RECENT ADVANCES IN CATALYTIC ASYMMETRIC CASCADE REACTIONS OF 3-ISOTHIOCYANATO OXINDOLES FOR SYNTHESIS OF SPIROOXINDOLES

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Abstract. *The spirooxindole skeleton can be found in lots of biologically active molecules and pharmaceutical compounds. The development of novel and efficient strategies for the rapid construction of these spirooxindole motifs is highly desirable in our current society. On the other hand, asymmetric cascade reaction plays an important role in the synthesis of complex molecules, and a vast majority of fine and useful compounds have been obtained by using this strategy. Recently, 3-isothiocyanato oxindoles have been widely employed as a class of highly reactive and novel reagents in the enantioselective synthesis of diverse spirooxindoles. This chapter aims to summarize the relevant 3-isothiocyanato oxindoles engaged asymmetric cascade reactions in the synthesis of spirooxindole derivatives during the last six years.*

Contents

1. Introduction

Spirooxindoles are privileged structural scaffolds which can be found in lots of biologically active natural alkaloids and pharmaceutical compounds.[1] Therefore, the development of some simple and efficient strategies to build these sophisticated blocks has become one of the most widespread concerns and still remains a challenging and attractive task for organic chemists.[2] However, the traditional methods are limited by the separation and purification of intermediates, the functional group protection and de-protection. As a state-of-the-art method, the cascade strategies have shown special advantages in the synthesis of optically active natural products and complex molecules, many related studies have been reported.[3] Recently, 3-isothiocyanato oxindoles, pioneered firstly by the Yuan group,[4] have been widely employed as a class of highly reactive and novel reagents in the enantioselective synthesis of diverse spirooxindoles.[5] In this regard, ketones, aldehydes, imines and electron-deficient alkenes or alkynes have served as different types of versatile C=X units and found wide applications in formal [3+2] cycloaddition reactions for their synthesis through metal- or organocatalysis. In addition, catalytic asymmetric ring-opening/closing cascade reaction

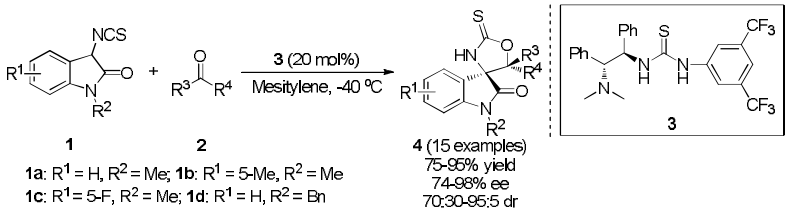
of 3-isothiocyanato oxindoles with aziridines also provided efficient methodology to construct these heterocyclic scaffolds. Thus, the main recent advances of 3-isothiocyanato oxindoles mediated some types of asymmetric cascade process for the synthesis of spirooxindoles, and working models, prospects of the concept will be discussed in this chapter.

2. Asymmetric aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles with ketones or aldehydes

Recently, the direct aldol reaction, that is the addition of the enol/enolate of a carbonyl compound (nucleophile) to an aldehyde or ketone (electrophile), has been established as one of the most powerful tools for the synthesis of β-hydroxy carbonyl compounds.[6] In this context, 3-isothiocyanato oxindoles are highly efficient reagents in the construction of the oxazolidine-2-thione core obtained in a aldol reaction/cyclization cascade process.

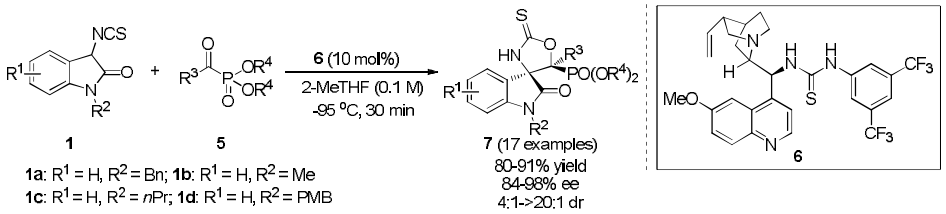
2.1. Aldol/cyclization cascade reaction of ketones

In 2011, the Yuan group[4] firstly reported a pioneering example of catalytic asymmetric aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles **1** with simple ketones **2** using a bifunctional thiourea-tertiary amine **3** as the catalyst, which affording the enantioenriched spirooxindoles **4** bearing two highly congested contiguous tetrasubstituted carbon stereocenters with excellent results (up to 95% yield, 98% ee and 95:5 dr) (Scheme 1). Remarkably, versatile transformations of the siprooxindole products were also demonstrated, (*S*)-Spirobrassinin and its related analogues could be obtained via a simple substitution reaction under basic conditions. This pioneering work leads to the development of various kinds of new cascade reactions.



Scheme 1. Aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles with ketones.

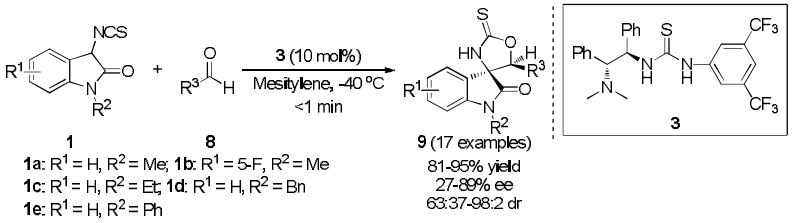
Inspired by Yuan's work on 3,2'-pyrrolidinyl spirooxindole derivatives synthesis via a cascade reaction of simple ketones and isatines/isatinimines,[7] in 2015, Mukherjee and co-workers[8] developed a quinine-based tertiary amino-thiourea derivative **6** catalyzed cascade aldol/cyclization reaction between 3-isothiocyanato oxindoles **1** and α-ketophosphonates **5** (Scheme 2). Under the optimal conditions, various spirooxindole derivatives **7** bearing two contiguous quaternary stereogenic centers would be delivered in high yields with excellent diastereo- and enantioselectivities (up to 91% yield, >20:1 dr and 98% ee). It is noteworthy that the products of this reaction can be modified to allow easy acess to other structurally diversed spirooxindole derivatives.



Scheme 2. Aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles with α-ketophosphonates.

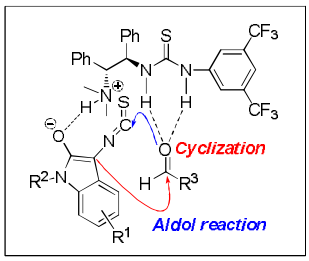
2.2. Aldol/cyclization cascade reaction of aldehydes

Different kinds of aldehydes could also be used as the important synthons to react with 3-isothiocyanato oxindoles for the synthesis of functionalized spirooxindoles. As part of their continuing work on the aldol/cyclization cascade reactions of 3-isothiocyanato oxindoles, the Yuan group[9] herein disclosed a highly efficient method for the construction of a family of spiro[oxazolidine-2-thione-oxindoles] **9** with 3-isothiocyanato oxindoles **1** and aldehydes **8** via a cascade aldol/cyclization process (Scheme 3). This method provides an access to spirooxindoles **9** bearing two vicinal quaternary/tertiary stereocenters in up to 95% yield, 89% ee and 98:2 dr with a chiral bifunctional thiourea-tertiary amine organocatalyst **3** based on DPEN scaffold. Good reactivity was observed and the reaction could be completed within 1.0 min.



Scheme 3. Aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles with aldehydes.

To account for the stereochemical course of this reaction, a possible transition state with a bifunctional model was tentatively proposed (Scheme 4). The tertiary amine moiety of organocatalyst **3** deprotonates the active hydrogen atom from 3-isothiocyanato oxindole tautomer **1'**, then stabilizes this specy by an intermolecular H-bonding interaction. Simultaneously, the thiourea moiety activates the aldehyde **8** via double H-bonding. In this model, the activated 3-isothiocyanato oxindole was much more accessible to attack the aldehyde through aldol reaction, and then via an intramolecular cyclization reaction to form the desired product.

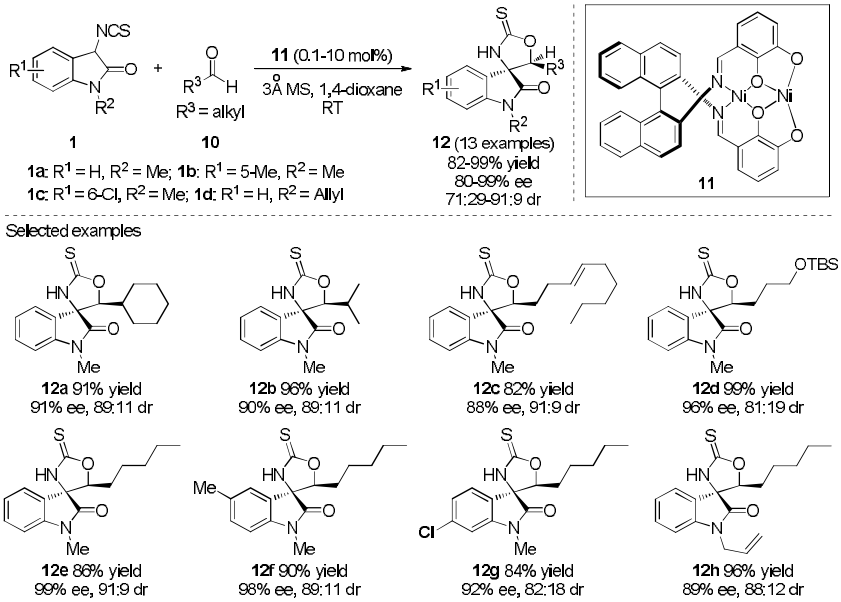


Scheme 4. Proposed transition state.

Almost at the same time, Kanai, Matsunaga and co-workers[10a] found that homodinuclear nickel Schiff base catalyst **11** can be utilized for the cascade aldol/cyclization process of 3-isothiocyanato oxindoles **1** and aliphatic aldehydes **10**, thus providing easy access to densely functionalized spirocyclic oxindoles **12** in only one step (Scheme 5). Importantly, the catalyst loading was successfully reduced to 1 and 0.1 mol%, and high TON, up to 850, was achieved. In addition, a number of different aliphatic aldehydes were suitable substrates for this reaction, whatever for α-branched or linear ones, giving the corresponding products in 81:19-91:9 dr and 80-99% ee. However, the result was not good for the benzaldehyde substrate.

3. Asymmetric Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with imines

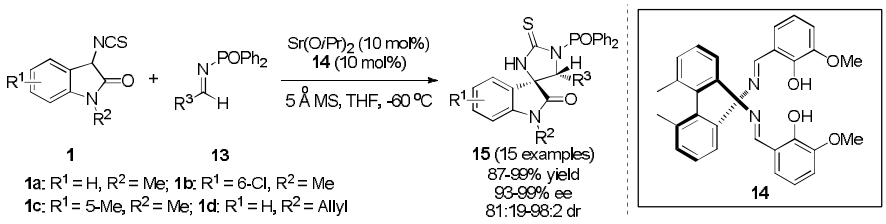
Generally, the addition of resonance-stabilized carbon nucleophiles to iminium salts and imines to afford aminoalkylated derivatives, is known as the Mannich reaction.[11] Herein, 3-isothiocyanato oxindoles could react with different imines and their derivatives under the base conditions to construct imidazolidine-2-thione scaffold via a cascade Mannich/cyclization reaction.



Scheme 5. Aldol/cyclization cascade reaction of 3-isothiocyanato oxindoles with alphatic aldehydes.

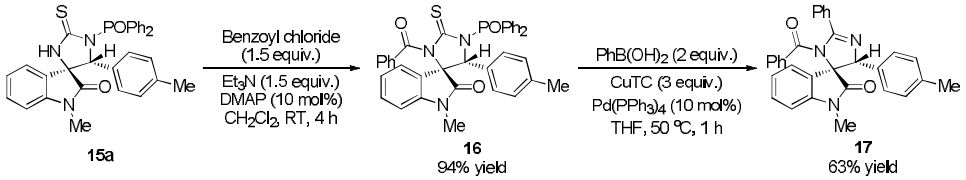
3.1. Mannich/cyclization cascade reaction of aldimines

As the remarkable success employing 3-isothiocyanato oxindoles in the asymmetric domino reaction with metal-schiff base or tertiary amine catalyst, the catalytic model was also suitable for the Mannich/cyclization process. In 2012, Kanai and Matsunaga[12] reported the first example of catalytic asymmetric Mannich/cyclization cascade reaction between 3-isothiocyanato oxindoles **1** and aldimines **13** catalyzed by a $Sr(OiPr)_2$/Schiff base complex **14**, which provides concise access to structurally diversed spiro[imidazolidine-4,3'-oxindole] compounds **15** in up to 99% yield, 99% ee and 98:2 dr (Scheme 6). In this reaction, investigation of Schiff base revealed that *ortho*-MeO substituent was very important to determine the diastereo- and enantioselectivity.



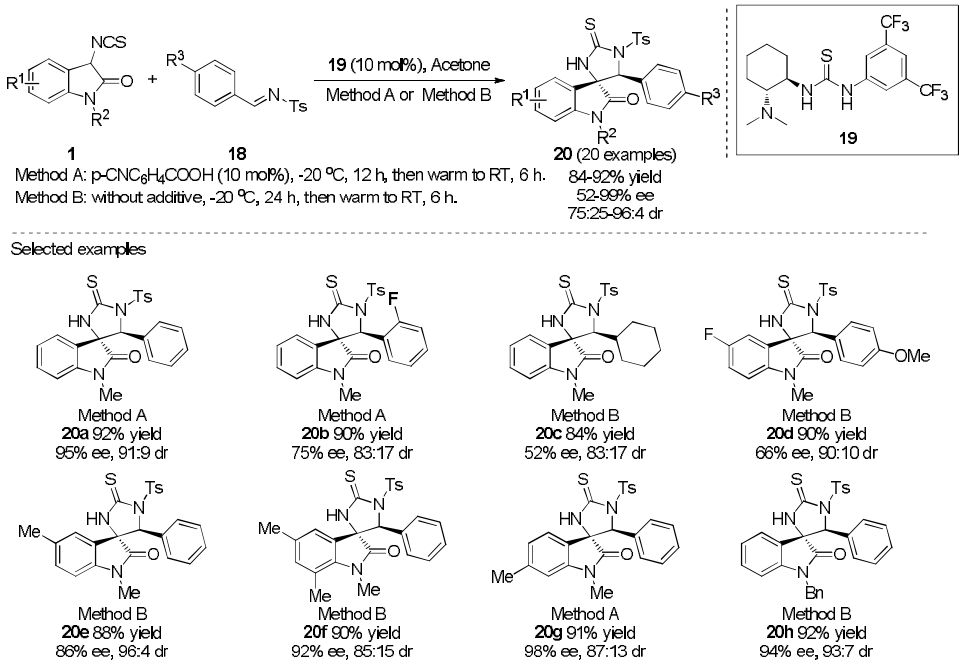
Scheme 6. Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with aldimines.

To demonstrate the synthetic utility of the current methodology, these spirooxindolic products can be easily converted into other significant building blocks and valuable complex targets (Scheme 7). Benzoylation of **15a** could afford compound **16** in 94% yield, then **16** was conducted to Pd-catalyzed desulfurative cross-coupling with $PhB(OH)_2$, and the novel spiro[imidazoline-4,3'-oxindole] **17** was obtained in 63% yield. Importantly, a cis-diaryl relationship was found in product **17** that can be regarded as a hybrid of two species: 1) Nutlin,[3] an imidozoline-based inhibitor of p53/E3-ubiquitin ligase Mdm2 interaction, 2) MI-219,[14] a spiro[pyrrolidin-3,3'-oxindole]-based p53/Mdm2 inhibitor. Therefore, the present method would be useful in the field of medicinal chemistry for the design and synthesis of new potent anti-tumor agents.



Scheme 7. Synthetic transformations.

Recently, the Liu group[15] developed an asymmetric cascade Mannich/cyclization reaction of 3-isothiocyanato oxindoles **1** with sulfimides **18** by using a commercially available organocatalyst **19** (Scheme 8). A series of novel spiro[imidazolidine-4,3'-oxindole] derivatives **20** were obtained with good yields (up to 92%) and excellent enantioselectivities (up to 99% ee). The reaction was proceeded smoothly under two kinds of conditions. The difference was mainly on improving the enantioselectivity with little decrease of diastereoselectivity when *para*-cyanobenzoic acid as an additive. Futhermore, the spirooxindoles were easily converted into Spirobrassinin analogues by simple substitution and subsequently desulfonylation with sodium naphthalenide in good overall yield.

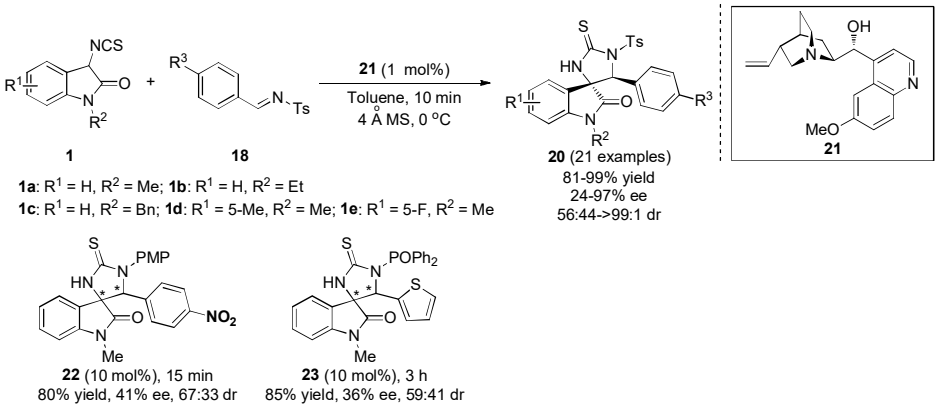


Scheme 8. Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with sulfimides.

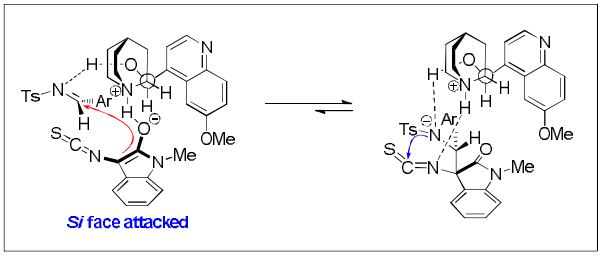
Shortly after, in 2015, Yuan and co-workers[16] also reported a highly efficient method for the synthesis of enantioenriched spirooxindoles with commercially available quinine **21** as a catalyst (Scheme 9). The reactions were accomplished via a cascade Mannich/cyclization reaction between 3-isothiocyanatooxindoles **1** and sulfimides **18** for delivering a range of spiro[imidazolidine-2-thione-4,3'-oxindole] derivatives **20** in good results (up to 99% yield, 97% ee and >99:1 dr). In addition, the method was compatible with *N*-PMP aldimine, *N*-diphenylphosphinoyl aldimine, affording the corresponding spirocyclic oxindoles **22** or **23** in good yields with moderate enantio- and diastereoselectivities.

A plausible dual activation working model was proposed to account for the stereochemistry of the cascade process (Scheme 10). Imine **18** was activated by H-bonding interaction between the hydrogen atom

of C9-OH of quinine **21** and the nitrogen atom of imine. 3-isothiocyanato oxindole **1** was enolized by deprotonation with the tertiary amine of quinine, which then through the *Si* face to attack the imine. Next, intramolecular cycloaddition reaction could lead to the optically active spirooxindole product **20**.



Scheme 9. Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with aldimines.



Scheme 10. Proposed transition state.

3.2. Mannich/cyclization cascade reaction of ketoimines

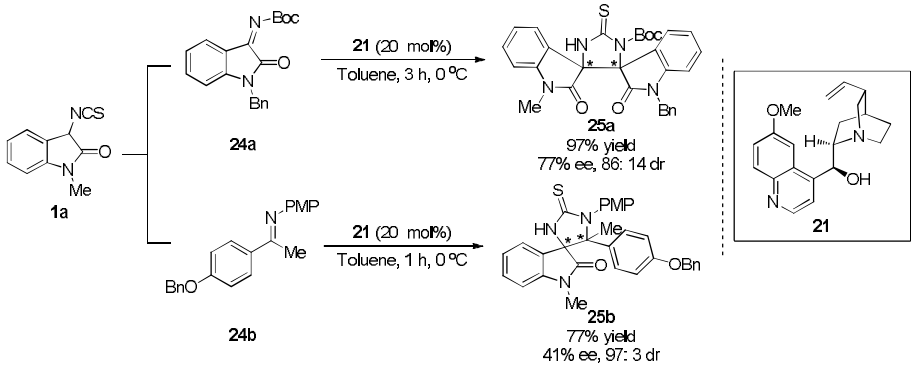
In the above work,[16] only two examples for quinine **21** mediated asymmetric cascade Mannich/cyclization reactions of isothiocyanato oxindoles **1** with ketoimines **24** were reported, delivering the enantioenriched spirooxindole derivatives **25** in 77% or 41% ee values, respectively (Scheme 11). Although the enantioselectivity was not very impressive, the substrate scope of the cascade Mannich/cyclization reaction was extending to some extent.

3.3. Mannich/cyclization cascade reaction of α,β-unsaturated aldimines

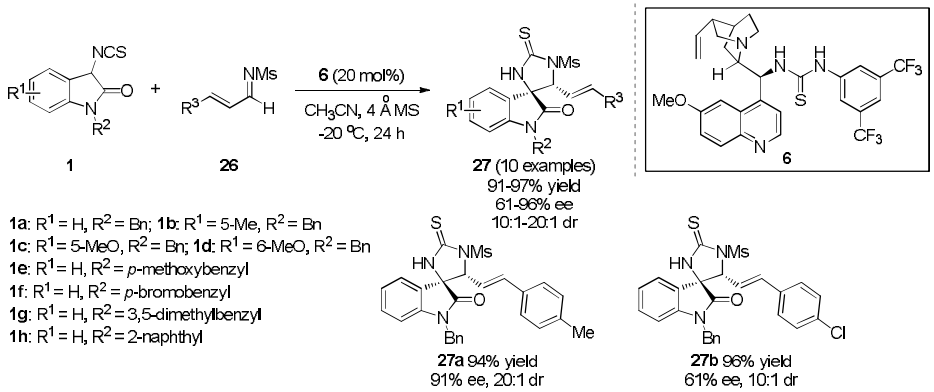
One year later, Shi and co-workers[17] successfully disclosed a regio- and stereocontrolled asymmetric cascade Mannich/cyclization process of 3-isothiocyanato oxindoles **1** with α,β-unsaturated aldimines **26**. A range of diversed spirooxindole derivatives **27** could be obtained in high yields along with good to excellent stereoselectivities (up to 97% yield, 96% ee and 20:1 dr) under certain conditions in the presence of cinchona alkaloid-derived organocatalyst **6** (Scheme 12). Additionally, oxidation of the target product, the C=S bond could be easily transformed into C=O bond, delivering the corresponding γ-lactam analogues in high efficiency.

4. Asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with electron deficient alkenes or alkynes

Michael reaction is the addition of stabilized carbon nucleophiles to activated π-systems and the products are called Michael adducts.



Scheme 11. Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with ketoimines.



Scheme 12. Mannich/cyclization cascade reaction of 3-isothiocyanato oxindoles with α,β-unsaturated aldimines.

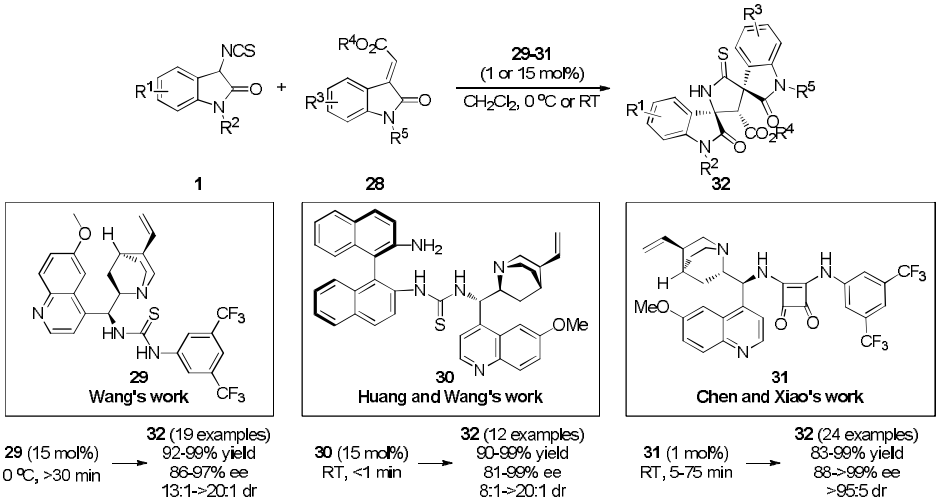
Currently, however, all reactions involving the 1,4-addition (conjugate addition) of virtually any nucleophile to activated π-systems are also referred to the Michael addition. It could be recognized as the most important and reliable tools for the formation of C-C and C-X bond. Moreover, in recent years, the Michael addition is to be applied in cascade reactions for the synthesis of structurally complexed molecules in a single step.[18] During this process, 3-isothiocyanato oxindoles could be considered as the robust synthon to react with diversed electron deficient alkenes or alkynes to synthesize 3,2'-pyrrolidinyl spirooxindole derivatives via a cascade Michael/cyclization reaction.

4.1. Michael/cyclization cascade reaction of 3-ylideneoxindoles

In 2013, three groups of Wang,[19] Huang and Wang,[20] Chen and Xiao[21] successfully developed an exceptionally highly efficient, atypically rapid, and stereocontrolled cascade Michael/cyclization reaction between 3-isothiocyanato oxindoles **1** and 3-ylideneoxindoles **28** catalyzed by bifunctional organocatalysts **29-31** (Scheme 13). Mild reaction conditions were used to construct bispirooxindoles **32** bearing three stereocenters with two spiro quaternary centers with excellent enantio- and diastereomeric purities. This versatile procedure will allow diversity-oriented synthesis of this intriguing class of compounds with potential biological activities. These works were accomplished with different kinds of organocataysts, and the dosage would have an impact on the effiency.

In the same year, Jing and co-workers[22] also explored the cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles with 3-ylideneoxindoles, which provides an access to the bispirooxindoles synthesis in a highly diastereoselective manner. In this context, the author developed only one example for

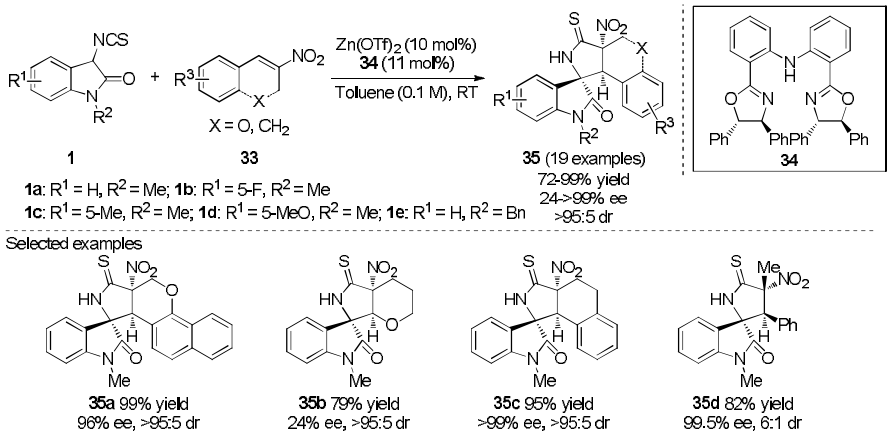
the asymmetric construction of this heterocyclic skeleton. In the presence of 10 mol% of DHQ, the cascade reaction was completed in 2.0 min, and the optical product **32** could be afforded in 98% yield, 98% ee and >95:5 dr.



Scheme 13. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 3-ylideneoxindoles.

4.2. Michael/cyclization cascade reaction of nitroolefins (cyclic or acyclic nitroolefins)

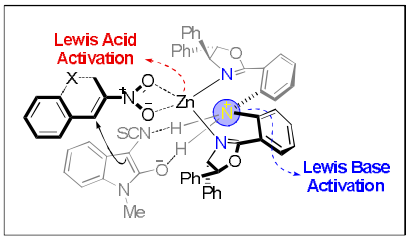
3-Nitro-2*H*-chromenes are a type of extremely useful cyclic nitroolefins and have been widely employed for the synthesis of various bioactive chroman derivatives. In 2014, the Xiao and Chen group[23] dislosed an unprecedented $Zn(OTf)_2$/**34** complex catalyzed asymmetric cascade Michael addition/cyclization of 3-isothiocyanato oxindoles **1** with 3-nitro-2*H*-chromenes **33** (Scheme 14). This transformation provides an efficient access to various synthetically important polycyclic spirooxindoles **35** in a highly stereoselective manner under mild conditions (up to 99% yield, >99% ee and >95:5 dr). More importantly, simple filtration of the reaction mixture gave the desired products in high yields with satisfied purity and excellent stereoselectivities.



Scheme 14. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 3-nitro-2*H*-chromenes.

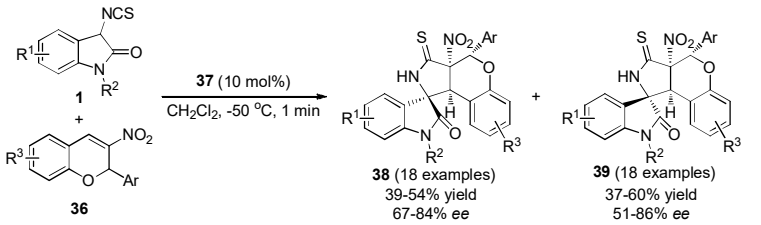
In addition to various 3-nitro-2*H*-chromenes, moreover, acyclic nitroolefins, such as β-methyl-β-nitrostyrene, could also be successfully employed in this process and furnished the desired product **35d** in 82% yield with 99.5% ee and 6:1 dr. But unfortunately, in the case of β-nitrostyrene, the corresponding product was obtained in only 29% yield with 4% ee and 3:1 dr.

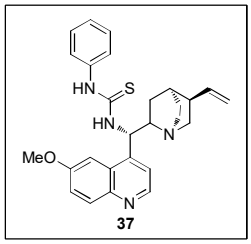
To understand the stereochemistry of this asymmetric Michael/cyclization cascade sequence, a possible transition state according to Du's hypothesis was proposed. As shown in Scheme 15, the chiral zinc(II) complex could play two roles: 1) the zinc(II) moiety serves as a Lewis acid to activate 3-nitro-2*H*-chromenes **33** through the coordination between Zn^{II} and the nitro group; 2) the N atom of the NH group could act as a Lewis base to direct the nucleophilic attack from the *Re* face of 3-nitro-2*H*-chromenes **33** through a hydrogen-bonding interaction with the enolate of 3-isothiocyanato oxindoles **1**.



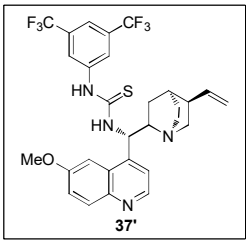
Scheme 15. Proposed transition state.

Xie's group[24] further extended this cascade Michael/cyclization strategy to another cyclic nitroolefins, 3-nitro-2*H*-chromene derivatives **36**, and found that the bifunctional thiourea **37** with a phenyl group proved to be more effective than the ditrifluoromethylated one **37'**(Scheme 16). Under the established conditions, the reaction between 3-isothiocyanato oxindoles **1** and 3-nitro-2*H*-chromene derivatives **36** proceeded smoothly, providing multi-functionalized spirooxindole derivatives **38** and their isomers **39** with four vicinal chiral carbon centers including two quaternary stereocenters in moderate to good results (up to 99% yield, 86% ee and 60:40 dr). In the presence of inorganic base, interestingly, the product **38** could be cleanly converted to the compound **39** in quantitative yield for about six days, and better ee was obtained.





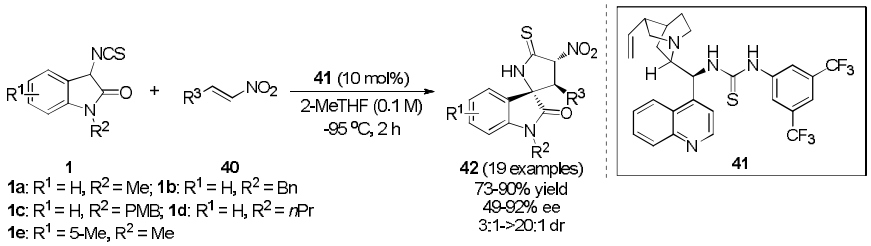
38a: 49% yield, -78% ee
39a: 43% yield, 72% ee



38a: 47% yield, 75% ee
39a: 39% yield, 60% ee

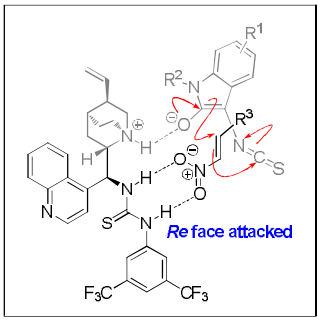
Scheme 16. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 3-nitro-2*H*-chromene derivatives.

β-Nitroolefins has recently proved to be a useful and versatile synthetic building block, which also serves as substrates in the organocatalytic asymmetric cascade Michael/cyclization process. Mukherjee and co-workers[25] developed the first organocatalytic asymmetric reaction of 3-isothiocyanatooxindoles **1** with β-nitroolefins **40** by using a cinchonidine-derived bifunctional catalyst **41** (Scheme 17). The resulting products, highly functionalized 3,2'-pyrrolidinyl-substituted spirooxindole derivatives **42**, were obtained in high yields with good diastereo- and enantioselectivities (up to 90% yield, >20:1 dr and 92% ee). This cascade reaction employs monosubstituted nitroolefins and complements the Zn^{II}-catalyzed variant, which is only applicable to disubstituted nitroolefins. It should be noted that the products are rather unstable and tend to decompose upon prolonged storage, even at –20 °C. The synthetic transformation would be no useful as the sensitive nature of the products, despite several attempts.



Scheme 17. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with β-nitroolefins.

The stereochemical outcome of this Michael/cyclization cascade reaction can be rationalized by the transition state presented in Scheme 18. In line with the well-established mode of action of bifunctional catalyst **41**, the thiourea moiety can be expected to activate the nitroolefin **40** by the double H-bonding. Nucleophilic activation by the tertiary amine of the catalyst then results in the stereodetermining addition of 3-isothiocyanato oxindole **1** (as its enol tautomer) to the *Re* face of the nitroolefin. Subsequently, the concerted cyclization of the resulting nitronate to the isothiocyanate generates the observed spirooxindole **42**.

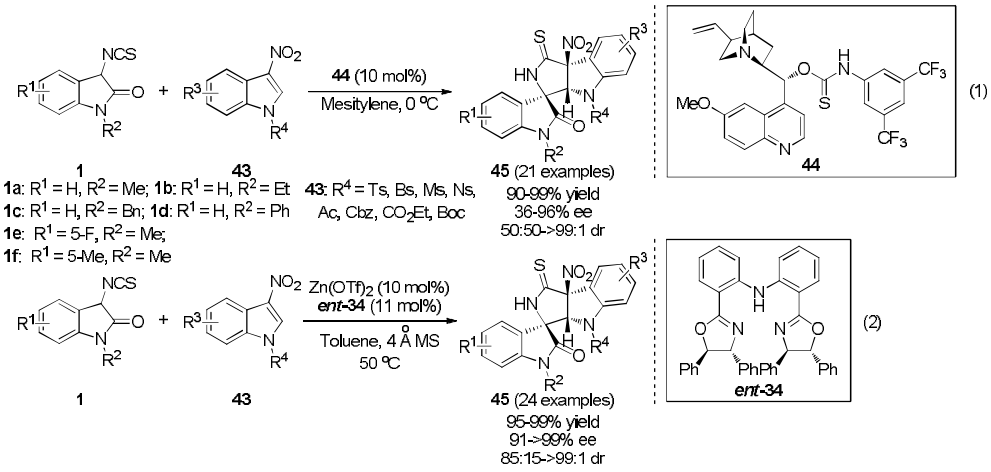


Scheme 18. Proposed stereochemical model.

4.3. Michael/cyclization cascade reaction of 3-nitroindoles

Indoles bearing two electron-withdrawing substitutions at the N(1)- and C(3)- positon, which would be recognized as a class of electron-deficient alkenes. 3-Nitroindoles are a class of potentially promising electrophilic reagents, had rarely been explored in the field of catalytic asymmetric synthesis. In 2015, the group of Yuan[26a] firstly disclosed an unprecedented asymmetric Michael/cyclization cascade process of 3-isothiocyanato oxindoles **1** and 3-nitroindoles **43** with amino-thiocarbamate bifunctional organocatalyst **44** (Scheme 19, eq. 1). A variety of polycyclic spirooxindoles **45** containing three contiguous stereocenters and two of them having quaternary centers could be obtained with satisfactory results (up to 99% yield, 96% ee and >99:1 dr). Soon after, they[26b] also developed a chiral $Zn(OTf)_2$/*ent*-**34** complex catalyzed diastereo- and enantioselective cascade reaction of 3-isothiocyanato oxindoles **1** and 3-nitroindoles **43** (Scheme 19, eq. 2).

The siprooxindole derivatives **45** could be afforded in quantitative yields with excellent stereoselectivities (up to 99% yield, >99% ee and >99:1 dr). Remarkably, the metal catalytic strategy in this work is significantly superior to the previous organocatalytic method in the enantio- and diastereoselectivities for almost all of the examined cases.



	organocatalysis	metal catalysis
R^4 = Ts, Bs; R^2 = Me	59-96% ee 82:18->99:1 dr	91-99% ee 93:7->99:1 dr
R^4 = Ms, Ns, Cbz, Boc, CO_2Et; R^2 = Me	31-83% ee 50:50-91:9 dr	98-99% ee >99:1 dr
R^4 = Ts; R^2 = Et, Bn, Ph	36-40% ee 79:21-86:14 dr	92-98% ee 85:15->99:1 dr

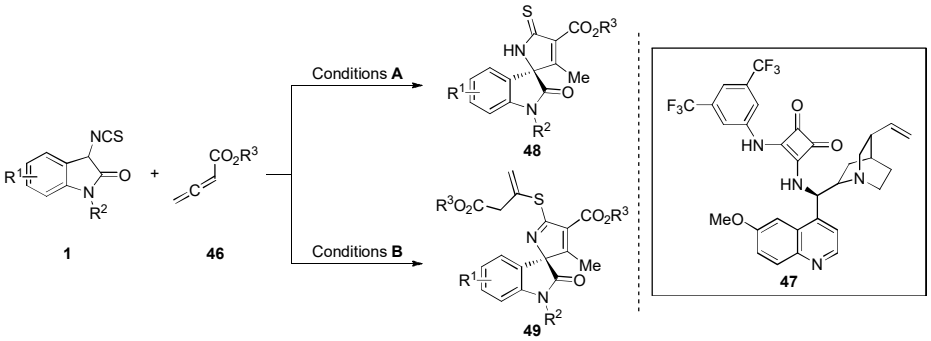
Scheme 19. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 3-nitroindoles.

4.4. Michael/cyclization cascade reaction of allenic esters or 2-butynedioic acid diesters or alkyne ketones

In 2013, Xu, Shi and co-workers[27] developed a novel cinchona alkaloid-derived organocatalyst **47** mediated asymmetric Michael/cyclization cascade reactions of 3-isothiocyanatooxindoles **1** with allenic esters **46** (Scheme 20). Interestingly, they also found that two types of functionalized spirooxindole derivatives (**48** and **49**) could be obtained in high yields along with good to excellent enantioselectivities under mild conditions (**48**: up to 93% yield and 94% ee; **49**: up to 96% yield and 97% ee) by changing the ratio of the substrates.

Encouraged by the success of above work in this context,[27] 2-butynedioic acid diesters **50** were also attempted to explore the asymmetric cascade process (Scheme 21), two different spirooxindoles (**51** and **52**) would be afforded separately with excellent results by simple changing the reaction conditions (**51**: up to 96% yield and >99% ee; **52**: up to 91% yield, 99% ee and *E*/*Z* = 20:1). Notably, the stereocontrol was considered via H-bonding effect with the cinchona alkaloid-derived organocatalyst **47** having stronger H-bonding donors. Moreover, versatile transformations of the cycloadducts would deliver other spirooxindoles.

As an extension of this work, Wang and their co-workers[28] further expanded the substrate scope to alkynyl ketones. They disclosed a highly enantioselective Michael/cyclization cascade reaction between 3-isothiocyanato oxindoles **1** and alkynyl ketones **53** for the first time (Scheme 22). In this process, an oxazoline-OH type chiral ligand **54** derived from *o*-hydroxyphenylacetic acid was employed to generate an effective magnesium catalyst in the current cyclization reaction and gave serials of diversified spirooxindoles **55** with excellent yields and good to excellent enantioselectivities (up to 99% yield and 94% ee).



Conditions **A**: **47** (10 mol%), **1** (0.30 mmol), **46** (0.10 mol), CH_2Cl_2/THF = 10/1, RT, 12 h.
Conditions **B**: **47** (20 mol%), **1** (0.10 mmol), **46** (0.50 mol), CH_2Cl_2/THF = 10/1, RT, 12 h.

Selected examples

Entry	R^1	R^2	R^3	**48** Yield [%]	**48** ee [%]	**49** Yield [%]	**49** ee [%]
1	H	Bn	Bn	92	92	94	95
2	4-Br	Bn	Bn	91	93	92	96
3	5-MeO	Bn	Bn	90	96	96	97
4	H	Me	Bn	92	90	93	91
5	H	*n*Pr	Bn	90	90	90	94
6	H	Ph	Bn	92	90	93	90
7	H	Bn	Et	90	92	91	88
8	H	Bn	*t*Bu	91	94	90	96

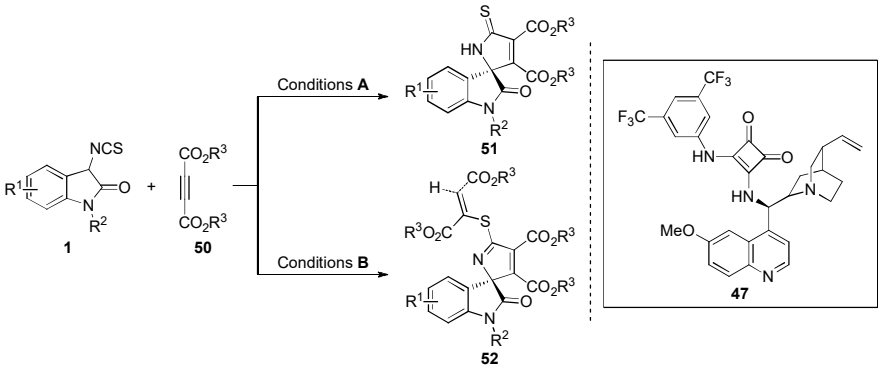
Scheme 20. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with allenic esters.

A possible mechanism for this cascade Michael/cyclization reaction was proposed on the basis of their recent work on Mg catalysis. As depicted in Scheme 23, the magnesium catalyst **A**, generated *in situ* from oxazoline-OH ligands and Bu_2Mg, existed in their dimeric form **B**. Firstly, the enolate of 3-isothiocyanato oxindoles **1a** could be activated by the magnesium catalyst to form the intermediate **C**. The alkynyl ketone **53a** coordinated to the magnesium center in the manner shown to bring about intermediate **D**. Then, intermolecular Michael/cyclization took place to give intermediate **E**. Finally, another molecule of **1a** could participate in the process to allow the cyclization product **55a** to release and regenerate the precatalyst **A** to allow the next catalytic cycle to proceed.

4.5. Michael/cyclization cascade reaction of miscellaneous electron-deficient alkenes

Chowdhury, Ghosh and co-workers[29] recently developed an enantioselective Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles **1** and arylidene malonates **56** for the synthesis of highly functionalized 3,2'-pyrrolidinyl spirooxindole derivatives **57** (Scheme 24). The reaction was catalyzed by a quinine derived bifunctional catalyst **6** or its pseudo-enantiomeric quinidine derived catalyst ***ent*-6**, providing both the enantiomers ***ent*-57** of the desired product. Under standard reaction conditions, the products were obtained in good yields with excellent diastereo- and enantioselectivities (up to 90% yield, 99: 1 dr and >99% ee).

Molecules containing the CF_3 group have been used in many fields, including biology, medicine, and agricultural chemistry as well as in materials science. Thus far, significant efforts have been devoted to the construction of CF_3-containing molecules.

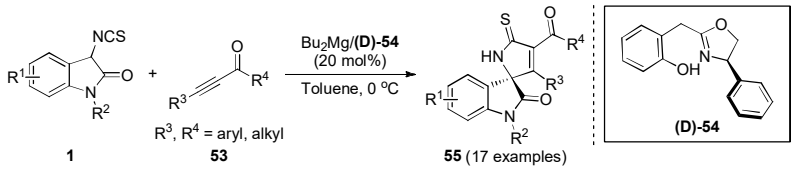


Conditions **A**: **47** (20 mol%), **1** (0.10 mmol), **50** (0.11 mol), CH_2Cl_2, -20 °C, 12 h.
Conditions **B**: **47** (20 mol%), **1** (0.10 mmol), **50** (1.00 mol), CH_2Cl_2, 4 Å MS, RT, 24 h.

Selected examples

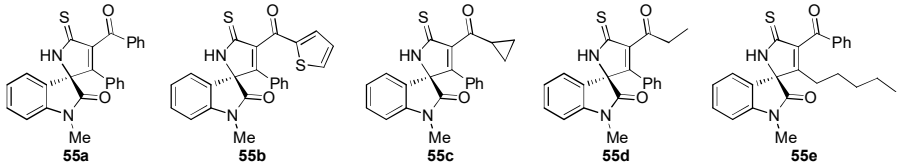
Entry	R^1	R^2	R^3	**51** Yield [%]	**51** ee [%]	**52** Yield [%]	**52** *E*/*Z*	**52** ee [%]
1	H	Bn	Me	92	94	89	5:1	94
2	4-Br	Bn	Me	95	90	91	20:1	94
3	5-MeO	Bn	Me	95	>99	88	5:1	96
4	6-Me	Bn	Me	92	95	86	5:1	90
5	H	Me	Me	94	94	83	10:1	90
6	H	*n*Pr	Me	96	95	88	10:1	91
7	H	Ph	Me	96	86	87	12:1	99
8	H	Bn	Et	91	86	83	10:1	94

Scheme 21. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 2-butynedioic acid diesters.



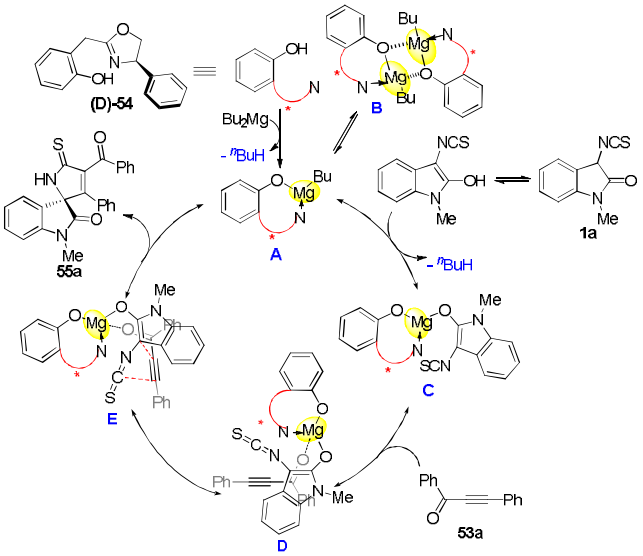
1a: R^1 = H, R^2 = Me; **1b**: R^1 = 5-Me, R^2 = Me
1c: R^1 = H, R^2 = *n*Pr; **1d**: R^1 = H, R^2 = Bn

Selected examples

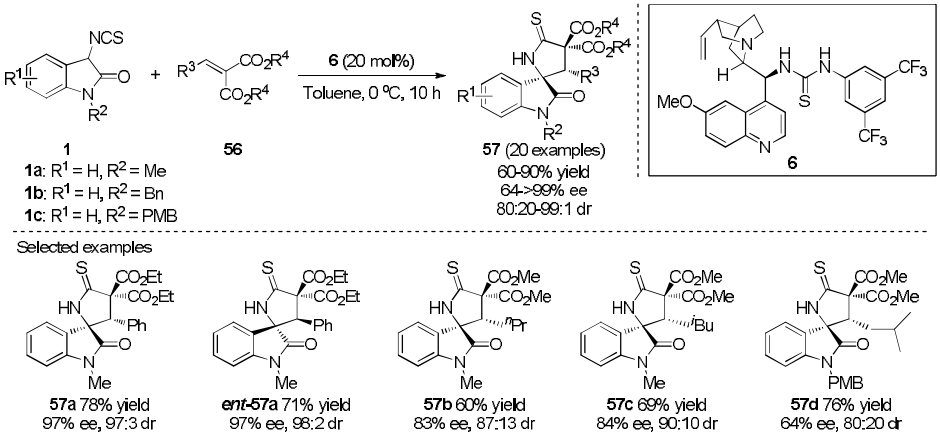


55a 97% yield 92% ee
55b 96% yield 94% ee
55c 89% yield 84% ee
55d 85% yield 92% ee
55e 85% yield 92% ee

Scheme 22. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with alkynyl ketones.



Scheme 23. Proposed mechanism.

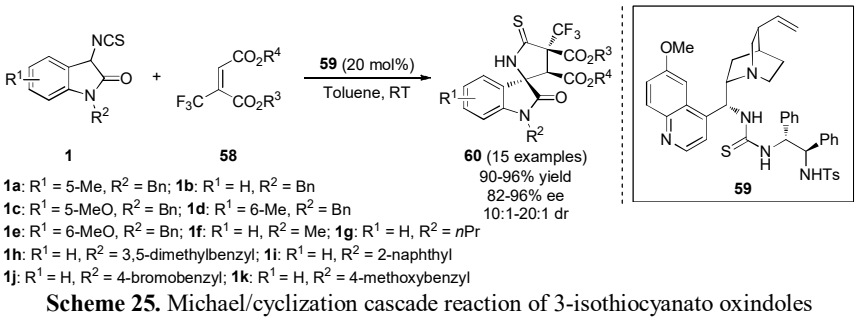


Scheme 24. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with arylidene malonates.

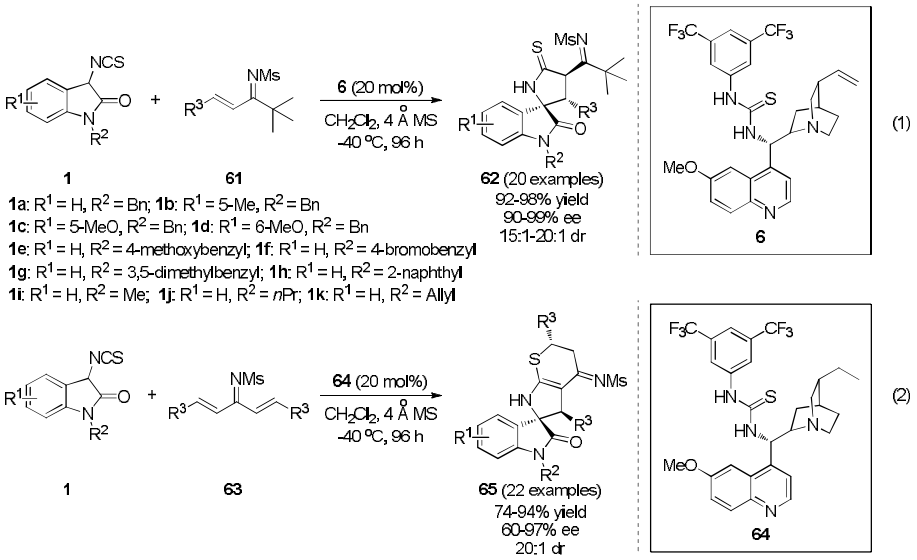
In 2015, the group of Xu and Shi[30] presented the first example of the efficient organocatalyst **59** mediated enantioselective Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles **1** with trifluoromethylated 2-butenedioic acid diesters **58** (Scheme 25), providing a rapid access to the construction of spirooxindoles **60** with a CF_3-containing quaternary carbon stereogenic center in high yields along with good diastereoselectivities and excellent enantioselectivities (up to 96% yield, 20:1 dr and 96% ee). In this reaction, two epimeric isomers were obtained with the same organocatalyst at different temperatures, which led to an enantiodivergent approach for the synthesis of spirooxindoles. Moreover, the potential application of this methodology was also demonstrated by performing it under different conditions, and the product could be smoothly transformed into other spirooxindole derivatives.

On the basis of the previous work about the cascade Mannich/cyclization process of 3-isothiocyanato oxindoles **1** with α,β-unsaturated aldimines **26**, to further investigate the reactivity of C=C and C=X in α,β-

unsaturated imines, Shi and co-workers[17] then synthesized α,β-unsaturated ketoimines **61** as the substrate for comparision to that of α,β-unsaturated aldimines. To their delight, the other regio- and stereocontrolled Michael/cyclization cascade reation was proceeded efficiently by using cinchona alkaloid-derived organocatalyst **6**, which producing the corresponding spirooxindoles **62** in excellent results (up to 98% yield, 99% ee and 20:1 dr) (Scheme 26, eq. 1). This dispency was probably due to the steric hindrance. Encouraged by the gratifying results mentioned above, a new compound **63** containing three electron-deficient unsaturated bonds was synthesized and employed as the substrate to investigate this reaction. Interestingly, a novel type of diversified S-containing heterocyclic spirooxindole derivatives **65** could be obtained in high yields with good to excellent stereoselectivities (up to 94% yield, 97% ee and 20:1 dr) through the simple [3+2]/[4+2] cascade process, which using DHQ-**64** as the bifunctional organocatalyst (Scheme 26, eq. 2).



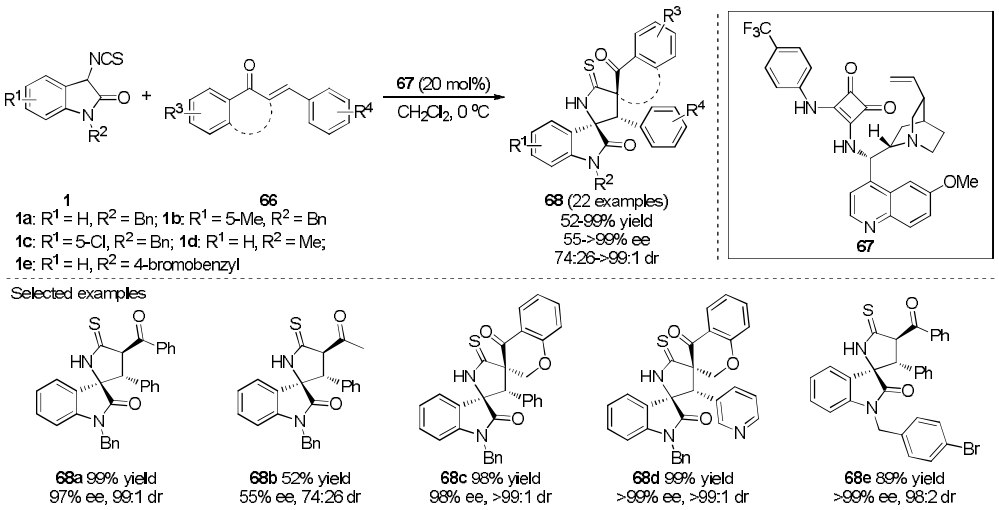
Scheme 25. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with trifluoromethylated 2-butenedioic acid diesters.



Scheme 26. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with α,β-unsaturated imines.

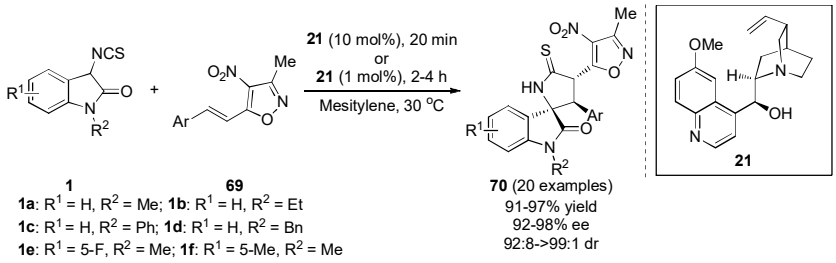
Quite recently, a cinchona-derived squaramide **67**-catalyzed asymmetric Michael/cyclization cascade reaction with 3-isothiocyanato oxindoles **1** and chalcones **66** was reported by Du's group[31] (Scheme 27). This method provides an access to the construction of pyrrolidinyl spirooxindoles **68** in very good yields with excellent diastereo- and enantioselectivities (up to 99% yield, >99:1 dr and >99% ee). In this context, a

quinine-derived thiourea was screened in comparison with squaramide. However, the outcome was unsatisfactory.



Scheme 27. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with chalcones.

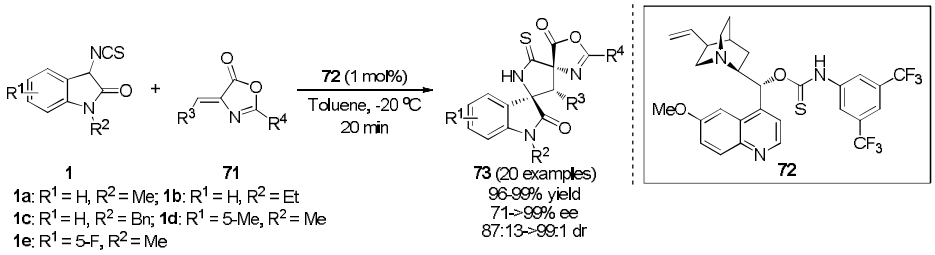
To further illustrate the versatility of 3-isothiocyanato oxindoles in the synthesis of structurally complex spirooxindole derivatives, 3-methyl-4-nitro-5-alkenylisoxazoles were developed to examine the Michael/cyclization cascade process. As early as in 2013, the Yuan group[32] found that a wide range of structurally diverse 3,2'-thiopyrrolidonyl spirooxindoles **70** bearing three contiguous stereogenic centers can be smoothly obtained via a cascade Michael/cyclization reaction between 3-isothiocyanato oxindoles **1** and 3-methyl-4-nitro-5-alkenyl-isoxazoles **69** with commercially available quinine **21** as the catalyst (Scheme 28). The protocol is significantly characterized by high reactivity (up to 97% yield), a low catalyst loading (1 mol%), and an excellent enantio- and diastereoselectivity (up to 98% ee and >99:1 dr). Importantly, treatment of the oxidation product with a NaOH solution of a solvent mixture of THF and water under reflux for 15 h, resulting in the elimination of the isoxazole moiety, in turn generating the corresponding spirooxindole adduct in high yield without loss of diastereo- and enantioselectivity (91% yield, 97:3 dr and 98% ee).



Scheme 28. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with 3-methyl-4-nitro-5-alkenyl-isoxazoles.

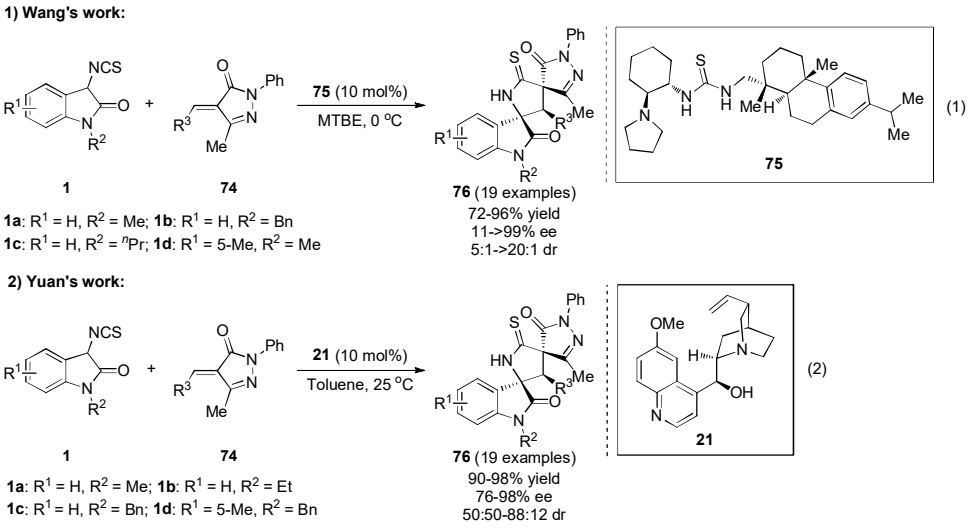
Inspired by these remarkable achievements in the construction of 3,2'-pyrrolidinyl spirooxindole derivatives using 3-isothiocyanato oxindoles as precursors via organocatalytic Michael/cyclization cascade processes, Yuan and co-workers[33] were prompted to investigate the reactions of 3-isothiocyanatooxindoles **1**

and alkylidene azlactones **71** (Scheme 29). It was observed that this reaction, with a quinine-derived thiocarbamate **72** as a catalyst under mild reaction conditions, affords the spirocyclic oxindole compounds **73** in high to excellent yields with very good enantio- and diastereoselectivities (up to 99% yield, >99% ee and >99:1 dr).



Scheme 29. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with alkylidene azlactones.

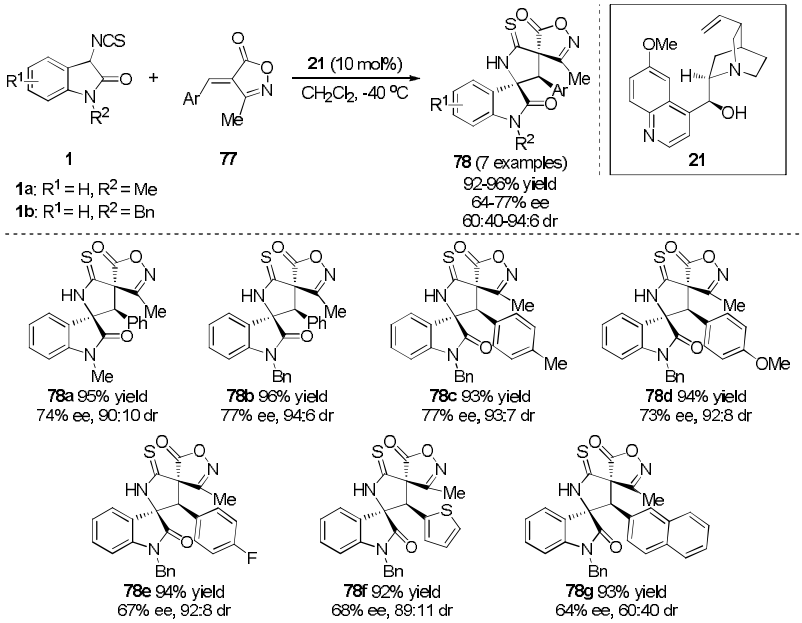
Pyrazolones is a kind of unquie reagents, which have attracted considerable attention because of their wide range of biological properties such as antibacterial and antifungal activities effect. Almost at the same time, the first Michael/cyclization cascade reaction between 3-isothiocyanato oxindoles **1** and unsaturated pyrazolones **74** by a chiral tertiary amine thiourea catalyst **75** was developed by Wang's group[34] (Scheme 30, eq. 1). The spiro[oxindole/thiobutyrolactam/pyrazolone] core structures **76** containing three contiguous stereogenic centers, including two spiro quaternary centers, were prepared in high yields with excellent stereoselectivities (up to 96% yield, >99% ee and >20:1 dr). In 2014, the Yuan group[35] also explored the synthesis of these spirooxindole derivatives **76** with the same starting materials (Scheme 30, eq. 2). It was observed that this reaction, quinine **21** was used as a catalyst under mild conditions, affording the desired product **76** in good results (up to 96% yield, 98% ee and 88:12 dr).



Scheme 30. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with unsaturated pyrazolones.

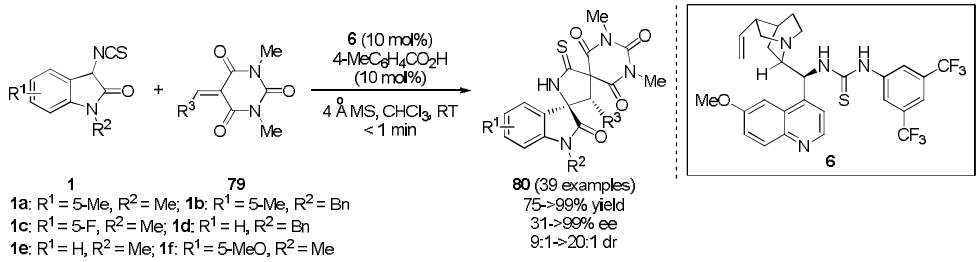
In the above work, in addition to unsaturated pyrazolones, Yuan and co-workers[35] selected unsaturated isoxazolones **77** as the precursors to explore the Michael/cyclization cascade reaction with 3-isothiocyanato oxindoles **1**. In the presence of quinine **21**, a range of another class of spirocyclic oxindoles **78** were

generated in excellent yields with moderate to good stereoselectivities (up to 96% yield, 77% ee and 94:6 dr) (Scheme 31).



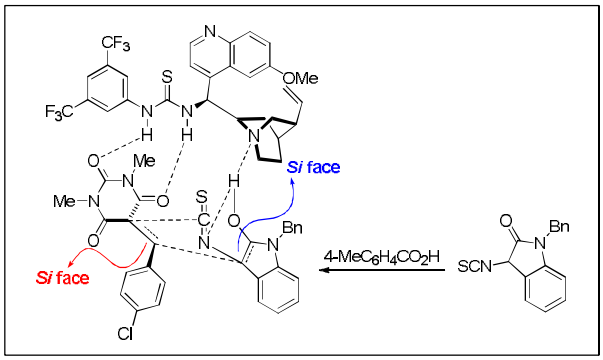
Scheme 31. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with unsaturated isoxazolones.

Spirobarbiturates represent a family of structurally unique spiroheterocycles and possess a wide range of biological activities. Numerous synthetic methodologies have been developed for the racemic construction of structurally diverse spirobarbiturates, but less in the asymmetric synthesis. Barbiturate-based olefins function as easily accessible and robust building blocks, and have been applied in the stereoselective synthesis of spirobarbiturates. Moreover, they have not been employed in the catalytic enantioselective synthesis of dispirobarbiturates so far. In 2016, the Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles **1** with barbiturate-based olefins **79** catalyzed by a cinchona-based thiourea **6**, was developed by the group of Zhao[36] (Scheme 32). This process proceeded readily, and furnished dispirobarbiturates **80** in excellent chemical yields with excellent enantio- and diastereoselectivities (up to >99% yield, >99% ee and >20:1 dr). Remarkably, 4-$MeC_6H_4CO_2H$ was identified as the most effective additive, which can improve the enantioselectivity of the model reaction to 97%.



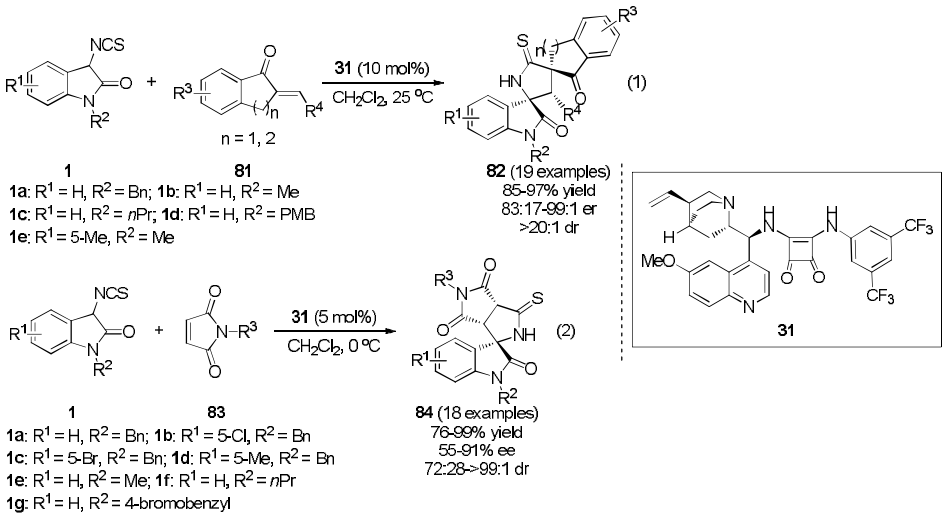
Scheme 32. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with barbiturate-based olefins.

To shed insights into the enantioselective formation of the product, according to the experimental results and related work about the catalytic model, the authors proposed a tentative transition state (Scheme 33). In the presence of 4-$MeC_6H_4CO_2H$, *N*-benzyl substituted 3-isothiocyanato oxindole tautomerizes into its enol. It is possible that organocatalyst **6** activates both the two substrates by means of the multiple H-bonding. Under the chiral environment, enol of 3-isothiocyanato oxindole **1** applies its *Si* face to attack the *Si* face of barbiturate-based olefin **79**, thus leading to the formation of the enantioenriched product **80**.



Scheme 33. Proposed transition state.

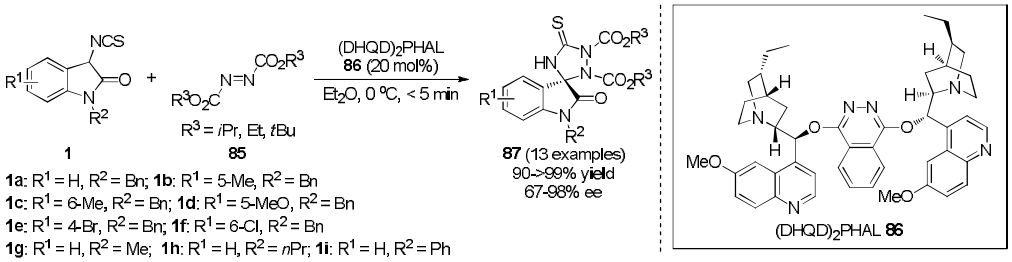
In 2016, Mukherjee and co-workers[37] disclosed a cascade Michael/cyclization reaction between 3-isothiocyanato oxindoles **1** and exocyclic α,β-unsaturated ketones **81**, which proceeding efficiently in the presence of a quinine-derived squaramide catalyst **31** and furnishing 3,2'-pyrrolidinyl bispirooxindoles **82** containing two spiro-quaternary and three contiguous stereocenters as a single diastereomer in high yields with excellent enantioselectivities (up to 97% yield, 99:1 er and >20:1 dr) (Scheme 34, eq. 1). Catalyzed by organocatalyst **31**, Du's group[38] developed a Michael/cyclization cascade process of isothiocyanato oxindoles **1** and maleimides **83** (Scheme 34, eq. 2). This protocol provided series of pyrrolidonyl spirooxindoles **84** bearing three contiguous stereocenters in excellent yields with high diastereo- and enantioselectivities (up to 99% yield, >99:1 dr and 91% ee).



Scheme 34. Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles with exocyclic α,β-unsaturated ketones or maleimides.

5. Asymmetric cascade reaction of 3-isothiocyanato oxindoles with azodicarboxylates

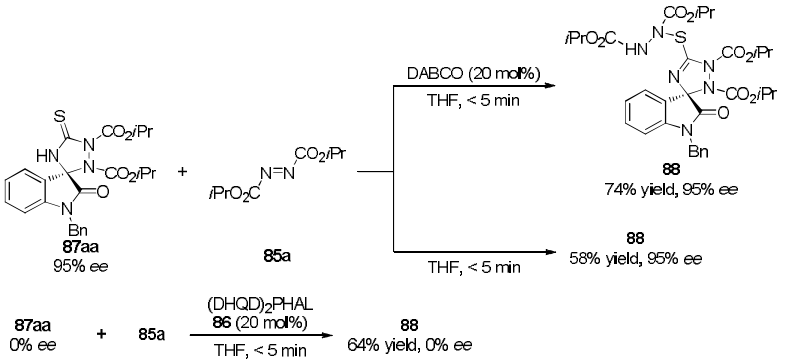
In 2013, Xu, Shi and co-workers[39] firstly explored a $(DHQD)_2PHAL$ **86**-catalyzed asymmetric cascade reaction of 3-isothiocyanato oxindoles **1** with azodicarboxylates **85**, which furnishing the corresponding spirooxindoles **87** in high yields along with high enantioselectivities (up to >99% yield and 98% ee) within 5.0 min (Scheme 35).



1a: R^1 = H, R^2 = Bn; **1b**: R^1 = 5-Me, R^2 = Bn
1c: R^1 = 6-Me, R^2 = Bn; **1d**: R^1 = 5-MeO, R^2 = Bn
1e: R^1 = 4-Br, R^2 = Bn; **1f**: R^1 = 6-Cl, R^2 = Bn
1g: R^1 = H, R^2 = Me; **1h**: R^1 = H, R^2 = *n*Pr; **1i**: R^1 = H, R^2 = Ph
1j: R^1 = H, R^2 = 3,5-dimethylbenzyl; **1k**: R^1 = H, R^2 = naphthalen-2-ylmethyl

Scheme 35. Asymmetric cascade reaction of of 3-isothiocyanato oxindoles with azodicarboxylates.

Interestingly, the authors found that the final adduct **87aa** could then react with another molecule of azodicarboxylate **85a**, which delivering a new product **88** in good yield with the same high enantioselectivity (up to 99% yield and 99% ee) under the standard conditions. A series of experiments revealed that **88** could be afforded in different yield but the ee value is almost the same as that of **87aa**, which suggested that the ee value of **88** is determined by the first reaction step in the production of **87aa**. As shown in Scheme 36, the control experiments further indicated that the second reaction step did not influence the ee value of the final product. In addition, various transformations of the cycloadduct **87aa** into other dispirocyclic oxindoles were also successfully realized. More importantly, the authors have evaluated the biological activities of these spirooxindoles. The proliferation inhibition effect of **87aa** and **88** with HeLa cells via the MTT assays were conducted. They found that when the concentration was 1 mg/mL, the cell viability was decreased sharply, which indicating their useful biological activity.

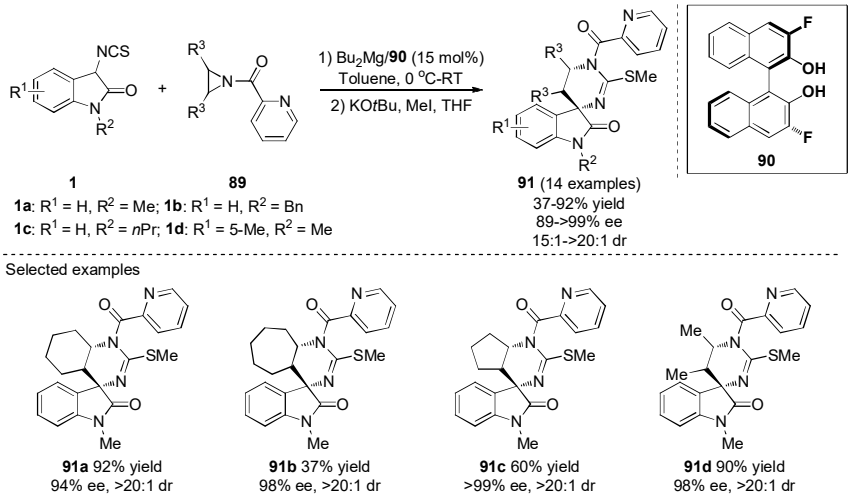


Scheme 36. Control experiments.

6. Asymmetric ring-opening/closing cascade reaction of 3-isothiocyanato oxindoles with aziridines

In recent years, 3-isothiocyanato oxindoles have been widely applied in different asymmetric formal [3+2] cyclizations, but less explored in [3+3] cycloaddition reactions. In 2015, Wang's group[40] successfully developed an enantioselective ring-opening/closing cascade reaction of 3-isothiocyanato oxindoles **1** with *N*-(2-picolinoyl)aziridines **89** for the first time (Scheme 37). The reaction was efficiently mediated by an *in situ* generated magnesium catalyst employing (*R*)-3,3'-fluorous-BINOL **90** as a simple chiral ligand. Serials of polycyclic frameworks **91** could be obtained after a ring-closing step in good yields with excellent

stereoselectivities (up to 92% yield, >99% ee and >20:1 dr). Factually, in early 2013, this group[41] reported an unprecedented Et_3N catalyzed diastereoselective [3+3] annulation of 3-isothiocyanatooxindoles and azomethine imines, affording 3,3'-triazinyl spirooxindoles in excellent yields and diastereoselectivities under mild conditions. Unfortunately, no asymmetric examples were reported till now.



Scheme 37. Ring-opening/closing cascade reaction of 3-isothiocyanato oxindoles with *N*-(2-picolinoyl)aziridines.

7. Conclusions

As dicussed in this context, great progress has been made in the asymmetric cascade reactions of 3-isothiocyanato oxindoles for the construction of structurally diverse spirooxindoles over the past six years. In this research field, we noticed that, for different formal [3+2] or [3+3] cyclizations, both organocatalysis and metal catalysis systems can be well applied to the corresponding transformations. Considering the reported work, we found that there are still some aspects needing to be thought deeply, such as the types of novel cascade reaction, catalytic model, substrate scope and so on. Therefore, exploring for efficient cascade progress, looking for appropriate catalytic model and developing novel synthon would be a formidable challenging task for chemists. On the basis of this, many new compounds with a spirooxindole skeleton would be synthesized, and they would be good candidates for new drug development. We believe that further exciting and ground-breaking discoveries can be expected with certainty in the near future.

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