ISO(THIO)CYANATE-STRATEGY FOR THE ORGANOCATALYTIC SYNTHESIS OF SELECTED HETEROCYCLIC STRUCTURES

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Abstract. Herein, the application of alkyl iso(thio)cyanates bearing an electron-withdrawing moiety in the α-position of the alkyl chain in organocatalytic reactions leading to the formation of selected groups of heterocycles is summarized. Such synthetic strategies employ differently substituted electron-deficient C=X and C=C double bonds as the second reaction partner and proceed in a cascade manner. Based on such an approach a wide variety of heterocycles bearing mainly 2-oxazolidinones, 2-imidazolidones, 2-oxazolidinethiones, 2-imidazolidinethiones, 2-pyrrolidinones or 2-pyrrolidinethione scaffolds have been efficiently and stereoselectively obtained.

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1. Introduction

Heterocyclic chemistry constitutes relevant and immensely developing field of research in the contemporary chemistry. In many cases the presence of heterocyclic architecture is crucial for the biological activity of a given molecule. Extraordinary richness of such structural motifs in various molecules relevant for life-science industry directly correlates to increased interest in the development of synthetic routes enabling the annulation of heterocyclic architectures. This area of synthetic organic chemistry has been recently raised to a new level by implementic enantioselective reactions. In such an approach chiral catalyst is employed to control stereochemical reaction outcome leading to enantiomerically enriched products. In particular, asymmetric organocatalysis has proven its potential in providing access to various heterocyclic structures from acyclic precursors. Importantly, various catalytic activation modes have been employed to accomplish this task. Furthermore, many of the developed organocatalytic protocols proceed in a cascade manner allowing for the formation of more than one chemical bond in a single reaction vessel thus significantly facilitating the process.

Among available heteroannulation strategies one particularly visible approach involves the utilization of alkyl iso(thio)cyanates activated by the presence of an electron-withdrawing moiety in the α-position of the alkyl chain. Such a group of reactants readily participate in various heteroannulation reactions proceeding in a cascade manner with differently substituted electron-deficient C=X and C=C double bonds. Given the importance of such a synthetic strategy the main goal of this book chapter is to summarize a recent progress in the application of the iso(thio)cyanate-strategy for the organocatalytic synthesis of selected heterocyclic structures. In most of the cases, the synthetic methodologies developed so far provide access to four main groups of heterocyclic systems, namely 2-oxazolidinones, 2-imidazolidones, 2-oxazolidinethiones, 2-imidazolidinethiones, 2-pyrrolidinones or 2-pyrrolidinethione (Scheme 1). These group of heterocycles are of synthetic relevance as their synthetic transformations have been widely studied opening access to various acyclic and cyclic derivatives.
2. Mechanistic considerations

Alkyl iso(thio)cyanates activated by the presence of an electron-withdrawing moiety in the \( \alpha \)-position of the alkyl group constitute a highly valuable building blocks for the synthesis of five-membered heterocycles. Due to the increased acidity of the hydrogen in the \( \alpha \)-position in the iso(thio)cyanate moiety they readily undergo deprotonation under mild, organocatalytic conditions (Scheme 2). Carbanions thus obtained, stabilized through the mesomeric effect, participate in various reaction cascades initiated through the nucleophilic addition reaction. When aldehydes, ketones or imines are employed as electrophilic counterparts such reaction furnishes oxygen- or nitrogen-centered anion undergoing intramolecular addition to the iso(thio)cyanate moiety. In such a manner five-membered heterocyclic structures are formed. Their protonation leads to target products containing two-heteroatoms. Such systems can be considered as a direct precursors of biologically relevant \( \beta \)-hydroxy-\( \alpha \)-amino acids and \( \alpha,\beta \)-diamino acids. In this context it is worth to note that \( \beta \)-hydroxy-\( \alpha \)-amino acids are fundamental building blocks for the synthesis of pharmaceuticals, especially glycopeptide antibiotics such as ristocetin or vancomycin. Furthermore, \( \alpha,\beta \)-diamino acids are found in important natural products, biologically active and therapeutically useful compounds.

Alternative group of reactants commonly employed in the reaction with alkyl iso(thio)cyanates activated with electron-withdrawing moiety and realized under Bronsted base conditions are electron-deficient olefins (Scheme 3). Initial deprotonation and Michael-type addition leads to carbanion participating in the reaction sequence involving intramolecular nucleophilic addition and subsequent protonation. In such a manner substituted 2-pyrrolidinones or 2-pyrrolidinethiones are obtained. Their synthetic transformations have been widely studied opening access to various pyrrolidine-derivatives.
Synthetic strategies based on these two mechanistic scenarios have recently emerged as very powerful approaches leading to diversely substituted heterocycles. Notably, two main groups of iso(thio)cyanate derivatives have been most commonly employed (Scheme 4). The first one is derived from glycine or α-substituted α-amino acids. Their utilization leads to the formation of β-hydroxy-α-amino acid and α,β-diamino acid precursors. The second main group of iso(thio)cyanate reactants is based on the oxindole scaffold with the heteroannulation reaction resulting in the synthesis of spirooxindole derivatives.

\[
\text{Scheme 4}
\]

In the following chapter organocatalytic strategies based on the application of these two groups of iso(thio)cyanate derivatives will be discussed in details. In this context it is worth to note that stereochemical reaction outcomes are controlled by bifunctional organocatalysts that possess two catalytic sites. The first one can be described as Brønsted base and is responsible for the activation of the corresponding iso(thio)cyanate via deprotonation. The second one is an H-bond donor responsible for the activation of the corresponding electron-poor C=X or C=C double bond through H-bonding interactions. Owing to such a dual activation strategy a proper alignment of reactants in space is achieved resulting in a highly stereoselective construction of the target heterocycle.

3. Application of iso(thio)cyanates in asymmetric organocatalysis

3.1. Electron-withdrawing-group-activated aliphatic iso(thio)cyanates in organocatalytic cascades

In 2008, Seidel and co-workers reported a direct reaction of α-isothiocyanato-esters 1 with both electron-rich and electron–poor aromatic aldehydes 2 to form protected syn-β-hydroxy-α-amino acids 4 in a highly enantio- and diastereoselective manner (Scheme 5). Initially, the reaction between ethyl α-isothiocyanato acetate 1a and benzaldehyde 2a as model substrates in the presence of different organocatalysts was studied. The highest enantiomeric excess was achieved in the presence of the catalyst 3. However, the desired product 4a (R=Ph) was obtained in unsatisfactory yield because of the formation of a side-product 5a arising from the subsequent reaction of thiocarbamate 4a with the isothiocyanate moiety in 1. Therefore, various α-isothiocyanato-imides 1 were evaluated in the reaction revealing that the formation of undesired product is possible to suppress when 1a is used. During the optimization studies, authors found that the best results were obtained using bifunctional thiourea 3 as a catalyst. Under optimized reaction conditions (employing 5 mol% of organocatalyst 3), the cascade reaction involving aldol addition of α-isothiocyanato-acetates 1 to a number of aromatic, heteroaromatic and α,β-unsaturated aldehydes 2 followed by a cyclization via intramolecular nucleophilic addition afforded the protected syn-β-hydroxy-α-amino acids 4 with high enantiomeric excesses.
Takemoto and co-workers reported an alternative strategy that constitutes enantioselective route for the synthesis of chiral 4-carboxyl oxazolidinones 9 which are synthetic equivalent of \( \beta \)-hydroxy-\( \alpha \)-amino acids (Scheme 6). In the presence of thiourea catalyst 8 isocyanato-malonate diesters 6 and aldehydes 7 underwent aldol reaction and subsequent cyclization to afford 9 with high stereoselectivities. In order to optimize procedure for the synthesis of 9, the reaction between various isocyanates 6 bearing different ester groups with benzaldehyde 7a \( (R=\text{Ph}) \) was studied. After selection of diethyl 2-isocyanato-malonate 6a as the most appropriate substrate for this reaction, the influence of the reaction temperature on yield and formation of side-product 10 was investigated. Higher yield and the suppression of side-product 10 generation was obtained for the synthesis conducted at -60 °C. The careful choice of the catalyst allowed for the development of more efficient catalyst 8 containing di-\( \alpha \)-pentylamine group instead of the dimethylamine moiety. Under optimized reaction conditions, a broad range of aromatic aldehydes containing either electron-rich or electron-poor groups as well as heteroaromatic substituents and even \( \alpha \)-branched aliphatic aldehydes were readily converted into oxazolidinones 9 within 72 hours in toluene. The authors presented application of this methodology in the synthesis of natural products. Total synthesis of mycestericin C containing anti-\( \beta \)-hydroxy-\( \alpha \)-amino acid moiety with a tetrasubstituted carbon center was successfully developed demonstrating high usefulness of oxazolidinones 9 for the preparation of \( \beta \)-hydroxy-\( \alpha \)-amino acid derivatives. In 2015, the same research group reported the first total synthesis of caprazamycin A which possesses significant antibacterial activity. The introduction of syn-\( \beta \)-hydroxy-\( \alpha \)-amino acid moiety was accomplished by a diastereoselective cascade aldol-cyclization reaction catalysed by thiourea catalyst 8 with diethyl 2-isocyanato-malonate 6 as a substrate.\(^8\)

![Scheme 6](image)

Enantioselective route to the syn-configured \( \alpha,\beta \)-diamino acid derivatives 15 was also developed by Seidel and co-workers (Scheme 7).\(^9\) The cascade reaction initiated by the Mannich reaction between dimethyl analogue of \( \alpha \)-isothiocyanato-imide 1a \( (R=\text{Me}) \) and benzenesulfonyl imines 13 employing readily available organocatalysts was examined. The highest level of enantioselectivity (95% ee) was obtained with the bifunctional quinidine-based catalyst 14 but low yield was achieved. When unsubstituted \( \alpha \)-isothiocyanato-imide 1 \( (R=\text{H}) \) was used as a starting material, a higher reaction rate and yield were observed. It has also been shown that the replacement of the tosyl group with a different analogue (particularly benzenesulfonyl group) accelerated the reaction 10 times and enabled to reduce the catalyst
loading to 1 mol%. The scope of the reaction was then examined with various benzenesulfonyl imines 13 derived from electron-rich, electron-poor, heteroaromatic and α,β-unsaturated aldehydes to afford syn-α,β-diamino acids 15 in good yields and in high to excellent diastereo- and enantioselectivity.\textsuperscript{10}

\begin{equation}
\text{KCN} + \text{RCHO} \rightarrow \text{RC} = \text{N} - \text{H}
\end{equation}

In 2010, two groups independently reported enantioselective aldol reaction of α-isothiocyanato-imides 1a with α-ketoesters 16 leading to the formation of β-hydroxy-α-amino acids 18 bearing a chiral quaternary stereogenic center (Scheme 8).\textsuperscript{11} In the first report, Wang and co-workers have developed an asymmetric approach for the synthesis of cyclic thiocarbamates 18 that utilized tertiary amine organocatalysts.\textsuperscript{11a} Optimization studies revealed that the best result was obtained using 1 mol% of tertiary amine-thiourea catalyst 17a in toluene at room temperature. Furthermore, it was shown that products 18 with the opposite configuration were obtained when the catalyst 17b was used. With optimized conditions in hand, a number of aromatic and aliphatic α-ketoesters 16 was explored, giving rise to the corresponding substituted cyclic thiocarbamates 18 with high enantiomeric excesses (81-99%) and excellent yields (78-99%). In the second contribution, Seidel showed that the highest enantiomeric excess was achieved in the presence of 5 mol% amine-thiourea catalyst 3, in methyl tert-butyl ether at room temperature.\textsuperscript{11b} Subsequently, a broad range of α-ketoesters 16 were utilized under optimized reaction conditions.

\begin{equation}
\text{RCON} + \text{R'COCH}_2 \rightarrow \text{RCONHCOCH}_2 \text{R'}
\end{equation}

\begin{equation}
\text{RCON} + \text{R'COCH}_2 \rightarrow \text{RCONHCOCH}_2 \text{R'}
\end{equation}

\begin{equation}
\text{RCON} + \text{R'COCH}_2 \rightarrow \text{RCONHCOCH}_2 \text{R'}
\end{equation}
Aldolization of α-isothiocyanato-imide 1a with either electron-rich or electron-poor aromatic or heteroaromatic α-ketoesters 16 catalysed by 3 afforded β-hydroxy-α-amino acids 18 in good yields (70-99%) with high enantioselectivities (79-98%) and moderate diastereoselectivities.

The Wang group has also reported studies on the reaction between α-isothiocyanato-imides 1 and electron-deficient isatins 19 (Scheme 9).12 In the first organocatalytic step, spirocyclic thiocarbamate was formed using tertiary amine-thiourea catalyst 17a as a catalyst. Subsequent methylation step led to chiral spirooxazolines 20 bearing a quaternary stereocenter. Furthermore, if the isothiocyanate derived from α-amino-γ-butyrolactone was used, the spirocyclic products 22 were formed. Later on, Zhao and co-workers showed the possibility to extend this protocol to the aldol-cyclization reaction sequence of α-isothiocyanato-imides 1a and different activated carbonyl compounds.13

Two research groups independently developed enantioselective approach for the synthesis of β-hydroxy-α-amino phosphonic acid derivatives 25 (Scheme 10). The reaction between α-isothiocyanato-phosphonates 23 and aldehydes 24 occurred in a cascade involving aldol reaction followed by a cyclization to give products 25 bearing quaternary carbon stereocenters. Yuan and co-workers reported that the best results regarding the yield and enantioselectivity of the cascade were achieved by using quinine-derived thiourea catalyst 26.14 The cascade reaction between α-isothiocyanato-phosphonates 23 with a wide range of aldehydes 24 proceeded smoothly in the presence of 20 mol% of 26 in CH2Cl2 to afford products 25 with up to 81% ee and 93% yield. Wang and co-workers reported that the highest enantioselectivity of 96% ee in the model reaction of diphenyl α-isothiocyanato-phosphonate 23a (R=Ph; R'2=Ph) with benzaldehyde 24a (R'2=Ph) was obtained in toluene when 20 mol% of quinine-derived squaramide catalyst 27 was employed.15 Diethyl ether was found to be the best suited solvent for this reaction. The scope of this reaction was evaluated with a number of benzaldehydes 24 with either electron-withdrawing or electron-donating groups on the aromatic ring bearing different substitution pattern.
Furthermore, a wide range of N-tosyl protected imines was also used affording α,β-diamino phosphonic acids in high yields (81-99%) and with excellent diastereo- (up to >20:1) and enantioselectivity (up to >99%).

Scheme 10

In 2011 Wang research group established an efficient protocol for the synthesis of spirooxindoles using previously utilized imidoisothiocyanates 1a and electron deficient 3-alkylidene oxindoles 28 (Scheme 11). Organocatalytic reaction occurred in a cascade manner involving Michael addition and cyclization. Optimization studies shown that the most appropriate catalyst for this process is rosin-derived catalyst 17a which provided high stereoselectivity and gave products 29 in almost quantitative yields. With the optimized reaction conditions authors delimited the scope of the reaction which was very wide. Differently substituted oxindoles 28 were utilized in a cascade which was successful for various substitution patterns of the aromatic ring in 28 yielding products 29 in high enantio- and diastereoselectivity. Furthermore, authors presented synthetic utility of the products 29 obtained in three transformations.
In 2018 Albrecht and co-workers developed a reaction cascade between phenylglycine derived isothiocyanates 13 and alkylidene barbiturates 30 catalyzed by squaramide catalyst 27 derived from quinine (Scheme 12). Authors utilized differently substituted barbiturates derived from either aromatic or alkyl aldehydes. Reaction appeared to be unbiased towards both electron character and position of substituents on aromatic rings providing products 32 in good yields and with high stereoselection. The scope of the reaction was broadened by utilizing phosphoglycine derived isothiocyanates which, after short reoptimization of reaction conditions, were successfully used in the cascade.

![Scheme 12](image)

### 3.2. Oxindole-derived isothiocyanates in organocatalytic cascades

Oxindole-derived isothiocyanates constitute a group of reactants that has been the most commonly employed in asymmetric organocatalytic cascades. In 2011, Yuan and co-workers reported stereocontrolled synthesis of spirooxindoles 36 bearing a quaternary stereogenic center for the first time (Scheme 13). Chiral bifunctional thiourea-tertiary amine catalyst 35 was the best catalyst to promote the asymmetric aldol reaction of 3-isothiocyanato-oxindoles 33 with ketones 34 followed by subsequent intramolecular cyclization. Higher catalyst loading (20 mol%) and lower reaction temperature (−40 °C) allowed for the cascade to proceed with higher enantioselectivity. Once the optimal reaction conditions were established, the scope of the reaction was examined. It was found that acetophenone derivatives 34 bearing either electron-donating or electron-withdrawing groups in the meta or para position of the aromatic ring as well as aliphatic ketones were well-tolerated providing 36 in good yields and stereoselectivities within 24 to 48 hours. Furthermore, various 3-isothiocyanato-oxindoles 33 bearing different N-protecting groups and substituents on the aromatic ring displayed similar reactivity and efficiency in the synthesis of spirocyclic oxindoles 36. Moreover, the oxazolidinethione ring present in the products 36 was readily transformed into N-Boc or N-unprotected oxazolidinones or oxazolidinimines, thus opening access to the formation of more structurally diversified spirooxindoles.

![Scheme 13](image)

Later on, following the strategy described above, the same research group extended the developed protocol to aldehydes 38 (Scheme 14). After extensive optimization, spiro[oxazolidine-2-thione-oxindoles]...
were obtained in high yields and good diastereo- and enantioselectivities even within 1 minute in the presence of 10 mol% of thiourea-tertiary amine catalyst 35 at -40 °C in mesitylene. Cascade involving aldol reaction and cyclization proceeded smoothly when aromatic aldehydes 38 containing either electron-donating or electron-withdrawing group as well as heteroaryl substituent were used as electrophiles. In contrast, when the reaction was carried out with n-butyraldehyde or 3-isothiocyanato-oxindole bearing different N-protecting groups instead of methyl group as substrates, significantly lower enantioselectivities were obtained.

\[
\begin{align*}
37 & \quad \text{NCS} \\
38 & \quad \text{O} \\
39 & \quad \text{N} \\
35 & \quad \text{mesitylene} \\
& \quad -40^\circ\text{C}, < 1\text{ min} \\
\end{align*}
\]

Scheme 14

Mukherjee and Kayal reported enantioselective synthesis of β-amino-α-hydroxyphosphonate derivatives 42 bearing an oxindole framework with two quaternary stereogenic centers (Scheme 15). A cascade aldol-cyclization reaction between N-benzyl-3-isothiocyanato-oxindole 40 and diethyl acetylationphosphonate 41a was studied as a model reaction. When the reaction was carried out at -95 °C for over 30 minutes in the presence of 10 mol% of quinine-derived thiourea catalyst 26 in 2-methyltetrahydrofuran, the corresponding product 42 was obtained with excellent diastereo- and enantioselectivity. The method was shown to be applicable for a wide range of both aromatic and aliphatic α-ketophosphonates 41. Additionally, the structure of 3-isothiocyanato-oxindoles 40 was readily varied by using different N-substituents as well as 1,5-dimethyl derivative.

\[
\begin{align*}
40 & \quad \text{NCS} \\
41 & \quad \text{P(O)OR}_2 \\
42 & \quad \text{S} \\
26 & \quad \text{Ar}=3,5-(CF_3)_2C_6H_3 \\
\end{align*}
\]

Scheme 15

The first attempt to construct spirooxindoles 46 bearing 1,2-diamine moiety using 3-isothiocyanato-oxindoles 43 and imines 44 in an enantioselective manner was reported by Liu and
In 2016 Shi and co-workers presented the asymmetric reaction between 3-isothiocyanato-oxindole 47 and N-mesyl-α,β-unsaturated imines 48-50 (Scheme 17). The regioselectivity of this process was possible to control by the change of reaction conditions. The possible reaction outcomes include: (1) [3+2]-cycladdition initiated by the Mannich reaction, which led to thioureas 52; (2) [3+2]-cycladdition occurring at the C-C double bond of 49 and giving the substituted thiooxopyrrolidines 53; (3) [3+2]/[4+2]-cascade initiated by the Mannich reaction and followed by the nucleophilic addition to isothiocyanate group and Michael reaction giving products 54. All three reaction modes were possible to achieve by simple modification of the structure of imine substrate and reaction conditions. Desired products 52-54 were efficiently obtained with high diastereo- and enantioselectivities.

In 2013 Xiao and co-workers reported the enantioselective method of synthesis of bispirooxindole derivatives 57 from 3-isothiocyanato-oxindoles 55 and 3-alkylideneoxindoles 56 (Scheme 18). Mechanism of that reaction involved Michael addition followed by the cyclization. Optimization studies revealed that the most suitable catalyst for the cascade was squaramide 27 derived from quinine and the best results were obtained when reaction was conducted in dichloromethane at room temperature. Generality of that method was tested under optimized conditions. Changes in the structure of both isothiocyanate 55 and 3-alkylideneoxindoles 56 were possible indicating excellent functional group tolerance. All of products 57 were obtained in high yields and high enantio- and diastereoselectivities. Low catalyst loading and short reaction times constitute interesting features of the developed methodology. Gram-scale synthesis and synthetic transformations of products 57 were also presented.

In 2013 Yuan and co-workers presented a highly enantioselective method of synthesis of dispiroyclic thiopyrrolidinooxindoles 61 or 62 from 3-isothiocyanato-oxindoles 58 or 4-alkylideneazlactones 59 (Scheme 19). The cascade reaction between these starting materials involved again Michael addition followed by nucleophilic addition to the isothiocyanate group. As shown in the optimization studies the best conditions for that cascade involved the use of amino-thiocarbamate bifunctional catalyst 63, toluene as a solvent at -20 °C. Reaction worked smoothly for differently substituted aromatic azlactones 59. Obtained results, in terms of yields as well as enantiom- and diastereoselectivity were excellent. Encouraged by these results, the authors broadened the scope of the methodology utilizing olefinic oxindoles 60 as electrophilic partners in the cascade. A small change in conditions (reaction carried out in mesitylene, at -10 °C) resulted in the formation of desired products 62 with excellent results comparable to those obtained for olefinic azlactones 59. It is worth to mention that the authors presented some synthetic transformations of the obtained products 61 and 62 as well as the possibility to perform the reaction on a gram scale.
A related methodology was developed independently by two research groups (Scheme 20). In both of the reports the construction of bispirooxindoles in an enantioselective manner using 3-isothiocyanato-oxindoles and α,β-unsaturated pyrazolones was described. In 2013 Wang and co-workers reported that the thiourea catalyst derived from dehydroabiatic amine catalyzed efficiently the devised reaction cascade. It was conducted in in methyl tert-butyl ether at 0°C. The obtained results were generally good. However, in some of the cases enantio- and diastereoselectivities were poor. Furthermore, relatively large scale synthesis and three transformations were presented. In 2014, Yuan and co-workers presented a very similar research. In this work quinine was employed as a catalyst, toluene as a solvent and the reaction cascade was carried out at room temperature. The enantio- and diastereoselectivities of the cascade were worse than those reported by Wang et al. It is worth to stress out that in the second report attempts to broaden the scope of the cascade to include α,β-unsaturated isoxazoles were presented.
In 2013 Chinese scientists reported an enantioselective, organocatalytic reaction of isothiocyanato-oxindoles 69 with alkenyl-isoxazoles 70 (Scheme 21). This type of Michael/cyclization cascade yielded 3,3'-pyrrolidinyl spirooxindoles 71. In the optimization studies the model reactants were 3-isothiocyanato-oxindole 69a (R₁=Me, R₂=H) and 3-methyl-4-nitro-5-alkenyl-isoxazole 70a (R₃=phenyl). Screening of the catalyst, solvent, temperature and time showed that performing reaction in mesitylene, at 30 °C, in the presence of quinine 68 gave the best result. After establishing the best conditions, the generality of that method was tested. Differently substituted isothiocyanates 69 and arylidene-isoxazoles 70 were utilized. Products 71 were obtained in high yields with excellent diastereoselectivities and very high enantioselectivities. Furthermore, the authors showed the possibility to lower the catalyst loading with the cascade proceeding efficiently even with 1 mol% of commercially available quinine 68. Moreover, to underline the synthetic importance of the methodology gram scale synthesis of 71a (R₁=Me, R₂=H, R₃=phenyl) and some transformations have been presented.

Scheme 21

In 2013 Wang and co-workers reported the catalytic asymmetric synthesis of 3,3'-pyrrolidinyl mono- and bis-spirooxindoles 74 and 77 (Schemes 22 and 23). 3-Isothiocyanato-oxindole 72a (R₁=H, R₂=Me) and electron-deficient olefin 73a (R₃=phenyl) were chosen as model reactants. In the optimization studies different bifunctional thiourea catalysts were tested. After short screening of the solvents and reaction temperature, the most suited conditions were found that involved usage of diethyl ether as a solvent with performing the reaction at 0 °C in the presence of thiourea catalyst 75 (derived from quinine and dihydroabietic amine). With optimal conditions in hand, the generality of the cascade was tested (Scheme 22).

Scheme 22
Reaction worked not only for olefinic benzaldehyde 73 derivatives but also for heterocyclic and alkyl olefins. Desired products 74 were obtained in high yields, excellent diastereoisomeric excesses and good enantiomeric excesses.

In the next step of scope studies, the synthesis of differently substituted bis-spirooxindole 77 derivatives using reoptimized reaction conditions was presented (Scheme 23). In this cascade, the commonly used quinine derived thiourea 26 was utilized as a catalyst. The reaction was performed in dichloromethane at 0 °C. Products 77 were efficiently obtained with high diastereo- and enantioselectivities.1

\[
\begin{align*}
\text{NCS} \quad \text{R}^2 \quad \text{R}^1 & \quad \text{R}^2 \quad \text{R}^1 \\
72 & \quad 76 & \quad 26 \quad 15 \, \text{mol}\% & \quad 30 \, \text{min} \\
\text{CHCl}_3, 0 \, ^\circ \text{C} & \quad \text{C} \quad \text{C} & \quad \text{C} \quad \text{C} & \quad \text{C} \\
77 & & & \\
\text{92.00% yield} & \quad \text{85-90% ee} & \quad \text{from 13:1 to >20:1 dr} \\
\end{align*}
\]

Scheme 23

In 2016 Shi and co-workers reported enantioselective cascade reaction involving Michael addition followed by the intramolecular nucleophilic addition of 3-isothiocyanato-oxindoles 78 with dibenzylideneketones 79 (Scheme 24).2 In this type of reaction two products 80 and 81 could be formed with the second product 81 arising from a subsequent intramolecular thia-Diels-Alder cycloaddition. To avoid side-product 81 formation, water was added to the reaction mixture to promote generation of enol 80. Optimization studies showed that the most suited conditions for that reaction involved the use of toluene as a solvent, quinine-derived squaramide 27 as a catalyst at -20 °C and water as an additive. With these optimal conditions in hand, the generality of the developed process was investigated. Dibenzylidene ketones 79 and isothiocyanates 78 with different structural features were tested. All of substrates tested gave excellent diastereoselectivities, very good enantiomeric excesses and high yields. Synthesis of the side-product 81 with moderate yield was also presented.

\[
\begin{align*}
\text{NCS} \quad \text{R}^2 \quad \text{R}^1 & \quad \text{R}^2 \quad \text{R}^1 \\
78 & \quad 79 & \quad 27 \quad 20 \, \text{mol}\% & \quad \text{H}_2\text{O} (\text{equiv}) \\
\text{toluene} & \quad -20 \, ^\circ \text{C}, 24 \, \text{h} & \quad \text{R}^3 & \quad \text{R}^1 \\
80 & & & \\
\text{87-92% yield} & \quad \text{85-90% ee} & \quad \text{>20:1 dr} \\
\end{align*}
\]

Scheme 24
In the same year, Mukherjee and co-workers presented a related work in which 3,2'-bis-spirooxindoles 84 were synthesized in enantioselective manner (Scheme 25).\textsuperscript{33} 3-Isothiocyanato-oxindoles 82 and α,β-unsaturated ketones 83 were employed as starting materials in the process. Optimization studies revealed that the bifunctional quinine-derived squaramide 27 was the most suited catalyst for that reaction and the best results were obtained when dichloromethane was employed as a solvent. With optimal results in hand, the generality of the process was investigated. Desired products 84 were obtained in high yields, excellent diastereomeric ratios and good to very good enantioselectivities. Three synthetic transformations were presented in order to demonstrate the utility of the products 84 obtained.\textsuperscript{34}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_25.png}
\caption{Scheme 25}
\end{figure}

In 2015, Shi and co-workers reported an enantioselective reaction between 3-isocyanato-oxindoles 85 and trifluoromethylated 2-butenedioic acid diesters 86 (Scheme 26).\textsuperscript{35} The choice of the electrophile 86 was explained by interesting properties of trifluoromethylated heterocycles. Isothiocyanate 85a (R_1=benzyl, R_2=Me) and ester 86a (R_3=ethyl, R_4=benzyl) were used as model reactants. In the optimization studies different bifunctional catalysts derived from cinchona alkaloids and solvents were tested. The catalyst 88 proved the best organocatalyst for that reaction and the best results were obtained when the cascade was performed in toluene at room temperature. With the most suitable conditions established, the generality of reaction was evaluated. Differently substituted isothiocyanates 85 and acceptors 86 yielded desired products 87 with high diastereoselectivities, good to very good enantioselectivities and excellent yields. Selected transformations were performed to demonstrate the synthetic utility of the developed method.\textsuperscript{36}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme_26.png}
\caption{Scheme 26}
\end{figure}
Nitroolefins can also be employed in a cascade involving Michael reaction followed by the cyclization via the carbanion addition to isothiocyanate group as demonstrated by Mukherjee and co-workers in 2014 (Scheme 27). The reaction between 3-isothiocyanato-oxindoles 89 and nitroolefins 90 was efficiently promoted by chiral bifunctional organocatalyst. N-Methyl-3-isothiocyanato-oxindole 89a and β-nitrostyrene 90a were chosen as model substrates. The optimization studies included the choice of solvent, catalyst and the appropriate temperature. The cascade reaction appeared to be very fast and had to be conducted at -95 °C, using 2-methyltetrahydrofuran as a solvent and cinchonidine-derived bifunctional thiourea 92 as a catalyst. Having optimized reaction conditions in hand, the authors tested the generality of the synthetic strategy. Initially, different aryl, alkyl and heteroaryl nitroolefins 90 were tested. Subsequently, isothiocyanates 89 bearing different structural features were evaluated. Target products 91 were obtained in good yields, medium to very good diastereoselectivities and good enantioselectivities in most of the cases. Interestingly, the products 91 proved generally unstable and had a tendency to decompose, even if stored at -20 °C. Therefore, no synthetic transformation of 91 was presented.

In 2015, Yuan and co-workers reported the cascade reaction between 3-isothiocyanato-oxindoles 93 and 3-nitroindoles 94 promoted by bifunctional amino-thiocarbamate catalyst 63 (Scheme 28).

That approach provided convenient access to polycyclic spirooxindoles 95. In the optimization studies, 93a (R1=methyl, R2=H) and 94a (R3=H, R4=tosyl) were used as a model reactants. Initially, different organocatalysts were tested. Subsequently, the best solvent and temperature for that reaction were identified. The best results were obtained with 63 as the catalyst in mesitylene at 0 °C. Under optimized reaction
conditions, the generality of the method was tested. Reactions between differently substituted 93 and 94 yielded desired products 95 with poor to very high diastereo- and enantioselectivities and excellent yields. Notably, authors presented the possibility to perform the reaction on a gram scale and selected transformations which confirmed the synthetic utility of the developed approach.

The group of Shi and Xu developed a convenient and attractive strategy for the asymmetric synthesis of functionalized spirooxindole derivatives 96 (Scheme 29).

![Scheme 29](image)

Enantioselective [3+2]-cycloadditions of 3-isothiocyanato-oxindoles 96 with allenic esters 97 or 2-butyne-1,4-dioic acid diesters 98 were performed in the presence of cinchona alkaloid derivative 27 bearing a strong hydrogen-bond donor moieties in the catalyst. Initially, reactions between a variety of 3-isothiocyanato-oxindoles 96 and allenic esters 97 were studied. Depending on the conditions employed, a library of structurally diversified spirooxindole derivatives 99 was synthesized. In the presence of isothiocyanato-oxindole 96 excess, cycloadducts 99 were obtained in excellent yield (89-93%) and with high enantioselectivity (85-96% ee). When the reaction was performed using excess of allenic ester 97, product 100 resulting from the nucleophilic addition of another equivalent of ester 99 to 97 was obtained in 85-97% ee and high yields (90-96%). Encouraged by these results, studies were expanded to include
acetylenedicarboxylic acid diesters $98$ as substrates in the explored asymmetric $[3+2]$-cyclization with isothiocyanato-oxindoles $96$. In a similar manner to that described above, when the ratio of the substrates was changed, different spirooxindoles $101$ were obtained with satisfactory yields and stereoselectivities. A broad range of structurally diverse 3-isothiocyanato-oxindoles $96$ (with electron-donating or electron-withdrawing groups at the phenyl ring or including different $N$-protecting groups) as well as a variety of allenic esters $97$ and acetylenedicarboxylic acid diesters $98$ (bearing different ester moieties) were applied leading to the formation of functionalized spirooxindole derivatives $99$-$102$.

### 3.3. Other isothiocyanates in organocatalytic cascades

In 2018 Du and co-workers reported the protocol in which they introduce a new type of isothiocyanate compound $103$ derived from 2-amino-1-indanone (Scheme 30). $41$ Presented approach gave access to bis-spirocyclic products $105$ in the cascade reaction between isothiocyanato-indanone $103$ and isatine derived imines $104$. Optimization studies revealed quinine derived bifunctional catalyst $27$ as the most appropriate catalyst for this process in 1,2-dichloroethane at room temperature. The scope of the reaction was investigated and the protocol worked well for differently substituted imines $104$ and indanone-isothiocyanate $103$ giving products $105$ in high yields and with high stereoselectivity. Moreover, authors demonstrated the synthetic utility of obtained compounds $105$ in five transformations.

![Scheme 30](image)

### 4. Conclusions

In conclusion, organocatalytic iso(thio)cyanate-strategies constitute a facile route to different groups of heterocyclic systems. The selection of iso(thio)cyanate reagents in combination with various electron-poor C=X and C=C double bonds provides access to a library of differently substituted products. Reactions designed up to now proceed mainly in a $[3+2]$-manner enabling the construction of five-membered heterocycles containing either one or two heteroatoms. Notably, strategies for the synthesis of six-membered heterocyclic frameworks are also known and have been highlighted in this book chapter. Heteroannulations developed so far benefit from the broad scope and high stereoselectivities. The control of stereochemical reaction outcome is usually achieved through the application of bifunctional organocatalyst enabling activation of the corresponding iso(thio)cyanate via deprotonation and electron-poor C=X or C=C double bonds through H-bonding interactions. Such a dual activation system results in a proper alignment of reactants in space leading to highly stereoselective construction of the target heterocycle. We believe that in the years to come organocatalytic iso(thio)cyanate-strategies will continue to develop and the identification of new, inspiring methodologies are only a matter of time.

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### References


36. For a related research, where maleimides were employed as doubly activated electrophiles, see: Liu, L.; Zhao, B.; Du, D. *Eur. J. Org. Chem.* **2016**, 4711.