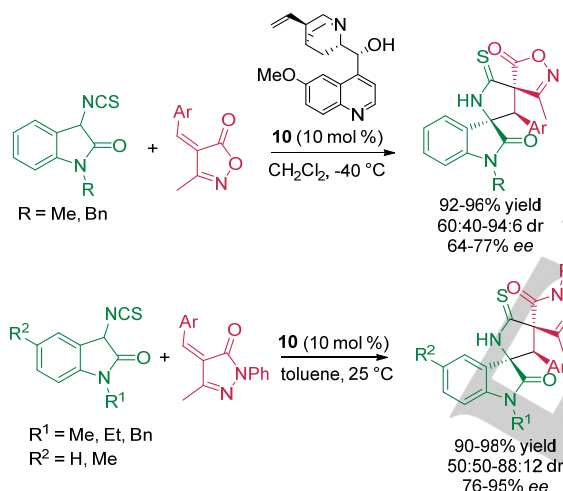
**Scheme 17.** Thiocarbamate-catalyzed Michael addition/cyclization of isothiocyanato oxindoles and methylidene indolinones.

In the same work, the authors explored the possibilities of other reaction partners taking the role of the electron-deficient olefin, and developed the Michael addition/cyclization of 3-isothiocyanato oxindoles and alkylidene azlactones. Using the same catalyst **9**, bi-spirocyclic oxindoles were obtained with overall excellent yields, diastereo- and enantioselectivities (Scheme 18). The reaction showed excellent results with azlactones bearing aromatic rings of different electronic character at either the exocyclic double bond or at position 2. On the other hand, the same dependence of enantioselectivity with respect to the *N*-substituent on the oxindole was observed.

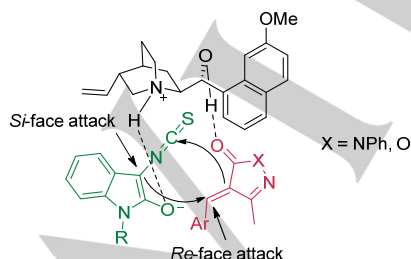


**Scheme 18.** Synthesis of bi-spirocycles by the reaction of isothiocyanato oxindoles and azlactones catalyzed by quinine carbamate **9**.

In 2014, in a new endeavor toward spirocyclic compounds featuring other heterocycles these authors described the reaction of isothiocyanato oxindoles with 4-alkylideneisoxazol-5-ones or 4-alkylidene-3-pyrazolones catalyzed by quinine (**10**) (Scheme 19).<sup>[37]</sup> Good diastereoselectivities and moderate enantioselectivities were obtained in the first case. On the other hand, the reaction with the unsaturated pyrazolones provided diastereoselectivities and enantiomeric excess, in general, lower than those obtained with Wang rosin thiourea **1** (Scheme 10).



**Scheme 19.** Asymmetric Michael addition/cyclization of isothiocyanato oxindoles with unsaturated isoxazol-5-ones and pyrazol-3-ones catalyzed by quinine.

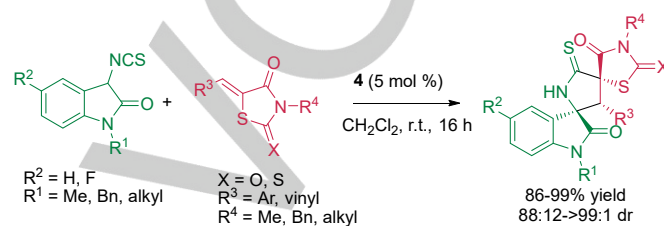


**Figure 8.** Mechanistic proposal for the reaction of isothiocyanato oxindoles with unsaturated isoxazol-5-ones and pyrazol-3-ones catalyzed by quinine.

The authors proposed a dual activation working model where the two substrates involved in the reaction are activated simultaneously: The 3-isothiocyanato oxindole by the tertiary amine and the dipolarophile by the OH group of the quinine,

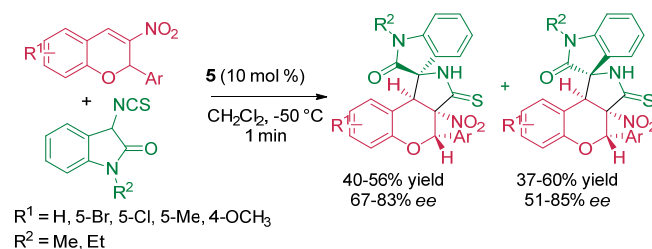
favoring the Michael addition of the isothiocyanate enolate to the Re face of the unsaturated heterocycle (Figure 8).

Expanding the range of dipolarophiles consisting on heterocycles bearing an exocyclic double bond, Song and Du described the reaction of 3-isothiocyanato oxindoles and unsaturated thiazolidinones to furnish thiopyrrolidonyl bi-spirocycles (Scheme 20).<sup>[38]</sup> The reaction is catalyzed by the quinine-derived squaramide **4**. In general, good to excellent yields are obtained, as well as excellent diastereo- and enantioselectivity, except for rhodamine derivatives (X = S), that gave low ee. Also, the protecting group at the nitrogen atom of the thiazolidinone was an important factor since the unprotected thiazolidinone was insoluble in the reaction medium and did not react.



**Scheme 20.** Diastereo- and enantioselective formal [3+2] cycloaddition reaction of unsaturated thiazolidinones and 3-isothiocyanato oxindoles.

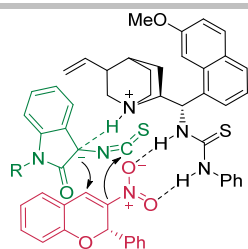
In 2014, Xie described the cascade Michael-cyclization reaction of isothiocyanato oxindoles and 3-nitro-2*H*-chromene to afford tetracyclic spirooxindole compounds, in an extremely fast reaction catalyzed by thiourea **5** (Scheme 21).<sup>[39]</sup> Although diastereoselectivities were poor to moderate, enantiomeric excess values were good. The biggest limitations regarding enantioselectivity were observed when the aromatic substituent at position 2 of the chromene was an *ortho*-substituted one. Interestingly, the second diastereomer could be epimerized at the spiro carbon under basic conditions (DABCO), a process that takes place with an increase of the enantiomeric excess.



**Scheme 21.** Synthesis of spirocyclic oxindoles from 3-nitro-2*H*-chromenes and isothiocyanato oxindoles.

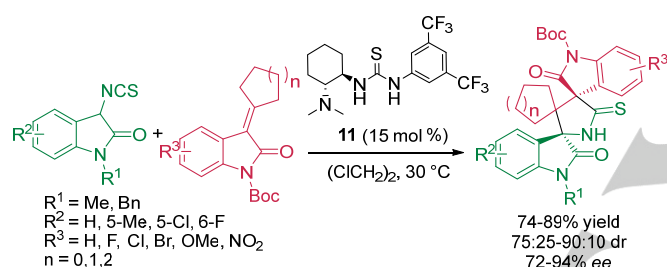
According to the experimental results obtained, a dual activation model with both substrates activated by the bifunctional thiourea **5** was proposed (Figure 9). The Michael acceptor is activated and oriented by the hydrogen bonds of the thiourea and the nitro group, while the tertiary amine of the catalyst deprotonates the 3-isothiocyanato oxindole increasing its nucleophilicity.





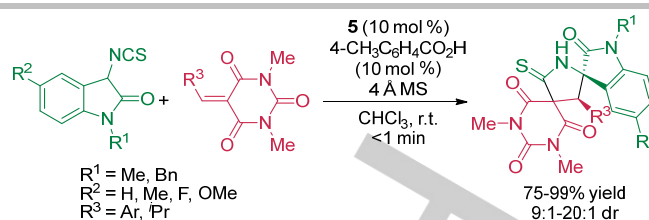
**Figure 9.** Dual activation mode for the reaction of isothiocyanato oxindoles and 3-nitro-2*H*-chromenes catalyzed by bifunctional thiourea **5**.

In 2016, the group of Jing and Qin described the asymmetric synthesis of trispirooxindoles with good enantiomeric excesses by the reaction of 3-isothiocyanato oxindoles and cycloalkylidene oxindoles, employing Takemoto thiourea (**11**) organocatalyst (Scheme 22).<sup>[40]</sup> Remarkably, the result was highly dependent on the size of the cycloalkyl ring attached to the exocyclic double bond of the alkylidene indolinone. The best results were obtained when this is a six-membered cycle. Surprisingly, no advance of the reaction was observed when it was a five-membered carbocycle.



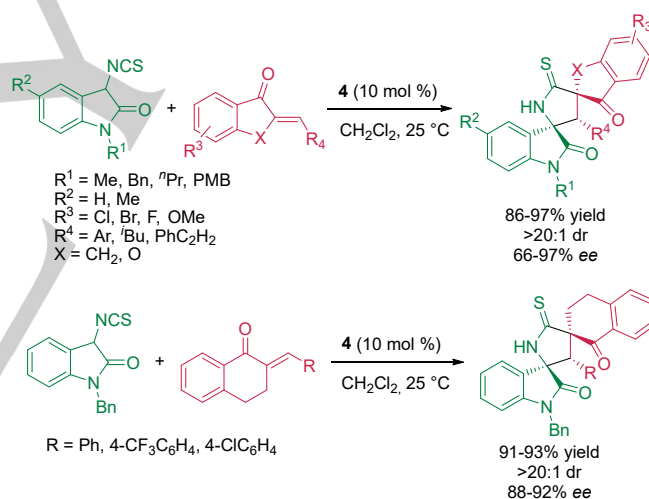
**Scheme 22.** Enantioselective synthesis of trispirooxindoles catalyzed by Takemoto thiourea.

Also in 2016, Zhao and coworkers described the asymmetric synthesis of dispirobarbiturates by the formal [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles and alkylidene barbiturates as dipolarophiles, catalyzed by thiourea **5** derived from quinine and 4-methylbenzoic acid (Scheme 23).<sup>[41]</sup> The acid additive seems to promote tautomerization of the isothiocyanato oxindole into its enol form, adding a hydrogen donor domain to the system that may be better suited to interact with the bifunctional thiourea catalyst than the carbonyl form. The reaction was complete in less than one minute and showed overall good to excellent yields, excellent diastereoselectivity and good to excellent enantioselectivity. However the presence of aliphatic, large aromatic (2-naphthyl) or heteroaromatic (2-thiophenyl) groups attached to the exocyclic double bond on the barbiturate reduced dramatically the enantioselectivity.



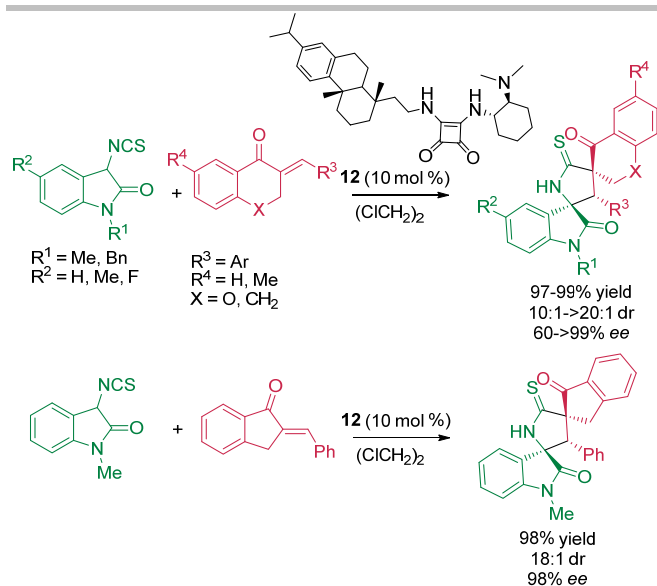
**Scheme 23.** Organocatalytic asymmetric synthesis of dispirobarbiturates from isothiocyanato oxindoles and barbiturate-based olefins.

Bifunctional squaramide **4** was used by Kayal and Mukherjee in the asymmetric cascade Michael addition/cyclization reaction of 3-isothiocyanato oxindoles with exocyclic  $\alpha,\beta$ -unsaturated ketones, such as indanones and benzofuranones, affording bispirocyclic oxindoles (Scheme 24).<sup>[42]</sup> The reaction showed broad scope, being compatible with groups of different electronic character on the aromatic ring of either reactant allowing good yields, excellent diastereoselectivity and fair to excellent enantioselectivity. The reaction conditions were also suitable for  $\beta$ -arylidene- $\alpha$ -tetralones. However, simple cyclic ketones conjugated with an exocyclic double bond failed to give good enantioselectivity.



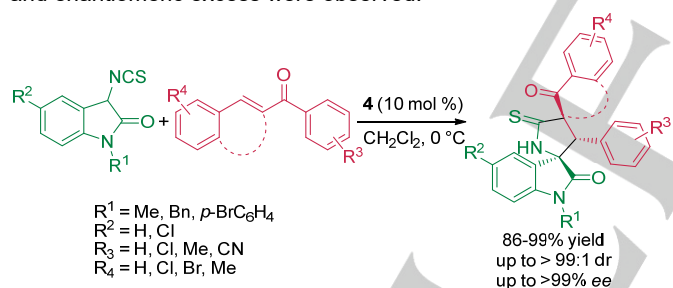
**Scheme 24.** Formal [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles with cyclic arylidene ketones catalyzed by squaramide **4**.

Related work was reported in 2018 by Lin, Weng, Lu and coworkers using  $\alpha$ -benzylidene chromanones, as well as the related tetralones and indanones as dipolarophiles (Scheme 25).<sup>[43]</sup> In this case, a new squaramide **12** derived from rosin and diaminocyclohexane was used as a bifunctional catalyst. Good results were obtained in all the studied cases. As in other previous examples, the *N*-methyl protected isothiocyanato oxindole provided better results than the *N*-benzyl protected one.



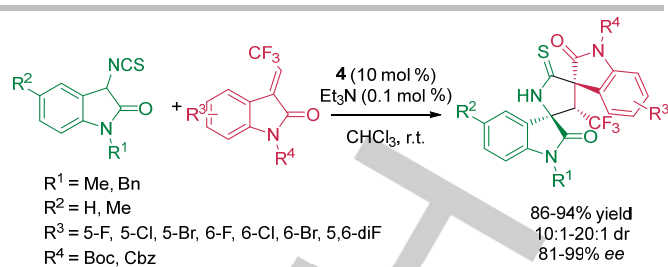
**Scheme 25.** Formal [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles with cyclic arylidene ketones catalyzed by squaramide **12**.

In 2017, the group of Du described an asymmetric cascade Michael addition/cyclization of isothiocyanate oxindoles and chalcones to provide oxindole-derived spiro compounds (Scheme 26).<sup>[44]</sup> Again, squaramide **4** led to the best results with excellent yields, diastereo- and enantioselectivities. Alkyl substitutions on the Michael acceptor were also compatible, although significant decreases in the yield, diastereoselectivity and enantiomeric excess were observed.



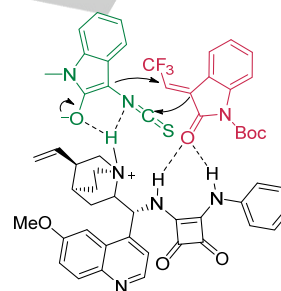
**Scheme 26.** Formal [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles with chalcones catalyzed by squaramide **4**.

3-Trifluoroethylidene oxindoles have been recently reported as dipolarophiles in this kind of reactions, which represented the first approach to 3'-trifluoromethyl substituted 3,2'-pyrrolidinyl spirooxindoles from isothiocyanates (Scheme 27).<sup>[45]</sup> Squaramide **4**, derived from quinine, gave the best results. 3-Trifluoroethylidene oxindoles were less reactive than non-fluorinated alkylidene oxindoles and addition of triethylamine was required to obtain short reaction times. The reaction displayed excellent compatibility with 3-isothiocyanato oxindoles or 3-trifluoroethylidene oxindoles bearing substituents of different electronic character, without any remarkable exceptions, and the protocol was also compatible with gram-scale synthesis of 3'-trifluoromethyl substituted 3,2'-pyrrolidinyl spirooxindoles.



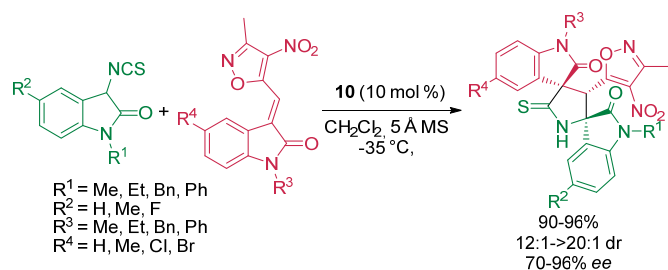
**Scheme 27.** Asymmetric reaction of 3-isothiocyanato oxindoles and 3-trifluoroethylidene oxindoles catalyzed by squaramide **4**.

In the proposed mechanism for this reaction, the squaramide moiety forms two hydrogen bonds with the carbonyl group of the 3-trifluoroethylidene oxindole while the tertiary amine moiety of the Cinchona alkaloid deprotonates and activates the 3-isothiocyanato oxindole via double hydrogen bonds, in a similar way as in other proposed mechanistic pathways (Figure 10).



**Figure 10.** Mechanistic proposal for the reaction of 3-isothiocyanato oxindoles and 3-trifluoroethylidene oxindoles catalyzed by squaramide **4**.

Providing a new electron-withdrawing moiety for alkylidene oxindoles acting as dipolarophiles, in 2019, Liu and coworkers described the asymmetric Michael addition/cyclization cascade reaction of 3-isothiocyanato oxindoles and 3-methyl-4-nitro-5-isatylidene isoxazoles catalyzed by quinine (**10**), yielding enantiomerically enriched isoxazole-dispirobisoxindoles (Scheme 28).<sup>[46]</sup>



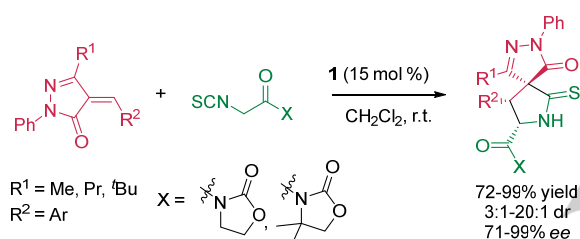
**Scheme 28.** Synthesis of isoxazole-dispirobisoxindoles from 3-isothiocyanato oxindoles and isatylidene isoxazoles by an organocatalytic process promoted by quinine.

Although enantioselectivities were found to be dependent on the protecting group of the nitrogen atom of the isothiocyanato oxindole and the isatylidenyl isoxazole, and on the electronic character of the substitution of both aromatic rings, excellent diastereoselectivity was achieved in almost all cases and high reactivity was observed, with reaction times of only 30 minutes.

### 3.2. Enantioselective synthesis of other spirocyclic compounds

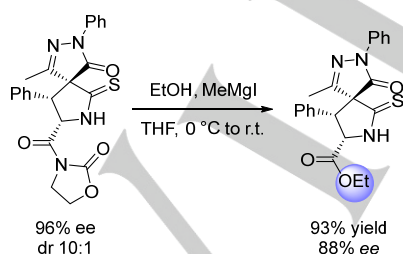
Although the vast majority of published reports outlining the synthesis of spiro compounds by formal cycloaddition reactions with isothiocyanates are related to the synthesis of spirooxindoles, other spirocyclic motifs have also been targeted, which are reviewed next.

In 2012, the group of Wang reported the asymmetric synthesis of spiropyrazolones via an organocatalyzed Michael addition of  $\alpha$ -isothiocyanato amides to unsaturated pyrazolones, followed by intramolecular cyclization to complete a formal [3+2] cycloaddition reaction (Scheme 29).<sup>[47]</sup> The rosin-derived thiourea **1**, previously used by the same authors in the synthesis of spirooxindoles, was chosen as the catalyst.



**Scheme 29.** Asymmetric synthesis of spiropyrazolones from unsaturated pyrazolones and isothiocyanates.

When the oxazolidinone moiety of the isothiocyanate was replaced by a methyl ester (X = OMe) the enantioselectivity dropped dramatically, highlighting the importance of the presence of that moiety for the successful interaction with the thiourea organocatalyst. The product can afterwards be converted into an ester as outlined in Scheme 30.

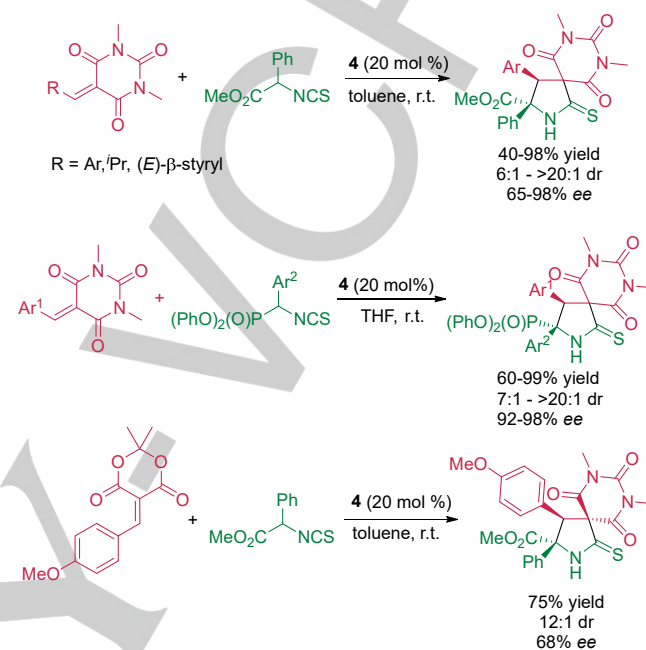


**Scheme 30.** Transformation of the oxazolidinone amide into an ethyl ester.

In 2018, the group of Albrecht demonstrated the usefulness of isothiocyanate esters derived from  $\alpha$ -substituted  $\alpha$ -amino acids as building blocks in heteroannulation reactions with electron-deficient olefins using squaramide **4** derived from quinine as the catalyst. Spirocyclic heterocycles bearing a quaternary  $\alpha$ -amino acid moiety were obtained by reaction with alkylidene

barbiturates with high diastereo- and enantioselectivity (Scheme 31).<sup>[48]</sup>

The reaction was proven to be compatible, after modulating the solvent, with isothiocyanates derived from phosphonate esters to give spirocyclic  $\alpha$ -aminophosphonates. Additionally, variability of the dipolarophile was shown by a single example with an olefin derived from Meldrum's acid, providing high diastereoselectivity, although only moderate enantioselectivity.



**Scheme 31.** Enantioselective reaction of isothiocyanate esters with electron-deficient olefins catalyzed by squaramide **4**.

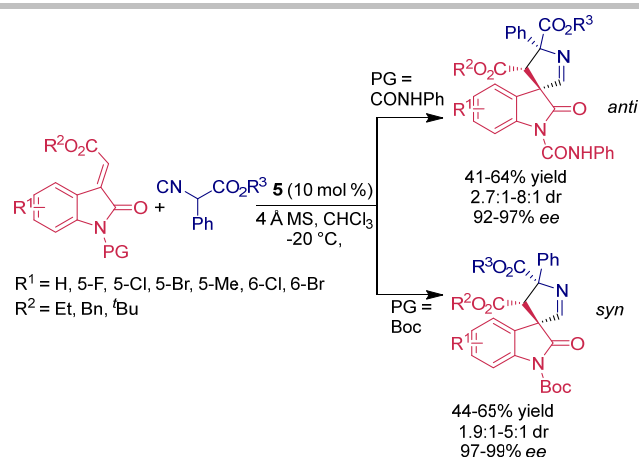
## 4. Spirocyclic synthesis from isocyanides

[3+2] Cycloaddition reactions between species containing an electrophilic double bond and isocyanides, promoted by the acidity of the  $\alpha$  position of the isonitrile group, have been widely employed for the formation of five-membered heterocycles, and somehow, it parallels the procedures with isothiocyanates describe in the previous sections.

### 4.1. Enantioselective synthesis of 3-spirooxindoles

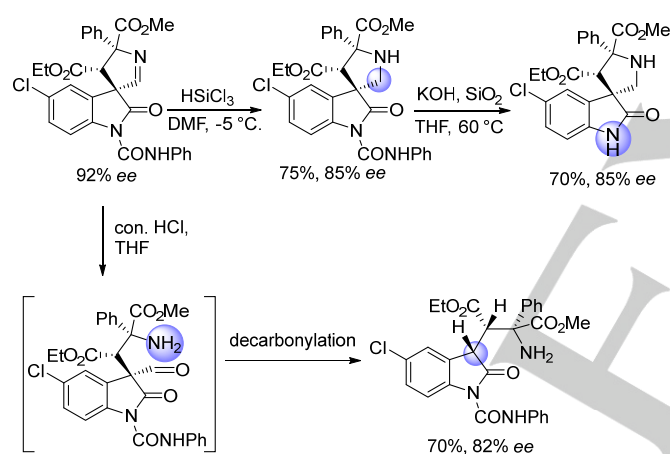
Many of the enantioselective cycloaddition reactions with isocynoacetate esters have been aimed to the synthesis of spirooxindoles. In 2012, Wang and coworkers described a diastereo- and enantioselective formal [3+2] cycloaddition reaction of isocyno acetates and methylene indolinones to give 3,3'-pyrrolidinyl spirooxindoles in the presence of thiourea **5** (Scheme 32).<sup>[49]</sup>

Remarkably, the reaction can take place in a diastereodivergent manner by simply changing the protecting group on the indolinone nitrogen, without the need of using a different catalyst. Thus, *N*-phenylamide protection favored the formation of the *anti* product while *N*-Boc protection favored the *syn* product.



**Scheme 32.** Asymmetric diastereodivergent synthesis of 3,3'-pyrrolidiny spirooxindoles from isocyano acetates and methylene indolinones catalyzed by thiourea **5**.

The reaction products could be successfully transformed into pyrroline derivatives or amino esters by reduction with trichlorosilane or acidic hydrolysis, respectively (Scheme 33).



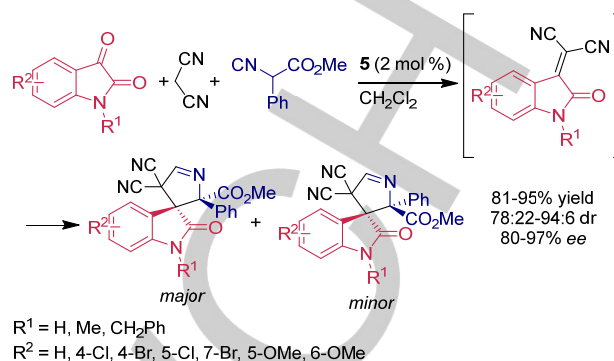
**Scheme 33.** Transformations of the pyrrolidiny ring.

In a later study, Zhong and coworkers reported the same reaction with the same catalyst under slightly different conditions, and found that the *N*-benzyl protected oxindoles gave rise to the *anti* product exclusively.<sup>[50]</sup>

Also in 2012, the group of Yan described the synthesis of 3,3'-dihydropyrryl-spirooxindoles through a stereoselective and enantioselective organocatalytic three-component reaction involving isatin, malononitrile and isocyanoacetates. In this reaction, the corresponding isatylidene malononitrile dipolarophile was generated *in situ* by the reaction of an isatin derivative and malononitrile before reaction with the isocyanoacetate catalyzed by thiourea **5** (Scheme 34).<sup>[51]</sup>

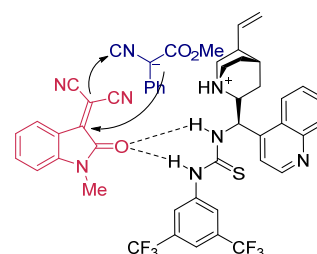
When the reaction was performed with  $\alpha$ -unsubstituted isocyanoacetates, the corresponding products were obtained with very good yield, albeit the enantioselectivity was poor. Good results were obtained with isocyano acetates bearing phenyl, *p*-methoxyphenyl or *p*-chlorophenyl groups at the  $\alpha$ -position. However, isocyanoacetates featuring groups with steric

hindrance in the *ortho* position like *o*-chlorophenyl were unreactive. The  $\alpha$ -aryl substitution was nevertheless essential, as  $\alpha$ -alkyl or benzyl isocyanoacetates also displayed no reactivity.



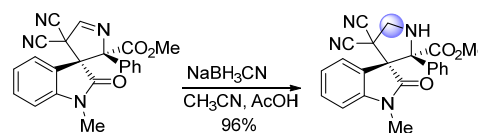
**Scheme 34.** Formation of 3,3'-dihydropyrryl-spirooxindoles through a Michael addition of isocyano esters to *in situ*-generated isatylidene malononitriles, followed by intramolecular cyclization.

A plausible reaction mechanism was proposed (Figure 11). The deprotonation of methyl  $\alpha$ -phenyl-isocyanoacetate in the presence of the organocatalyst **5** generates the nucleophilic anion, which forms an ion pair with protonated **5**. In addition, the H-bond interaction of **5** with isatylidene malononitrile increases its electrophilic reactivity and also directs the attack of the isocyanoacetate anion. A  $\pi$ - $\pi$  interaction of the isatylidene malononitrile with the  $\alpha$ -phenyl-isocyanoacetate anion would account for the preferential formation of the major diastereomer.



**Figure 11.** Stereochemical model for the three-component synthesis of 3,3'-dihydropyrryl-spirooxindoles

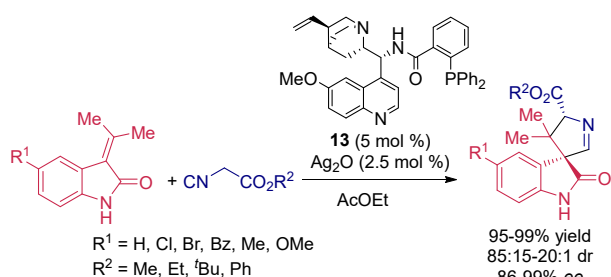
In this work, the authors reported the reduction of the pyrroline ring with sodium cyanoborohydride to give the corresponding 3,3'-pyrrolidiny spirooxindole (Scheme 35)



**Scheme 35.** Reduction of the pyrroline ring

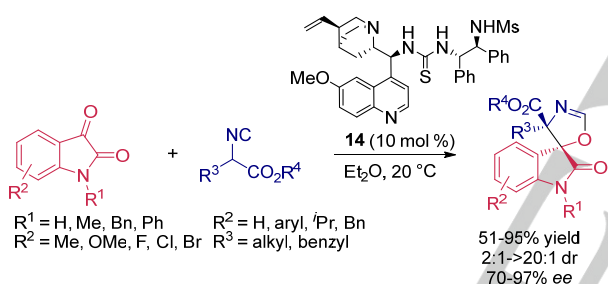
A last synthesis of 3,3'-pyrrolidiny spirooxindoles was reported in 2017 by He and coworkers (Scheme 36).<sup>[52]</sup> Compared to previously mentioned approaches by Wang and Yan, this procedure employs  $\alpha$ -unsubstituted isocyanides and less active methyldene indolinones, which are not provisioned with an

electron-withdrawing group in the exocyclic double bond. A cooperative system using silver oxide and a phosphine organocatalyst **13** previously developed by the group of Dixon was employed.



**Scheme 36.** Formal [3+2] cycloaddition reaction of  $\alpha$ -unsaturated isocyanoacetates and methylidene indolinones under cooperative catalysis.

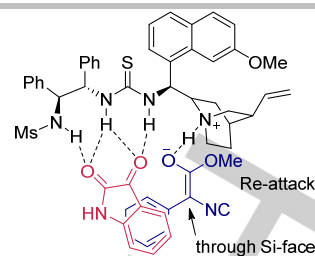
In 2013, Zhao, Shi and coworkers described the synthesis of optically active spirooxindoles featuring an oxazoline ring by the formal [3+2] cycloaddition reaction of isatins and isocyanoacetates.<sup>[53]</sup> The reaction is catalyzed by the chiral thiourea **14** derived from quinine and diphenylethane diamine (Scheme 37).



**Scheme 37.** Synthesis of oxazolanyl spirooxindoles by formal [3+2] cycloaddition reaction of isatin derivatives and isocyano esters.

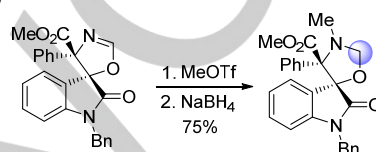
The reaction showed compatibility with isatins equipped with substituents of different electronic character. The enantioselectivity was highly dependent on the protecting group of the nitrogen atom of the isatin. *N*-Benzyl protected isatin displayed better results than the corresponding *N*-methyl or *N*-phenyl-protected isatins. Remarkably, unprotected isatin was also compatible with the catalytic system with good diastereo- and enantioselectivity. The presence of an aryl group at the  $\alpha$ -position of the isocyanoacetate, was required. However, no reaction was observed if this aryl group was substituted at the *ortho* position.

To explain the stereochemical outcome, the authors proposed a transition model as depicted in Figure 12. The isocyanoacetate is deprotonated by the quinuclidine nitrogen of the catalyst, while the isatin interacts with the catalyst through multiple hydrogen bonds. Additionally, the  $\pi$ - $\pi$  stacking interaction between the phenyl group of isocyanoacetate and the isatin moiety would lead to the formation of two newly generated stereocenters diastereoselectively.



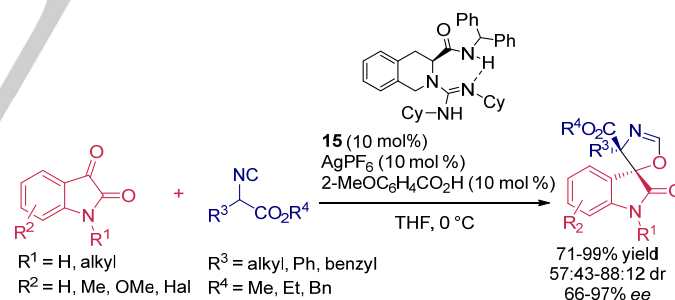
**Figure 12.** Proposed transition state for the reaction of isatins and isocyanoacetates catalyzed by thiourea **14**

Spirooxindole oxazolidines could be obtained by Meyers *N*-methylation/reduction from the oxazolanyl spirooxindoles (Scheme 38)



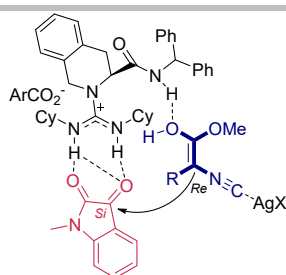
**Scheme 38.** Synthesis of spirooxindole oxazolidines

A similar reaction of isocyanoacetate esters with isatin derivatives was described in 2015 by the group of Liu and Feng (Scheme 39).<sup>[54]</sup> This procedure employed a cooperative metal-organocatalytic system that combined a Ag(I) salt with a chiral guanidine **15**. Compared with the previous example, this catalytic system provided overall lower stereoselectivity. However, besides aryl groups, the reaction could be also performed with isocyano esters bearing alkyl or benzyl groups at the  $\alpha$ -position.



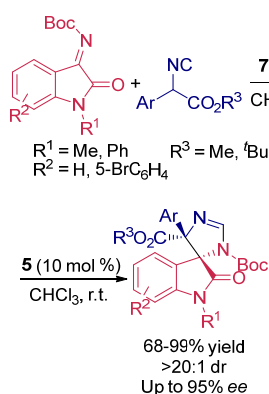
**Scheme 39.** Enantioselective spirooxindole oxazolines catalyzed by a cooperative guanidine/AgPF<sub>6</sub> system.

Based on the results obtained, the authors postulated a cooperative activation mode (Figure 13). Coordination of AgPF<sub>6</sub> with the terminal carbon of the isocyanide increases the acidity of its  $\alpha$ -proton. On the other hand, isatin is activated by the guanidinium unit of the chiral catalyst through organized multipoint hydrogen binding so the reacting species are oriented to account for the observed stereochemistry.



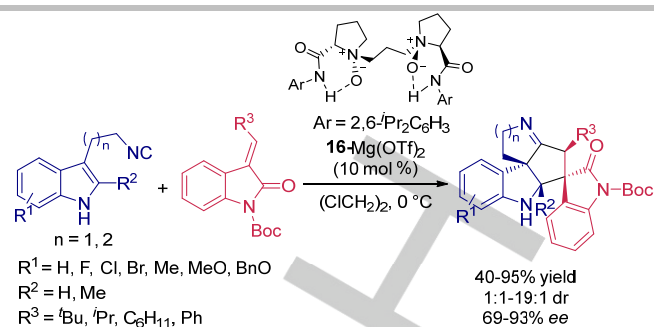
**Figure 13.** Proposed model for the synthesis of spirooxindole oxazolines catalyzed by a cooperative guanidine/AgPF<sub>6</sub> system

Later in 2015, Zhao and coworkers described the synthesis of spirooxindole imidazolines via a two-step procedure consisting of a Mannich-type reaction of isocyanoacetates and isatin imines followed by cyclization (Scheme 40).<sup>[55]</sup> Although the reaction could be performed in just one step with a single catalyst when it was performed at room temperature, better stereoselectivities were obtained if both steps were carried out separately avoiding the cyclization step by lowering the temperature. Each step was catalyzed by a different thiourea. The reaction was compatible with isatin imines bearing substituents of different electronic nature, as well as with a number of  $\alpha$ -aryl isocyanoacetates with different ring substitution. Unfortunately, again the reaction failed with isocyanoacetates having benzyl or *ortho*-substituted aryl groups.



**Scheme 40.** Two-step diastereo- and enantioselective synthesis of spirooxindole imidazolines.

Finally, although not organocatalytic, it is worth mentioning a synthesis of polycyclic 3-spirooxindole alkaloids from isocyanoalkyl indoles and alkyldiene indolinones via a Michael/Friedel-Crafts/Mannich cascade reaction, described by Feng and coworkers (Scheme 41).<sup>[55]</sup> The reaction was catalyzed by a complex of magnesium triflate and a *N,N'*-dioxide ligand **16**.

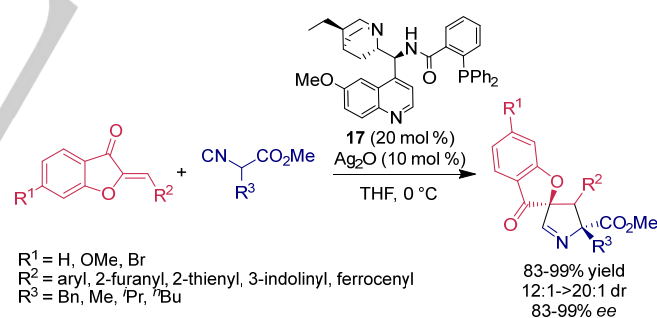


**Scheme 41.** Asymmetric synthesis of polycyclic 3-spirooxindole alkaloids via a Michael/Friedel-Crafts/Mannich cascade reaction.

The protecting group on alkyldiene indolinone nitrogen had a remarkable influence on the reaction outcome. Methyl-protected or unprotected alkyldiene indolinones were unreactive. A *tert*-butyloxycarbonyl group provided the best yield, diastereo- and enantioselectivity. Additionally, the geometry of the double bond of the alkyldiene indolinone was also relevant, with diastereoselectivity sharply decreasing with *Z* double bonds.

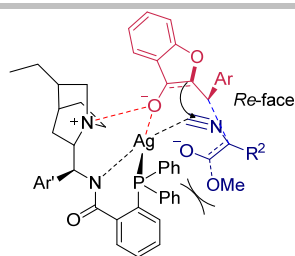
## 4.2. Enantioselective synthesis of other spirocyclic compounds

In 2018, the group of Shao and He described the synthesis of spiropyrrolines from aurones and isocyanoacetates via a formal [3+2] cycloaddition involving a Michael addition reaction and subsequent intramolecular cyclization (Scheme 42).<sup>[56]</sup> As in their previous work (Scheme 36) a cooperative catalytic system composed of Ag(I) and a phosphine **17**, derived in this case from dihydroquinine, was used.



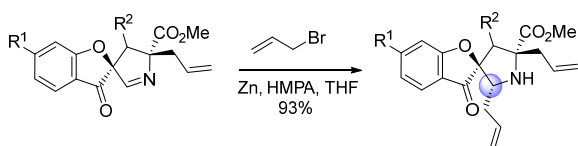
**Scheme 42.** Asymmetric Michael addition of isocyanoacetates to aurones and intramolecular cyclization to give rise to spiropyrrolines

In the proposed activation model, the  $\alpha$ -proton of isocyanoacetate is easily deprotonated by the tertiary amine due to the activation chelation of the isocyanide with Ag(I), which could also chelate the amide nitrogen and the Lewis base phosphorus on precatalyst **17**. Due to the steric repulsion, the ester group is situated below the phenyl groups, exposing the *Re*-face of the double bond of the aurone which is hydrogen-bonded to the precatalyst and coordinated to Ag(I) to stabilize the transition-state (Figure 14).



**Figure 14.** Proposed transition state for the reaction of isocyanoacetates and aurones

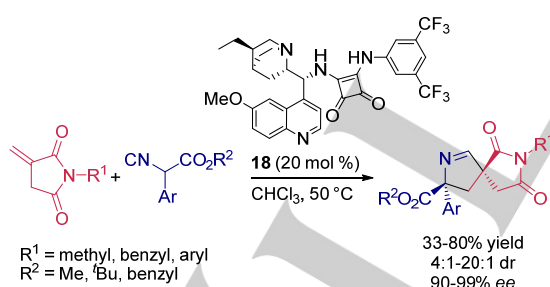
The authors described the allylation of the imine on the pyrroline moiety providing a diallyl substituted pyrrolidine in excellent yield and good stereoselectivity (Scheme 43). This transformation has the potential to furnish highly substituted biologically active pyrrolidine derivatives.



**Scheme 43.** Allylation of spiropyrrolines

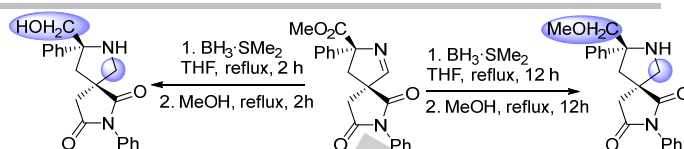
In 2019, Zhao and coworkers described another asymmetric synthesis of spiropyrrolines from isocyanoacetates and *N*-itaconimides as Michael acceptors (Scheme 44).<sup>[57]</sup> The process is catalyzed by squaramide **18** derived from dihydroquinine and provide the corresponding spirocyclic compounds with good diastereo and enantioselectivity.

Like in other related reactions, isocyanoacetates bearing an  $\alpha$ -aryl group were required.  $\alpha$ -*Ortho*-fluorophenyl methyl isocyanoacetate as well as  $\alpha$ -benzyl methyl isocyanoacetate were unreactive in the established reaction conditions.



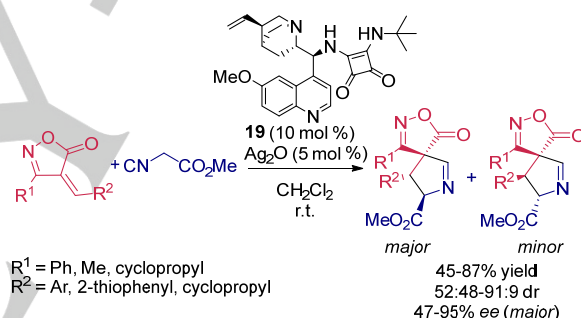
**Scheme 44.** Formal [3+2] cycloaddition reaction of *N*-itaconimides and isocyanoacetates catalyzed by a chiral squaramide.

Reduction of the imine and the ester group was achieved by reaction with the borane dimethylsulfide complex to give the corresponding amino alcohol. Interestingly, by prolonging the reaction time an amino ether was produced (Scheme 45).



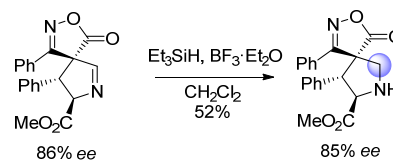
**Scheme 45.** Treatment of spiropyrrolines with borane

In a further increase on the structural variety of spirocyclic compounds, diazaspirocycles bearing three contiguous stereocenters and high functional groups were prepared diastereo- and enantioselectively by the group of Pedro and Blay in 2020.<sup>[58]</sup> The new compounds were obtained by the reaction of isocyanoacetate esters and 4-arylideneisoxazol-5-ones promoted by a bifunctional squaramide/Brønsted base organocatalyst **19** derived from quinine cooperative and silver oxide as Lewis acid (Scheme 46). The reaction was compatible with the presence of aromatic substituents of different electronic character in the C4 position of the isoxazole-5-one as well as in the exocyclic double bond. In this case, the use of  $\alpha$ -substituted isocyanoacetates reduced the yield and stereoselectivity of the reaction.



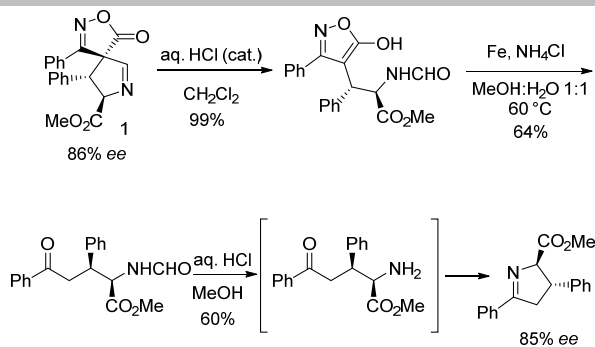
**Scheme 46.** Functionalized diazaspirocyclic synthesis from 4-benzylideneisoxazol-5-ones and isocyanoacetate esters.

In this work, selective reduction of the C–N double bond of the pyrroline ring was achieved (Scheme 47).



**Scheme 47.** Reduction of the diazaspirocycles by the use of triethylsilyl hydride and a Lewis acid.

Furthermore, the diazaspirocycles could be hydrolyzed to oxazolidinyl amino esters, which after reductive cleavage of the isoxazol-5-one ring with iron and further acidic treatment provided chiral pyrrolines (Scheme 48).



**Scheme 48.** Synthesis of chiral pyrrolines from diazapyrocyclic compounds.

## 5. Conclusions

The spirocyclic motif is present in natural products as well as in interesting synthetic compounds and chiral ligands. Furthermore, the spirocyclic motif has become a prevalent template in drug discovery. Consequently, the synthesis of spirocyclic compounds has received a growing interest from organic chemists. In this context, the formal [3+2] cycloaddition reaction involving the special reactivity of isothiocyanates and isocyanides has emerged as a valuable methodology for the synthesis of aza-spirocyclic compounds. With this regard, organocatalytic methods, especially those based on hydrogen-bonding activation, have proved to be especially suitable to carry out these reactions in an enantioselective manner. A good number of procedures leading to spirooxindoles have been developed while other spyranic scaffolds have been less studied. Surprisingly spirocycle synthesis based on related isocyanates have not been reported. Further efforts to apply this formal 1,3-dipoles based on this functional group, as well as the expansion of these methodologies to new functionalized dipolarophiles and formal dipoles which allow access to a wider variety of spiro compounds are expected in the future.

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**Keywords:** Organocatalysis • Enantioselectivity • Isocyanides • Isothiocyanates • Spiro compounds

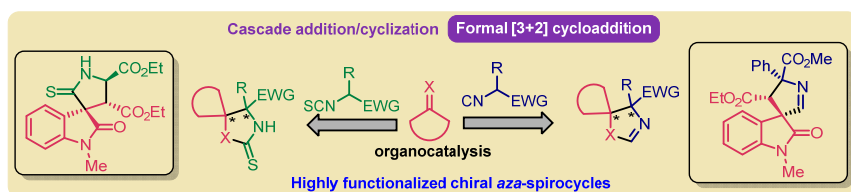
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## Entry for the Table of Contents



Formal [3+2] cycloaddition reactions of compounds bearing exocyclic unsaturated functional groups and isothiocyanate or isocyanide derivatives as formal 1,3-dipoles provide spirooxindoles and other *aza*-spirocyclic compounds. This review surveys the latest developments of these reactions under asymmetric organocatalysis.

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