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# Organocatalyzed Asymmetric Reaction Using $\alpha$ -Isothiocyanato Compounds

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Additional information is available at the end of the chapter

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## Abstract

Organocatalyzed asymmetric reaction using  $\alpha$ -isothiocyanato compounds has received much attention in the past 5 years, and significant progress has been made for three types of isothiocyanato compounds, including  $\alpha$ -isothiocyanato amides, esters, and phosphonates. This chapter covers the recent advances of  $\alpha$ -isothiocyanato compounds in the organocatalytic asymmetric reaction.

**Keywords:** Organocatalysis, Asymmetric synthesis, Enantioselectivity,  $\alpha$ -Isothiocyanato compounds, Cascade reaction

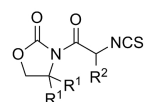
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## 1. Introduction

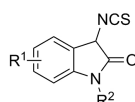
The development of efficient approaches to construct stereochemically complex compounds by catalytic asymmetric cascade reaction has received significant attention in the past 15 years [1–3]. Isothiocyanate, a new and versatile reagent for various catalyzed asymmetric cascade reactions, was firstly prepared from thiocyanate by Hofmann in 1880 [4]. However, isothiocyanato compounds, such as 3-(2-isothiocyanatoacetyl)-oxazolidin-2-one (**Figure 1, 1a**), were not applied in catalyzed asymmetric cascade reaction until 2005 by Willis. In this process, chiral bis(oxazoline)-magnesium(II) complex was used as catalyst, delivering protected aryl  $\beta$ -hydroxyl- $\alpha$ -amino acids in good results [5]. Afterwards, different kinds of isothiocyanato compounds, including  $\alpha$ -isothiocyanato amides, esters, and phosphonates (**Figure 1**), were developed by chemists and applied to the catalytic asymmetric syntheses [6]. In addition, the

general methods for the synthesis of  $\alpha$ -isothiocyanato compounds were shown in **Scheme 1** [5, 7–9].

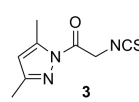
**$\alpha$ -isothiocyanato amides**



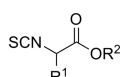
- 1a:** R<sup>1</sup> = H, R<sup>2</sup> = H  
**1b:** R<sup>1</sup> = Me, R<sup>2</sup> = H  
**1c:** R<sup>1</sup> = Me, R<sup>2</sup> = Me



- 2**  
 R<sup>1</sup> = H, Me, MeO, F, Cl, Br, NO<sub>2</sub>  
 R<sup>2</sup> = Me, Et, <sup>i</sup>Pr, Ph, Bn, Ac, allyl, MOM, PMP, 4-bromobenzyl, 3,5-dimethylbenzyl, naphthalen-2-ylmethyl



**$\alpha$ -isothiocyanato esters**

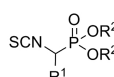


- 4a:** R<sup>1</sup> = H, R<sup>2</sup> = Me  
**4b:** R<sup>1</sup> = H, R<sup>2</sup> = Et  
**4c:** R<sup>1</sup> = H, R<sup>2</sup> = <sup>i</sup>Pr  
**4d:** R<sup>1</sup> = H, R<sup>2</sup> = <sup>t</sup>Bu  
**4e:** R<sup>1</sup> = Me, R<sup>2</sup> = Me  
**4f:** R<sup>1</sup> = Et, R<sup>2</sup> = Me



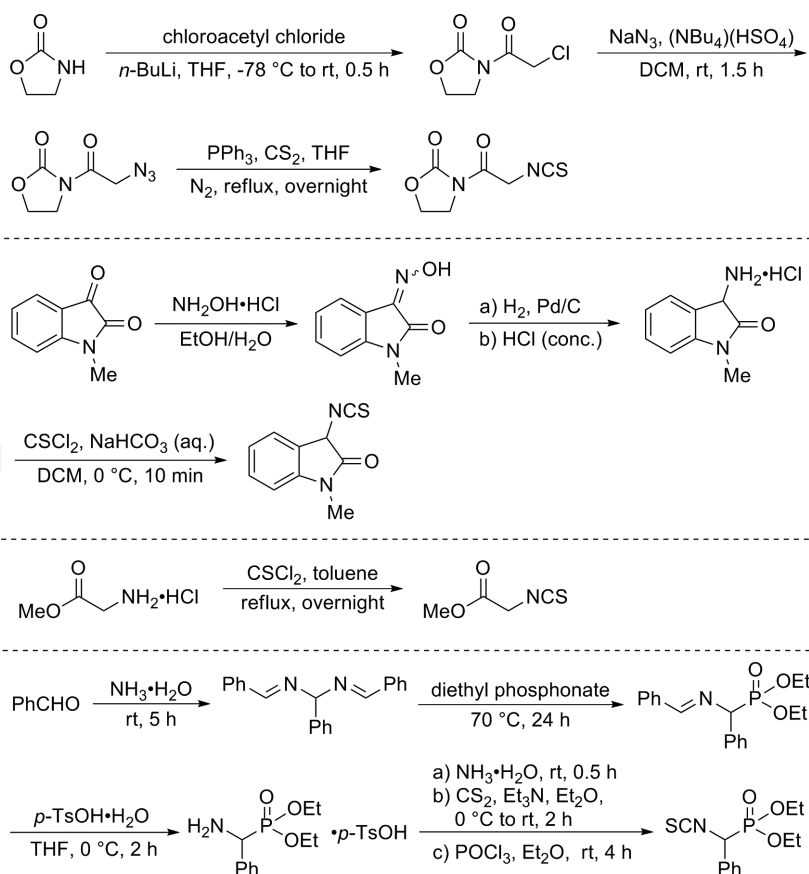
**5**

**$\alpha$ -isothiocyanato phosphonates**

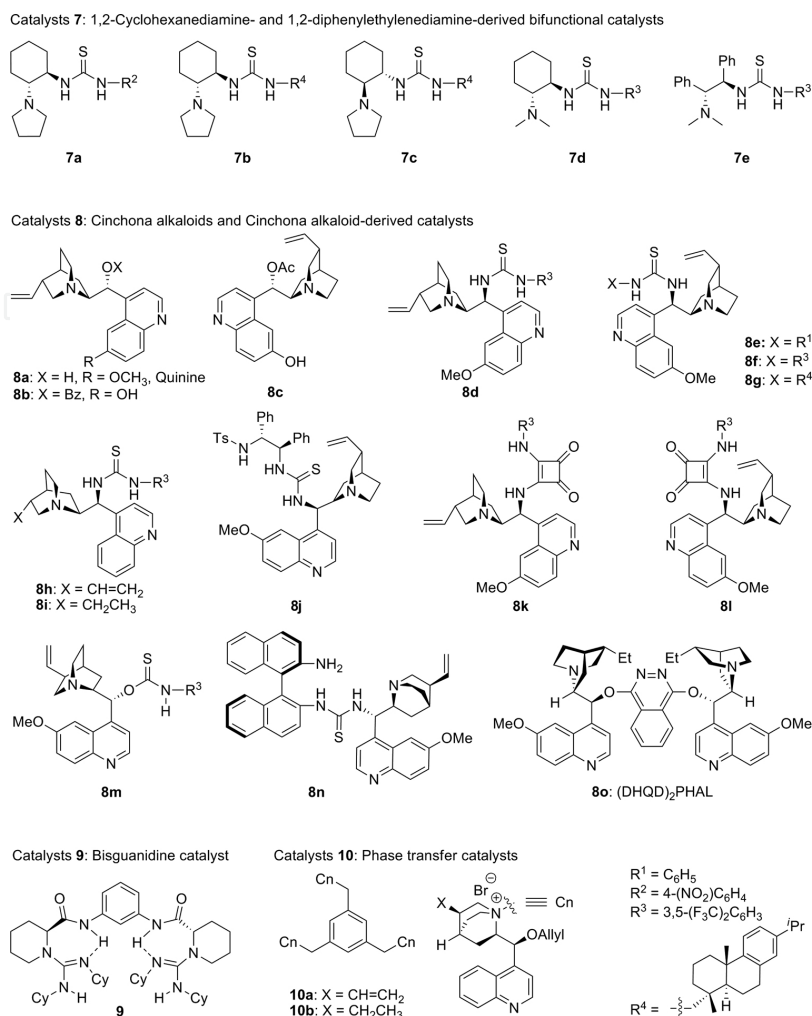


- 6a:** R<sup>1</sup> = Ph, R<sup>2</sup> = Et  
**6b:** R<sup>1</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Et  
**6c:** R<sup>1</sup> = 4-MeOC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Et  
**6d:** R<sup>1</sup> = 4-FC<sub>6</sub>H<sub>4</sub>, R<sup>2</sup> = Et  
**6e:** R<sup>1</sup> = Ph, R<sup>2</sup> = <sup>i</sup>Pr  
**6f:** R<sup>1</sup> = Ph, R<sup>2</sup> = Ph

**Figure 1.**  $\alpha$ -Isothiocyanato amides, esters, and phosphonates developed for the catalytic asymmetric reactions.



**Scheme 1.** Representative synthetic methods for the  $\alpha$ -isothiocyanato compounds.



**Figure 2.** Organocatalysts involved in this chapter.

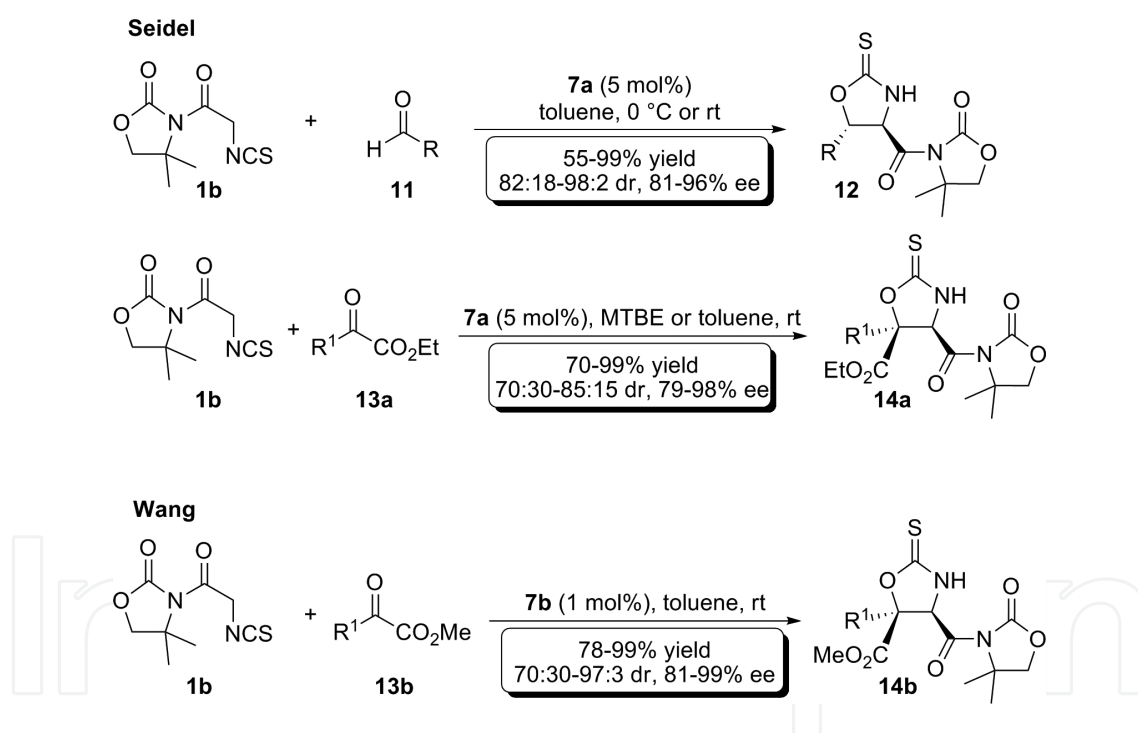
This chapter focuses on the synthesis of stereochemically enriched compounds based on these three kinds of isothiocyanato compounds via organocatalytic asymmetric cascade reactions, including aldol/cyclization, Mannich/cyclization, Michael/cyclization, [3+2] cyclization with allenic esters, [3+2] cyclization with 2-butyne-1,3-dioic acid diesters, [3+2] cyclization with azodicarboxylates, as well as self-cyclization/addition with aziridines and is classified on the basis of the types of acceptors. Some common organocatalysts involved in this chapter are listed in **Figure 2**, including 1,2-cyclohexanediamine- and 1,2-diphenylethylenediamine-derived bifunctional catalysts **7**, Cinchona alkaloids and Cinchona alkaloid-derived catalysts **8**, bisguanidine catalyst **9**, phase transfer catalysts **10**.

## 2. Cascade aldol/cyclization

In 2008, Seidel and coworkers successfully established the first cascade aldol/cyclization reaction of  $\alpha$ -isothiocyanato imides (**1b**) and various aldehydes (**11**) with a chiral bifunctional

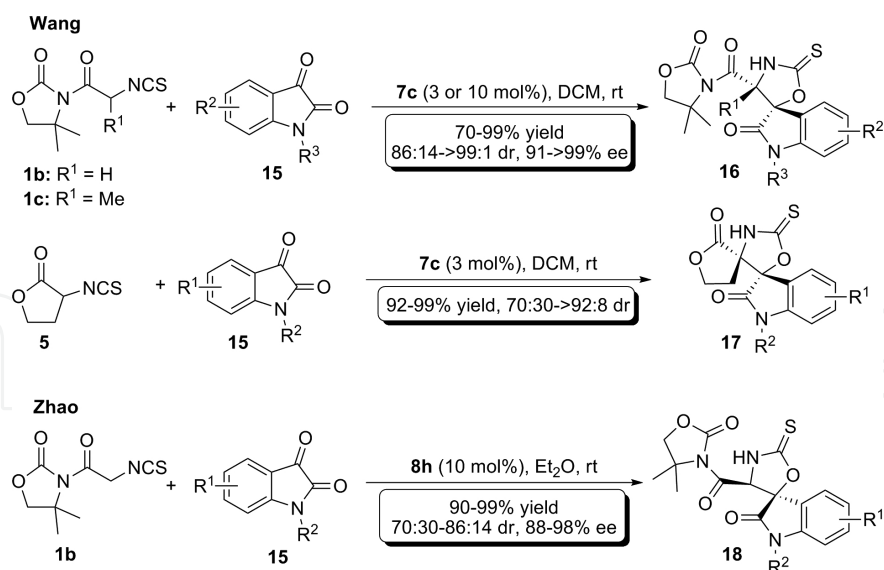
thiourea–tertiary amine (**7a**) as catalyst (**Scheme 2**) [10]. With this method, a wide range of protected *syn*  $\beta$ -hydroxyl- $\alpha$ -amino acids (**12**) could be readily generated in very good results (up to 99% yield, 98:2 dr, and 96% ee) with low catalyst loading (5 mol%) and under mild reaction conditions. More importantly, in some instances, due to the product precipitation, the corresponding products even could be directly isolated with high diastereoselectivities and enantioselectivities by simple filtration.

Afterwards, another type of protected  $\beta$ -hydroxyl- $\alpha$ -amino acids was obtained in good results using the same strategy by Seidel and coworkers in 2010 (**Scheme 2**) [11]. Almost at the same time, Wang's group also reported the organocatalytic asymmetric aldol additions of  $\alpha$ -isothiocyanato imide (**1b**) to  $\alpha$ -ketoesters (**13b**) (**Scheme 2**) [12]. They developed the rosin-derived amine-thiourea catalyst (**7b**), and the corresponding products were obtained in good to high yields (78–99% yields) with high levels of diastereoselectivities and enantioselectivities (70:30–97:3 dr, and 81–99% ee). In comparison, Wang achieved excellent results (up to 99% ee and 97:3 dr) at very low catalyst loadings (1 mol%), but the stereocenters of bifunctional catalyst (**7a**) are more atom-economic for asymmetric synthesis.



**Scheme 2.** Organocatalyzed aldol additions of  $\alpha$ -isothiocyanato imides to aldehydes and  $\alpha$ -keto esters.

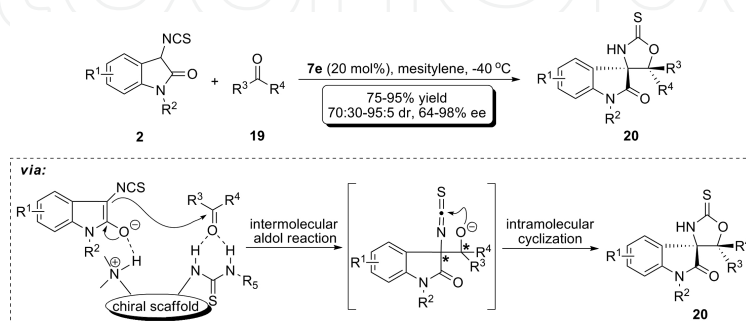
Using the rosin-derived amine–thiourea **7c** as a bifunctional catalyst, a highly efficient and convenient cascade aldol/cyclization of  $\alpha$ -isothiocyanato amides (**1b** and **1c**) or  $\alpha$ -isothiocyanato ester (**5**) with isatins (**15**) was disclosed by Wang's group (**Scheme 3**) [13]. In this process, optically active spirocyclic thiocarbamates (**16** or **17**) were obtained in good to excellent results. Additionally, the products were readily transformed into biologically active spirooxazolines. Importantly, using a model of acute neuroinflammation, several of the spirooxazolines were found to significantly reduce LPS-induced fever.



**Scheme 3.** Synthesis of spirocyclic thiocarbamates.

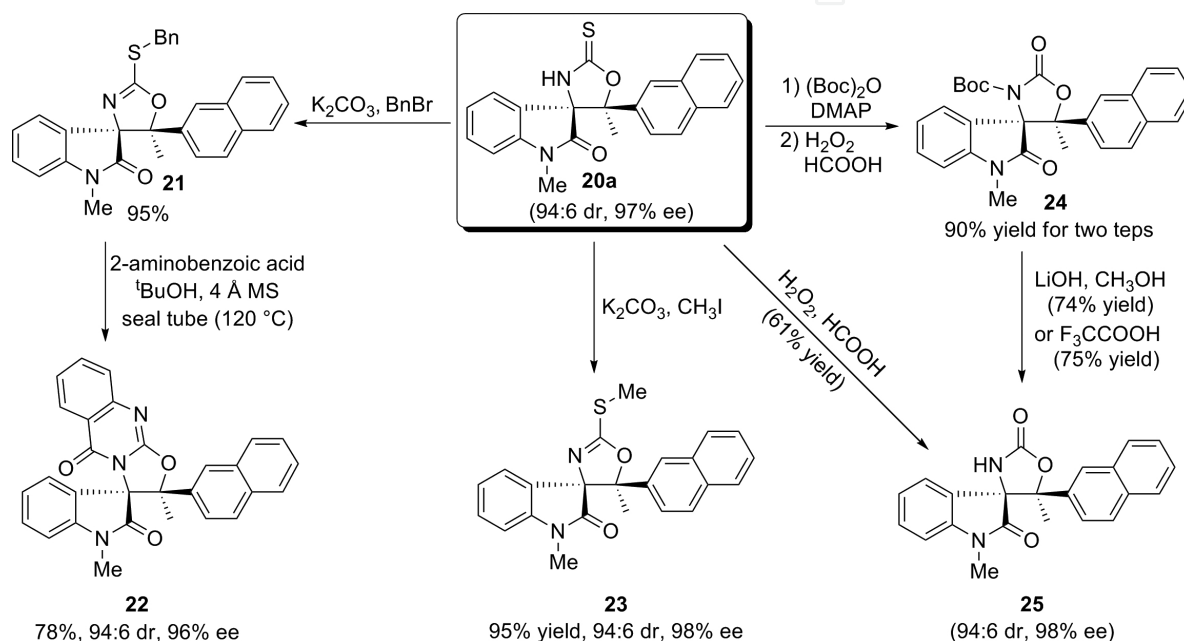
Shortly after this report, a similar protocol was reported by Zhao's group in 2011 (**Scheme 3**) [14]. Using catalyst **8h** derived from cinchonidine in diethyl ether at room temperature, a series of spirocyclic thiocarbamate compounds **18** were obtained in high yields (up to 99%) with good diastereoselectivities and enantioselectivities (up to 86:14 dr and 98% ee).

Inspired by  $\alpha$ -isothiocyanato esters or amides are efficient nucleophilic reagents to construct chiral heterocyclics [10–14], and considering the potential applications of spirocyclic oxindole skeletons which have particularly emerged as attractive synthetic targets in the field of natural products synthesis and medicinal chemistry [15–17]. 3-Isothiocyanato oxindoles (**2**), a novel kind of  $\alpha$ -isothiocyanato amides, were designed and synthesized by our group in 2011 [7]. Using chiral organocatalyst (**7e**), a class of 3,3'-spirooxindoles (**20**) could be formed by the reaction of 3-isothiocyanato oxindoles (**2**) with aryl and alkyl ketones (**19**). Additionally, a plausible mechanism including a sequential asymmetric aldol reaction and intramolecular cyclization of the aldol adduct with isothiocyanate unit was tentatively suggested (**Scheme 4**).

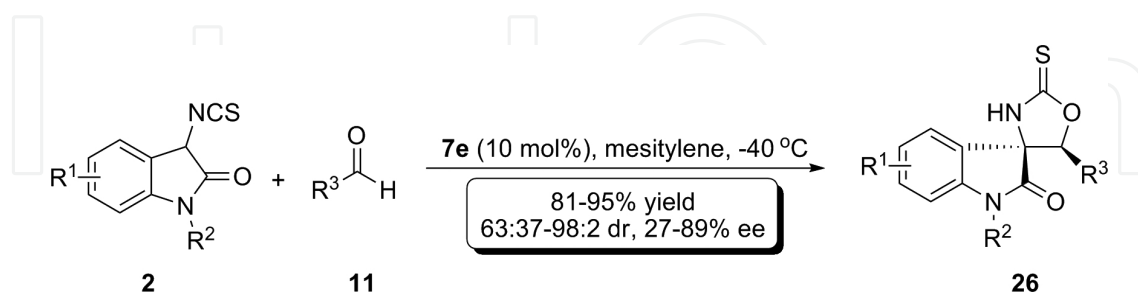


**Scheme 4.** Organocatalytic asymmetric aldol reactions of 3-isothiocyanato oxindoles to ketones.

Although isothiocyanates have previously been applied in the synthesis of cyclic aldol products [10–14], this represents the first example in the construction of spirocyclic oxindoles using 3-isothiocyanato oxindoles through direct aldol reaction. In the reaction of 3-isothiocyanato oxindoles (**2**) with simple ketones (**19**), a range of spirooxindole derivatives (**20**) containing two highly congested adjacent tetrasubstituted carbon stereocenters were obtained in good to excellent results (up to 95% yield, 95:5 dr, and 98% ee). Moreover, the utilities of this method were also demonstrated by the transformation of product **20a** to more structurally diverse spirooxindoles (**21–25**) (Scheme 5). It is worthy to note that there is no change in the stereoselectivities during the various transformations.



Scheme 5. Transformations of the product **20a** to other spirocyclic oxindoles.

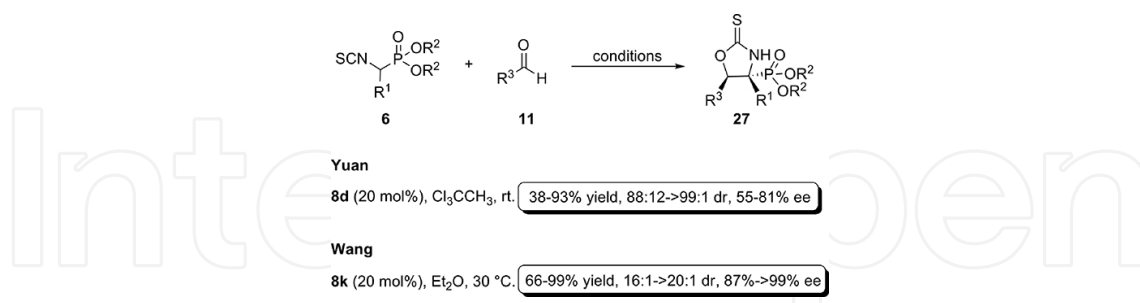


Scheme 6. Organocatalytic asymmetric aldol reactions of 3-isothiocyanato oxindoles to aldehydes.

Following this work, our group further disclosed a highly efficient approach for the synthesis of spiro[oxazolidine-2-thione-oxindoles] (**26**) with 3-isothiocyanato oxindoles (**2**) and aldehydes (**11**) via a cascade aldol/cyclization reaction process (Scheme 6) [18]. In this process, spiro[oxazolidine-2-thione-oxindole] compounds **26** were obtained in up to 95% yield, 98:2 dr,



and 89% ee. Importantly, in most instances, high reactivity was observed and the reaction could be completed even within 1.0 min.

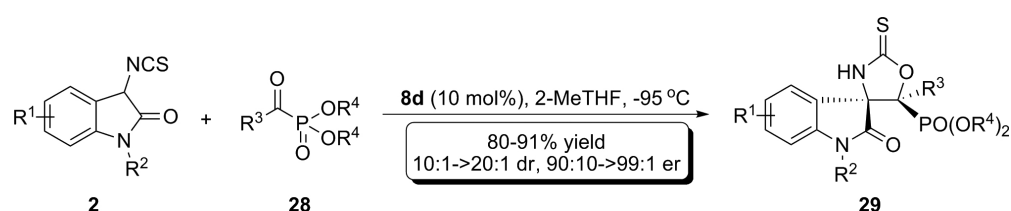


**Scheme 7.** Asymmetric synthesis of  $\beta$ -hydroxyl- $\alpha$ -amino phosphonic acid derivatives via organocatalytic direct aldol reaction of  $\alpha$ -isothiocyanato phosphonates with aldehydes.

In 2013, our group firstly developed an asymmetric cascade aldol/cyclization reaction between  $\alpha$ -isothiocyanato phosphonates (**6**) and aldehydes (**11**) for the construction of  $\beta$ -hydroxyl- $\alpha$ -amino phosphonic acid derivatives (**27**) [19]. Using bifunctional thiourea catalyst **8d** derived from quinine, a range of protected  $\beta$ -hydroxyl- $\alpha$ -amino phosphonates derivatives (**27**) containing contiguous quaternary-tertiary stereocenters was obtained in up to 93% yield, >99:1 dr, and 81% ee. The potential application of this method was demonstrated by a large-scale experiment and by the further transformation of one product.

Afterwards, a catalytic asymmetric 1,2-addition reaction of  $\alpha$ -isothiocyanato phosphonates (**6f**) with aldehydes (**11**) was also reported from Wang's group (**Scheme 7**) [20]. Using squaramide-based hydrogen-bonding catalyst (**8k**) derived from quinine, a series of  $\beta$ -hydroxyl- $\alpha$ -amino phosphonic acids were obtained in high yields (up to 99% yield) with excellent stereoselectivities (up to >20:1 dr and >99% ee).

Recently, a novel cascade aldol/cyclization reaction of 3-isothiocyanato oxindoles with  $\alpha$ -ketophosphonates was disclosed by Mukherjee's group (**Scheme 8**) [21]. This protocol provides an alternative approach to the  $\beta$ -amino- $\alpha$ -hydroxyphosphonate derivatives which contains a spirooxindole scaffold bearing two contiguous quaternary stereogenic centers in high yields with excellent diastereoselectivities (up to >20:1 dr) and enantioselectivities (up to >99:1 er). In addition, the products of this reaction can be modified to allow easy access to differently functionalized spirooxindoles.



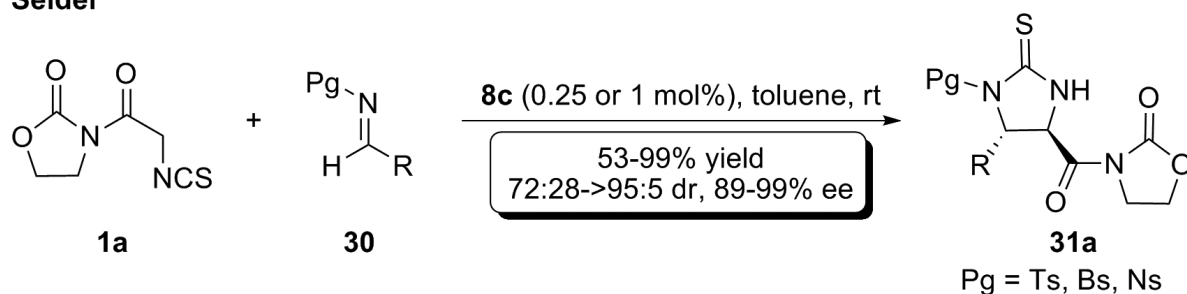
**Scheme 8.** Enantioselective synthesis of  $\beta$ -amino- $\alpha$ -hydroxyphosphonates between 3-isothiocyanato oxindoles and  $\alpha$ -ketophosphonates.



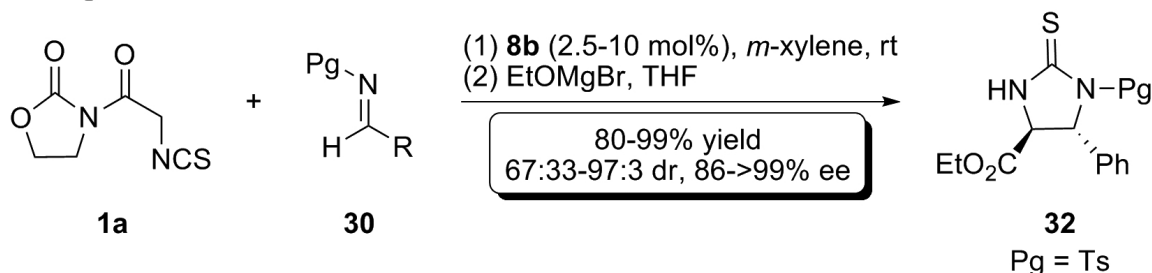
### 3. Cascade Mannich/cyclization

Based on the remarkable success in the organocatalyzed asymmetric aldol reaction using  $\alpha$ -isothiocyano imides (**Scheme 2**) [10], Seidel's group reported a highly stereoselective cascade Mannich/cyclization reaction between  $\alpha$ -isothiocyanato imides (**1a**) and *N*-sulfonyl imines (**30**) in 2009 (**Scheme 9**) [22]. In this process, a diverse range of imines (Ts, Bs, and Ns) bearing substituted aromatic, heteroaromatic, and  $\alpha,\beta$ -unsaturated groups could react with **1a** using quinidine derived **8c** as chiral catalyst, delivering *syn*- $\alpha,\beta$ -diamino acid derivatives (**31a**) in excellent results. Because of the solubility difference in the products, the reactions with Ns- and Bs-imines were much faster than Ts-imines, and the reaction of  $\alpha$ -isothiocyanato imides with Ns- and Bs-imines carried out smoothly at a low catalyst loading (0.25–1.0 mol%).

#### Seidel

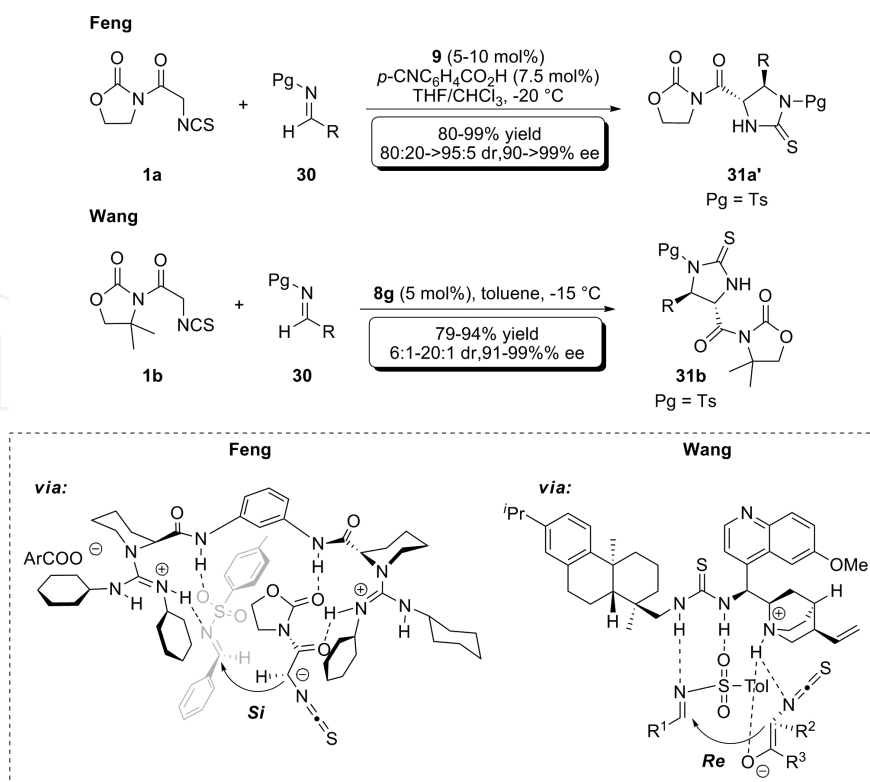


#### Zhong



**Scheme 9.** Catalytic enantioselective synthesis of  $\alpha,\beta$ -diamino acid derivatives.

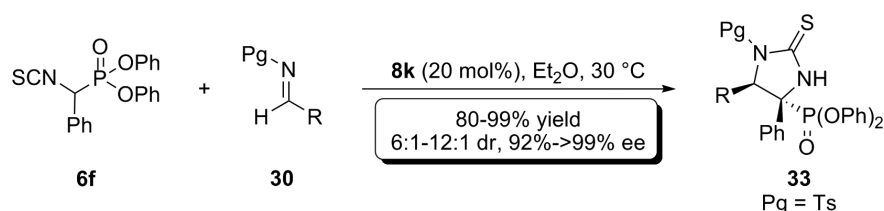
At the same time, a similar reaction between  $\alpha$ -isothiocyanato imide (**1a**) and Ts-imines (**30**) catalyzed by the catalyst (**8b**) derived from quinine was developed by Zhong and coworkers (**Scheme 9**) [23]. It was observed that Mannich adducts (**32**) could be achieved in good results (up to 99% yield, 97:3 dr and >99% ee).



**Scheme 10.** Synthesis of  $\alpha,\beta$ -diamino acid derivatives using bisguanidine or rosin-derived catalyst.

In 2011, Feng's group [24] and Wang's group [25] independently reported highly efficient asymmetric cascade Mannich–cyclization reaction of  $\alpha$ -isothiocyanato imides (**1a** and **1b**) with  $N$ -Ts-protected imines (**30**) (**Scheme 10**). A highly efficient chiral bisguanidine catalyst (**9**) was used into the reaction of **1a** with **30** in Feng's group. In that reaction, significant progress including broad substrate scope, affording chiral  $\alpha,\beta$ -diamino acid derivatives in excellent yields (up to 99%) with high diastereoselectivities (up to >95:5 dr) and excellent enantioselectivities (up to >99% ee) had been made. Notably, the additive ( $p\text{-CNC}_6\text{H}_4\text{CO}_2\text{H}$ ) in the reaction had an important influence on the reactivity and asymmetric induction, which attribute to the hydrogen and the guanidine moiety both played crucial roles in the process. On the other hand, Wang's group used the bifunctional catalyst (**8g**) derived from rosin affording corresponding Mannich products **31b** in high yields (up to 94%) with good to high stereoselectivities (up to 20:1 dr, and 99% ee). And preliminary biological studies revealed that several of the methylthioimidazoline derivatives showed extremely promising antipyretic activity.

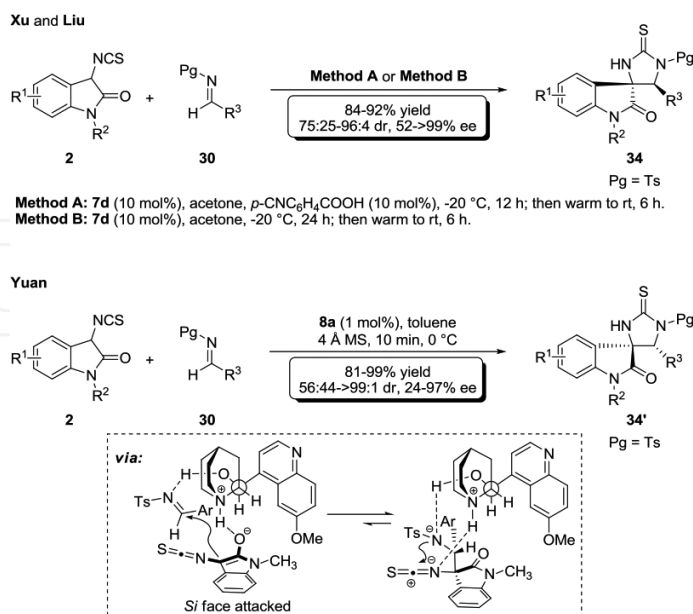
Feng and Wang also gave a proposed active model for the reaction in their work, respectively (**Scheme 10**). Feng proposed that the weakly acidic additive ( $p\text{-CNC}_6\text{H}_4\text{CO}_2\text{H}$ ) could protonate one of the guanidine moieties leading to a guanidinium salt, which activates the  $N$ -Ts-imine via hydrogen bond to the nitrogen of the  $N$ -Ts-imine. Meanwhile, the active hydrogen atom of  $\alpha$ -isothiocyanato imide was deprotonated by the other guanidine group, and then, an intermolecular hydrogen bond stabilizes the  $\alpha$ -isothiocyanato imide. Simultaneously, the  $N\text{-H}$  group of the amide on the same side of guanidine moiety might play as a Brønsted acid to locate  $\alpha$ -isothiocyanato amide (**1a**). In this active model, the activated  $\alpha$ -isothiocyanato imide



**Scheme 11.** Synthesis of  $\alpha,\beta$ -diamino phosphonic acid derivatives.

(**1a**) preferentially attacked the activated  $N$ -Ts-imine from the *Si*-face, affording the desired major product with (4*S*,5*R*) configuration. On the other hand, Wang proposed that the rosin-derived tertiary amine–thiourea (**8g**) would act in a bifunctional fashion. The  $\alpha$ -carbon atom of  $\alpha$ -isothiocyanato amide (**1b**) was enolized by the tertiary amine moiety of the catalyst (**8g**). Concurrently,  $N$ -Ts-imine (**30**) was located and activated by two hydrogen atoms of the thiourea moiety through hydrogen-bond interaction. Afterwards, the nucleophile would preferentially attack at the  $N$ -Ts-imine (**30**) from the *Re*-face, since the *Si*-face of the  $N$ -Ts-imine (**30**) was restricted by the quinone moiety of the catalyst.

After the success in the asymmetric cascade aldol/cyclization reaction of diphenyl  $\alpha$ -isothiocyanato phosphonate (**6f**) with aldehydes (**Scheme 7**) [20], the asymmetric cascade Mannich/cyclization reaction between  $\alpha$ -isothiocyanato phosphonate (**6f**) and  $N$ -Ts-imine (**30**) was explored by Wang and coworkers, giving the  $\alpha,\beta$ -diamino phosphonic acid derivatives (**33**) in high yields (up to 99%) with moderate diastereoselectivities and excellent enantioselectivities (up to >99% ee) (**Scheme 11**) [20]. In general, the diastereoselectivity of the cascade Mannich/cyclization reaction was lower than that of the cascade aldol/cyclization process, but the enantioselectivities of the Mannich products were slightly higher.



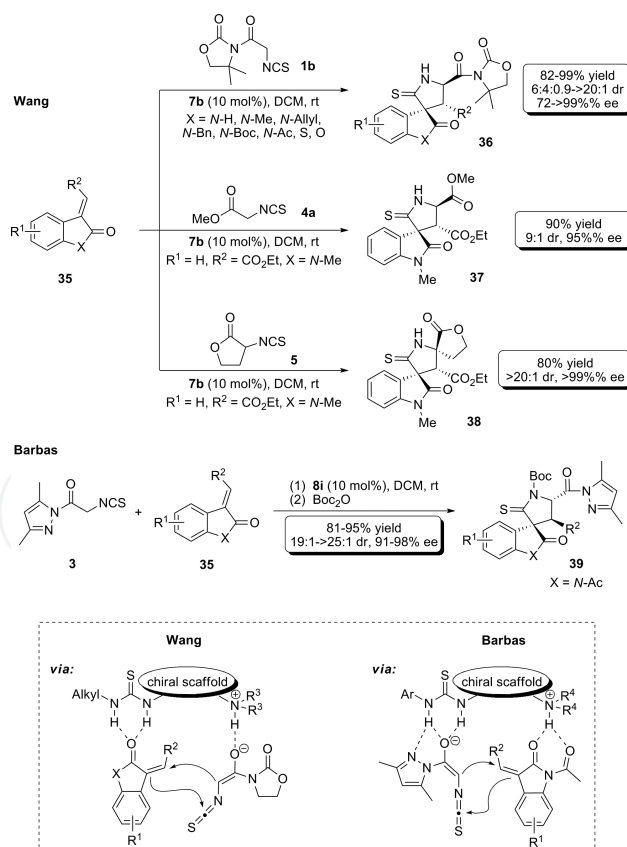
**Scheme 12.** Synthesis of  $\alpha,\beta$ -diamino derivatives based on 3-isothiocyanato oxindoles.

Organocatalytic asymmetric cascade Mannich/cyclization reaction between 3-isothiocyanato oxindoles (**2**) and *N*-Ts imines (**30**) was reported by Xu and co-workers in 2014 (**Scheme 12**) [26]. With the developed method, the spiro[imidazolidine-4,3'-oxindole] products (**34**) were smoothly prepared in up to 92% yield, 96:4 dr, and >99% ee.

Meanwhile, a similar strategy to access spirooxindole derivatives using quinine **8a** as catalyst for the reaction of 3-isothiocyanato oxindoles (**2**) and *N*-Ts imines (**30**) was discovered in our group (**Scheme 12**) [27]. With the developed protocol, a range of structurally complex spirocyclic oxindoles derivatives (**34'**) was obtained in good results (up to 99% yield, >99:1 dr, and 97% ee). Importantly, *N*-PMP aldimine, *N*-diphenylphosphinoyl aldimine, and *N*-Boc isatinimine were also good substrates for reacting with 3-isothiocyanato oxindoles (**2**). A possible model for explaining the stereochemistry of the domino Mannich–cyclization reaction was proposed.

## 4. Cascade Michael/cyclization

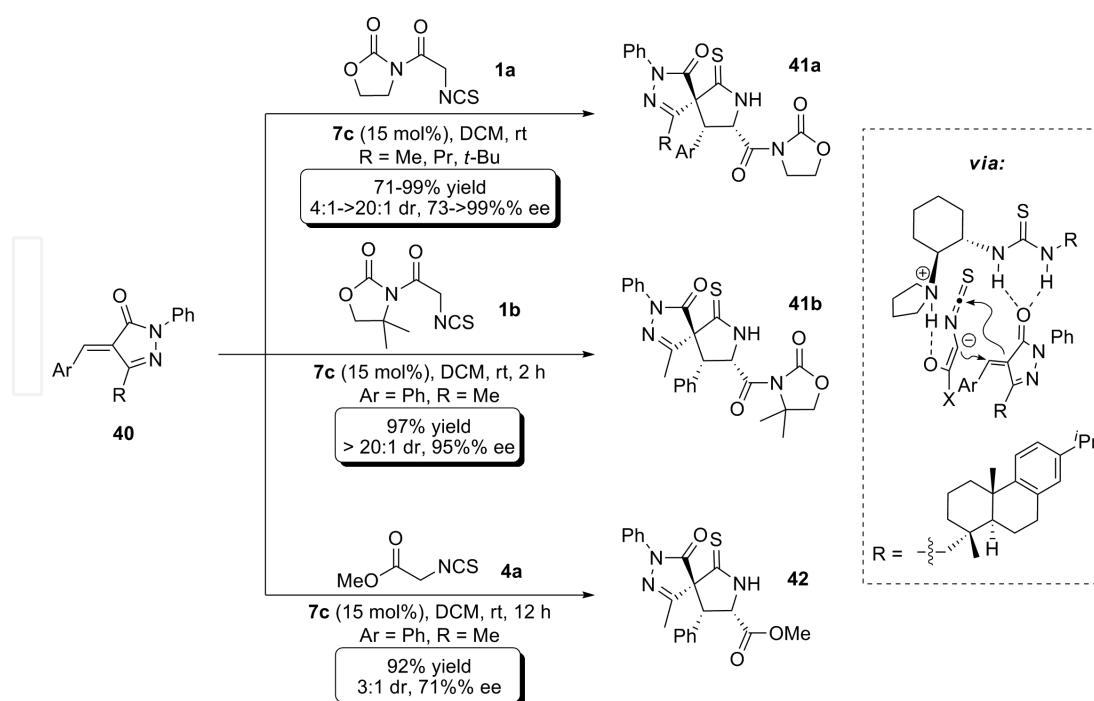
In 2011, Wang and coworkers explored the unprecedented reaction of organocatalytic asymmetric cascade Michael/cyclization reaction using  $\alpha$ -isothiocyanato amides [28], which



**Scheme 13.** Enantioselective Michael/cyclization reaction with  $\alpha$ -isothiocyanato imide or ester.

attribute to the stereoselectivity and reactivity of the  $\alpha$ -isothiocyanato compounds with electron-deficient olefins is challenging. As shown in **Scheme 13**, rosin-derived thiourea (**7b**) catalyzed the asymmetric cascade Michael/cyclization reaction of  $\alpha$ -isothiocyanato imides (**1b**, **4a**, and **5**) with various methyleneindolinones (**35**), affording the densely functionalized 3,3'-pyrrolidonyl spirooxindoles (**36–38**) in excellent results (up to 99% yield, >20:1 dr, and >99% ee).

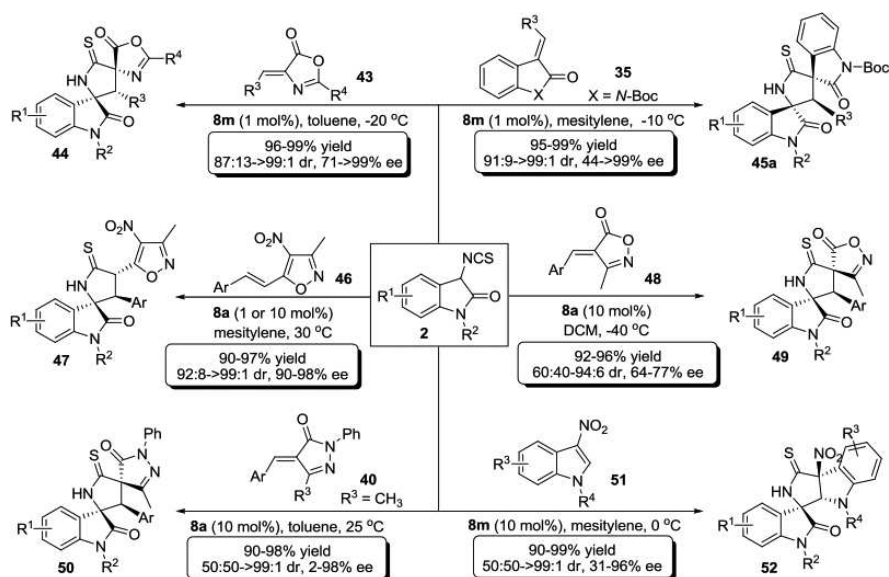
Another kind of asymmetric cascade Michael/cyclization reaction between dimethylpyrazole isothiocyanato imides (**3**) and methyleneindolinones (**35**) using bifunctional catalyst (**8i**) derived from cinchonidine was also explored by Barbas and coworkers in 2012 (**Scheme 13**) [29]. Dimethylpyrazole was selected as the directing group, because there would have interaction between the pyrazole group and the thiourea moiety of the catalyst. Additionally, the acetyl protecting group played a crucial role in the enantioselectivity. The reaction provided smoothly a range of highly functionalized spirocyclic oxindoles (**39**) in excellent results (up to 95% yield, >25:1 dr, and 98% ee). Notably, for this kind of asymmetric cascade Michael/cyclization reactions with bifunctional thiourea–tertiary amine catalyst, although two substrates were simultaneously activated by the catalyst, Wang and Barbas gave their respective transition states (**Scheme 13**). Wang proposed that the oxindole scaffold was activated by double H-bonding, and the  $\alpha$ -carbon atom of isothiocyanate imide was activated via enolate anion by the tertiary amine moiety of the catalyst. However, Barbas thought that the oxindole scaffold was activated by the tertiary amine moiety of catalyst and that the  $\alpha$ -carbon atom of isothiocyanato imide was deprotonated by double H-bonding.



**Scheme 14.** Asymmetric Michael/cyclization sequence of  $\alpha$ -isothiocyanato imides and esters with pyrazolones.

On the basis of the works from Wang's and Barbas' group (**Scheme 13**) [28, 29], organocatalytic asymmetric cascade Michael/cyclization reaction of  $\alpha$ -isothiocyanato imides and esters (**1a**, **1b**, and **4a**) with various unsaturated pyrazolones (**40**) was also explored by Wang and coworkers in 2012 (**Scheme 14**) [30]. With the developed method, a series of spirocyclic pyrazolone compounds were observed (**41a**, **41b**, and **42**) in high diastereoselectivity and enantioselectivity (up to 20:1 dr, and >99% ee). Undoubtedly, this methodology provides a convenient and highly efficient approach for the construction of spiropyrazolone skeletons with high enantioselectivities.

3-Isothiocyanato oxindoles (**2**) are important reagents for the stereoselective construction of structurally diverse spirocyclic oxindoles via cascade aldol/cyclization process [7, 18, 21, 31] and Mannich/cyclization process [26, 27, 31]. It is worthy to note that organocatalytic asymmetric cascade Michael/cyclization reactions using 3-isothiocyanato oxindoles as donors to construct densely functionalized spirooxindoles derivatives rapidly appeared during the past four years. The following examples illustrate the progress in this area.



**Scheme 15.** Asymmetric Michael/cyclization based on 3-isothiocyanato oxindoles (**2**) by Yuan's group.

In 2013, an efficient asymmetric cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles (**2**) with alkylidene azlactones (**43**) or 3-methylene-2-oxindoles (**35**) to construct more complex dispirocyclic thiopyrrolidineoxindoles was explored by our group [32], providing a range of highly functionalized dispirocyclooxindole compounds (**44** and **45a**) in excellent results (up to 99% yield, >99:1 dr, and >99% ee) only using 1 mol% of readily available aminothiocarbamate catalyst (**8m**) (**Scheme 15**).

To further investigate the versatility of 3-isothiocyanato oxindoles for constructing more complex spirocyclic oxindole scaffolds, the cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles (**2**) with 3-methyl-4-nitro-5-alkenyl-isoxazoles (**46**) was subsequently explored in our laboratory (**Scheme 15**) [33]. To our delight, optically active 3,3'-pyrrolidonyl



spirooxindole derivatives (**47**) could be smoothly obtained in high yields (up to 97%) with excellent stereoselectivities (up to >99:1 dr and 98% ee) with cinchona alkaloid quinine as catalyst. Nevertheless, the potential application of this method was also demonstrated by the large-scale experiment and the versatile transformation of the product into other heterocyclic compounds.

Encouraged by our these progresses using 3-isothiocyanato oxindoles (**2**) as powerful and versatile precursors in the organocatalytic asymmetric cascade Michael/cyclization reactions [32, 33], we further attempted to investigate the reactions of 3-isothiocyanato oxindoles (**2**) with unsaturated isoxazolones (**48**) and pyrazolones (**40**) (**Scheme 15**) [34]. It was observed that the reaction also worked well with quinine as catalyst under mild reaction conditions, delivering two kinds of spirooxindole derivatives (**49** and **50**) in high to excellent yields with moderate to good stereoselectivities.

Recently, an organocatalytic asymmetric Michael/cyclization cascade reaction of 3-isothiocyanato oxindoles (**2**) with 3-nitroindoles (**51**) was disclosed by our groups [35]. With the developed protocol, a wide range of polycyclic spirooxindoles (**52**), containing three contiguous chiral centers with two of them having quaternary stereocenters, could be obtained with satisfactory results (up to 99% yield, >99:1 dr, and 96% ee). This method is very promising because the reaction is scalable, and the versatile transformations of the products into other spirocyclic oxindoles are also feasible.

In 2013, catalytic asymmetric cascade Michael addition/cyclization reaction of 3-isothiocyanato oxindoles (**2**) with electron-deficient olefins (**53** or **35**) using bifunctional thiourea catalyst derived from quinidine was reported by Wang and coworkers. In their developed method, the reaction proceeded well under mild reaction conditions and afforded structurally complex 3,2'-pyrrolidiny spirooxindole derivatives (**54**) (up to 99% yield, >20:1 dr, and 96% ee) and bispirooxindoles (**45b**) (up to 99% yield, >20:1 dr, and 98% ee), respectively, (**Scheme 16**) [36].

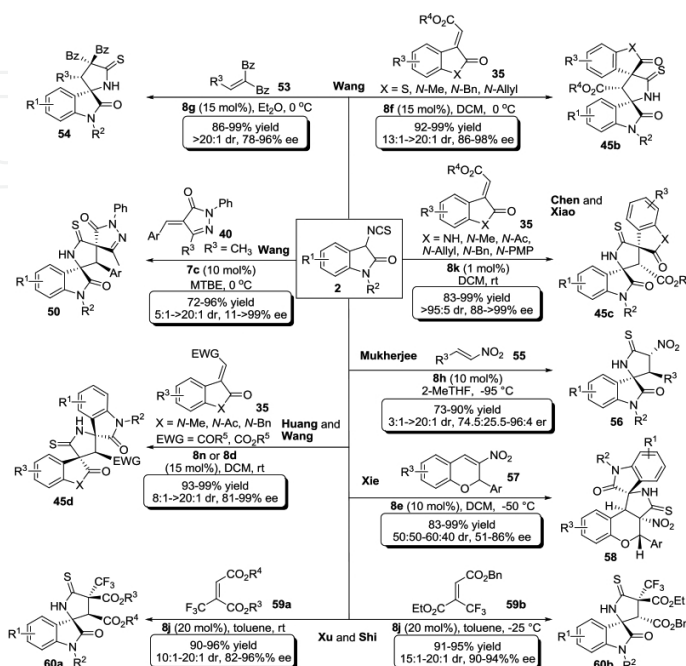
Having achieved remarkable success in organocatalytic asymmetric Michael/cyclization reaction with  $\alpha$ -isothiocyanato imides and esters as versatile precursors [28, 30, 36], the asymmetric Michael/cyclization process of 3-isothiocyanato oxindoles (**2**) with unsaturated pyrazolones (**40**) using bifunctional thiourea-tertiary amines (**7c**) as catalyst was explored by Wang's group (**Scheme 16**) [37]. The reaction also provided densely functionalized spirocyclic oxindole compounds (**50**) in excellent results (up to 96% yield, >20:1 dr, and 99% ee).

In 2013, Chen and coworkers reported a formal [3+2] cycloaddition reaction between 3-isothiocyanato oxindoles (**2**) and 3-ylideneoxindoles (**35**) with quinine-derived squaramide (**8k**) as catalyst (**Scheme 16**) [38], getting multicyclic spirooxindole derivatives (**45c**) in excellent results (up to 99% yield, >95:5 dr, and >99% ee) with very low catalyst loading (1 mol%).

At the same year, a similar reaction between isothiocyanato oxindoles (**2**) and methyleneoxindoles (**35**) through a cascade Michael/cyclization process for the construction of bispirooxindole scaffolds (**45d**) was also successfully explored in Huang's group (**Scheme 16**) [39]. In this process, trifunctional organocatalyst (**8n**) based on BINAM and quinine scaffolds was efficient for the methyleneoxindole substrates bearing ketone moieties. However, bifunctional organocatalyst (**8d**) derived from quinine was the optimal catalyst for the methyleneoxindole



substrates bearing different ester substituents. It should be noted that all of the reactions could complete in less than 1.0 min, providing structurally complex bispirooxindole derivatives (**45d**) in high yields (up to 99% yield) with excellent stereoselectivities (up to >20:1 dr, and 99% ee).



**Scheme 16.** Asymmetric Michael/cyclization based on 3-isothiocyanato oxindoles (**2**) by other groups.

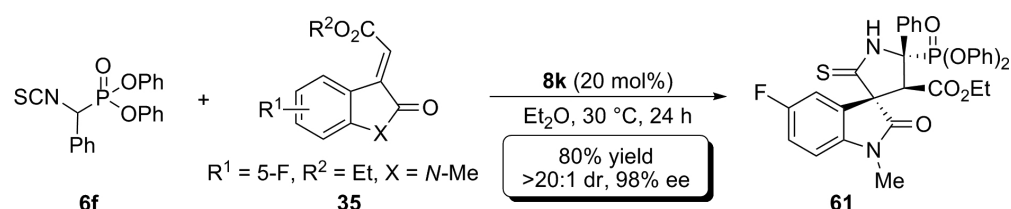
Besides,  $\beta$ -substituted nitro olefins (**55**) were also good substrates for the reaction with 3-isothiocyanato oxindoles (**2**) in asymmetric Michael/cyclization process (**Scheme 16**) [40]. Structurally complex 3,2'-pyrrolidiny-substituted spirooxindoles (**56**) were obtained in high yields (up to 90% yield) with moderate to good stereoselectivities (up to >20:1 dr, and 96:4 er).

In 2014, Xie and coworkers further developed this process by employing 3-nitro-2*H*-chromene compounds (**57**) as substrates. Their study revealed that thiourea-tertiary amine catalyst (**8e**) containing phenyl group was more efficient than the catalyst with (3,5-ditrifluoromethyl)phenyl group (**Scheme 16**) [41]. Under the optimal reaction conditions, the asymmetric cascade Michael/cyclization reaction of 3-isothiocyanato oxindoles (**2**) with 3-nitro-2*H*-chromene derivatives (**57**) proceeded smoothly, affording highly functionalized spiro[chromeno[3,4-*c*]pyrrole-1,3'-indoline] derivatives (**58**) in moderate results (up to 99% yield, 60:40 dr, and 86% ee).

The development of efficient methods to construct complex molecules containing the F atoms has been attracting considerable interest due to the potential applications of this kind of compounds in biology, medicine, and agricultural chemistry as well as in materials science. Recently, Shi's group explored a novel Cinchona alkaloid-derived multifunctional amine **8j** catalyzed asymmetric [3+2] cycloaddition of 3-isothiocyanato oxindoles (**2**) with trifluoromethylated maleates (**59a**) or fumarate (**59b**) to afford the corresponding spirooxindoles (**60**)

possessing a CF<sub>3</sub>-containing quaternary carbon stereocenter in good to excellent results (up to 96% yield, 20:1 dr, and 96% ee) (**Scheme 16**) [42]. Interestingly, two epimeric isomers were obtained with the same organocatalyst at different temperatures, which led to an enantiodivergent approach for the synthesis of spirooxindoles (**60**). From a synthetic standpoint, this study explored a new trifluoromethylation system for the synthesis of enantioenriched heterocycles with CF<sub>3</sub>-containing quaternary carbon stereocenters.

In order to further expand the scope of  $\alpha$ -isothiocyanato phosphonate in organocatalyzed asymmetric cascade reaction, the application of  $\alpha$ -isothiocyanato phosphonate (**6f**) in the asymmetric Michael reaction was also investigated by Wang and coworkers [20]. Using methyleneindolinone (**35**) as Michael acceptor, the corresponding phosphonate-substituted spirooxindole (**61**) was obtained with 80% yield, >20:1 dr, and 98% ee (**Scheme 17**).



**Scheme 17.** Synthesis of phosphonate-substituted spirooxindole through Michael/cyclization of  $\alpha$ -isothiocyanato phosphonate with an activated olefin.

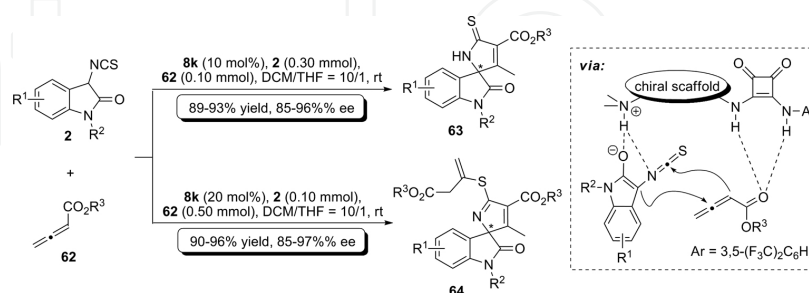
## 5. Asymmetric [3+2] cyclization of 3-isothiocyanato oxindoles with allenic esters

A novel asymmetric [3+2] cycloaddition of 3-isothiocyanato oxindoles (**2**) and allenic esters (**62**) with quinine-derived organocatalyst (**8k**) was explored by Xu and coworkers in 2013 (**Scheme 18**) [43]. Interestingly, the same reaction could generate different kind of spirocyclic oxindole products (**63** or **64**) in very good results (up to 96% yield, and 97% ee) only by adjusting the ratio of the two substrates. The authors considered that organocatalyst (**8k**) having stronger hydrogen-bonding donors plays a vital structure-directing effect on the stereocontrol through the hydrogen bonds.

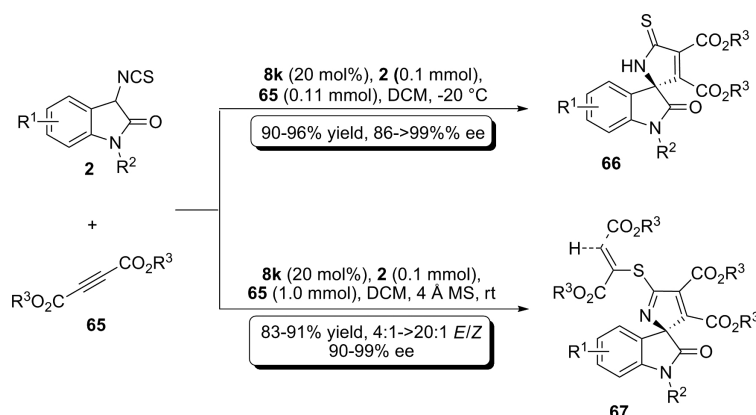
## 6. Asymmetric [3+2] cycloaddition of 3-isothiocyanato oxindoles with 2-butynedioic acid diesters

Encouraged by the achievements in the enantioselective construction of two classes of spirooxindole derivatives (**63** and **64**) (**Scheme 18**) [43], Xu and coworkers further investigated the asymmetric [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles (**2**) and acetylenedicarboxylic acid diesters (**65**) for the construction of another kinds of spirooxindoles

(**Scheme 19**) [43]. Similarly, two kinds of spirocyclic oxindoles derivatives (**66** and **67**) were also respectively obtained in good to high yields with good to excellent diastereoselectivities and enantioselectivities by changing the ratio of the two substrates. Additionally, the application of this approach was also demonstrated by a large-scale experiment and by the further conversion of the cycloadduct into other more spirocyclic oxindoles.



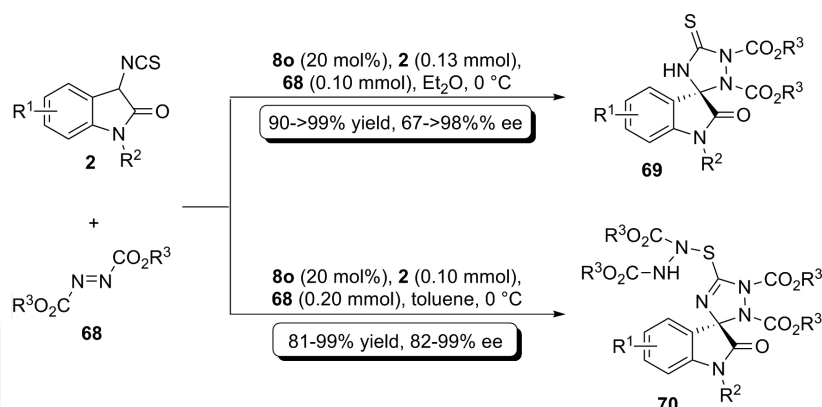
**Scheme 18.** Asymmetric [3+2] cycloaddition of 3-isothiocyanato oxindoles with allenic esters.



**Scheme 19.** Asymmetric [3+2] cyclization of 3-isothiocyanato oxindoles with 2-butynedioic acid diesters.

## 7. Asymmetric [3+2] cyclization of 3-isothiocyanato oxindoles with azodicarboxylates

In 2013, (DHQD)<sub>2</sub>PHAL (**80**)-catalyzed asymmetric [3+2] cycloaddition reaction of 3-isothiocyanato oxindoles (**2**) and azodicarboxylates (**68**) was firstly explored by Xu and coworkers. In the developed method, the desired spirooxindoles (**69**) could be obtained in high yields (up to >99% yield) with high enantioselectivities (up to 98% ee) in diethyl ether with the ratio of **2** –**68** in 1.3:1 (**Scheme 20**) [44]. Similarly, another kind of spirooxindoles (**70**) could also be afforded in excellent results (up to 99% yield and 99% ee) in toluene with the ratio of **2** –**68** in 1:2. Nevertheless, various transformations of the cycloadduct into other highly functionalized spirooxindole derivatives were also realized, and some products showed promising antitumor activity via the MTT assays.

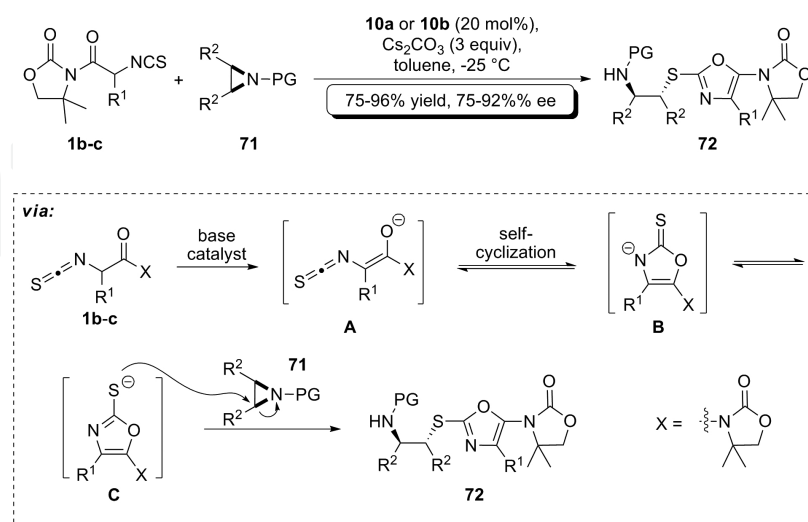


**Scheme 20.** Asymmetric [3+2] cyclization of 3-isothiocyanato oxindoles with azodicarboxylates.

## 8. Organocatalytic asymmetric ring-opening reaction of aziridines with $\alpha$ -isothiocyanato imides

In 2013, Wang's group developed a catalytic asymmetric ring-opening reaction of *meso*-aziridines (**71**) with  $\alpha$ -isothiocyanato imides (**1b–c**) using trimeric quaternary ammonium salts (**10a** and **10b**) derived from cinchonine as catalysts (**Scheme 21**) [45]. This novel approach provides an efficient channel to access  $\beta$ -aminothiooxazole compounds (**72**) in up to 96% yield and 92% enantioselectivity.

In Wang's report [45], a plausible mechanism was proposed. As shown in **Scheme 21**, the enolized  $\alpha$ -isothiocyanato intermediate **A** might self-cyclize by trapping the oxygen anions in the enolate. The enolized intermediate might exist in two  $\alpha$ -isothiocyanate–thiooxazole states, such as **B** and **C** tautomerisms (**Scheme 21**). Subsequently, the sulfur-based nucleophiles in



**Scheme 21.** Catalytic enantioselective ring-opening reaction of *meso*-aziridines with  $\alpha$ -isothiocyanato imides.

the thiooxazole intermediate **C** attack the activated *meso*-aziridines (**71**), and consequently with the aziridine ring-opening process, leading to a series of  $\beta$ -aminothiooxazole compounds (**72**). Notably, this methodology extends the scope of sulfur-based nucleophiles for asymmetric ring opening of *meso*-aziridines.

## 9. Summary and outlook

Using  $\alpha$ -isothiocyanato amides, esters, and phosphonates as new type of versatile reagents for the organic synthesis have been extensively studied and significant process has been made in this area over the past ten years. With these  $\alpha$ -isothiocyanato compounds as powerful precursors, the scope of the asymmetric cascade reactions with various organocatalysts has been greatly expanded. Importantly, these developed protocols provided new access to structurally diverse and complex heterocyclic compounds which were difficult to obtain with other reactions. Despite rapid progress in organocatalytic asymmetric cascade reactions with  $\alpha$ -isothiocyanato compounds as reagents has been made, the types of chemical reaction in this area are still limited in number. Accordingly, it might be one promising and exciting research field to develop novel asymmetric cascade reactions between the  $\alpha$ -isothiocyanato compounds and other accepters, such as nitrosoarenes [46], *N*-sulfinylanilines [47], oxaziridines [48], nitrones [49], azomethine imines [50],  $\alpha$ -halo *N*-acyl hydrazones [51], epoxidation [52], et al. Moreover, making further insight into the reaction mechanism concerning  $\alpha$ -isothiocyanato reagents will facilitate the rapid development of the new methodology in this realm. In summary, the research by employing  $\alpha$ -isothiocyanato compounds for the construction of complex heterocyclic compounds via organocatalytic asymmetric cascade process has broad development space. Further ground-breaking and exciting discoveries regarding to the application of the powerful and versatile will be reported in the near future.

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