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

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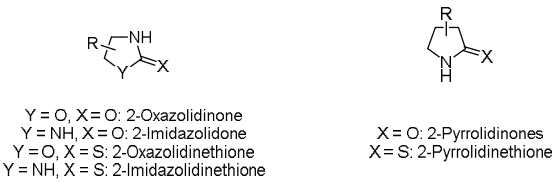
Abstract. *Herein, the application of alkyl iso(thio)cyanates bearing an electron-withdrawing moiety in the α-position of the alkyl chain in organocatalytic reactions leading to the formation of selected groups of heterocycles is summarized. Such synthetic strategies employ differently substituted electron-deficient 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.*

Contents

1. Introduction

Heterocyclic chemistry constitutes relevant and immensely developing field of research in the contemporary chemistry.[1] 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.[2] 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.[3] Importantly, various catalytic activation modes have been employed to accomplish this task.[4] 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.[5]

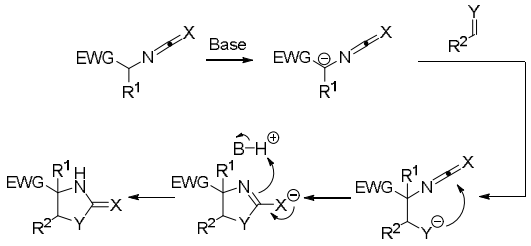
Among available heteroannulation strategies one particularly visible approach involves the utilization of alkyl iso(thio)cyanates activated by the presence of an electron-withdrawing moiety in the α-position of the alkyl chain. Such a group of reactants readily participate in various heteroannulation 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.



Scheme 1

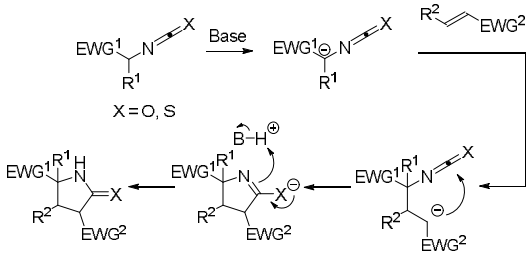
2. Mechanistic considerations

Alkyl iso(thio)cyanates activated by the presence of an electron-withdrawing moiety in the α-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 α-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 β-hydroxy-α-amino acids and α,β-diamino acids. In this context it is worth to note that β-hydroxy-α-amino acids are fundamental building blocks for the synthesis of pharmaceuticals, especially glycopeptide antibiotics such as ristocein or vancomycin. Furthermore, α,β-diamino acids are found in important natural products, biologically active and therapeutically useful compounds.



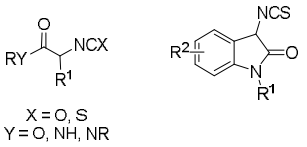
Scheme 2

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.



Scheme 3

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.



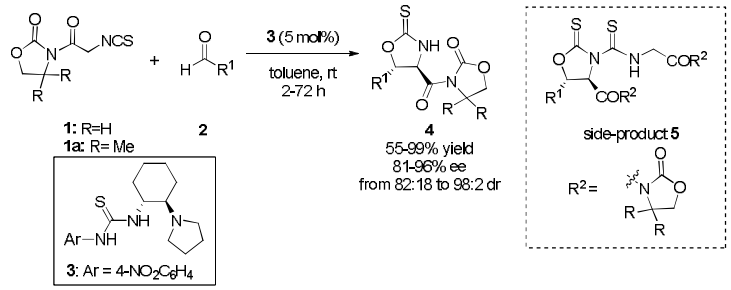
Scheme 4

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 Bronsted 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

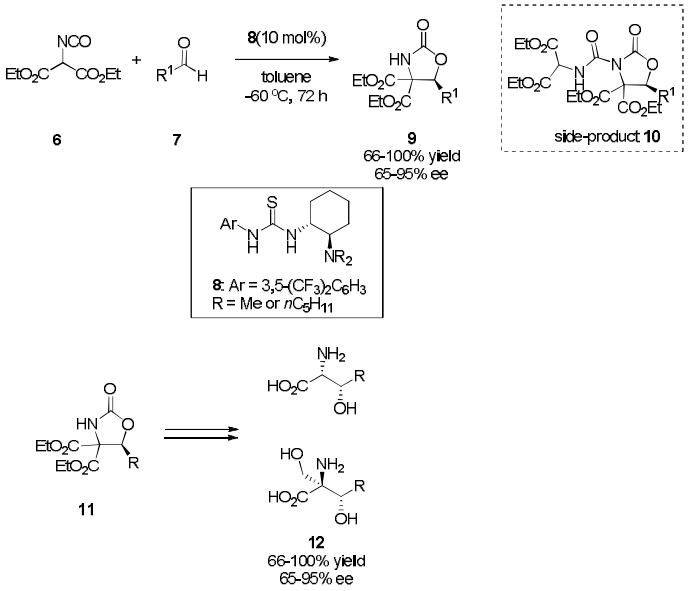
3.1. Electron-withdrawing-group-activated aliphatic iso(thio)cyanates in organocatalytic cascades

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).[6] 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^1=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.



Scheme 5

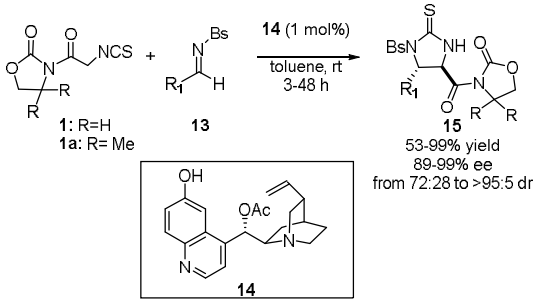
Takemoto and co-workers reported an alternative strategy that constitutes enantioselective route for the synthesis of chiral 4-carboxyl oxazolidinones **9** which are synthetic equivalent of β-hydroxy-α-amino acids (Scheme 6).[7] In the presence of thiourea catalyst **8** isocyanato-malonate diesters **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_1=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-*n*-pentylamine group instead of the dimethylamine moiety. Under optimized reaction conditions, a broad range of aromatic aldehydes **7** containing either electron-rich or electron-poor groups as well as heteroaromatic substituents and even α-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*-β-hydroxy-α-amino acid moiety with a tetrasubstituted carbon center was successfully developed demonstrating high usefulness of oxazolidinones **9** for the preparation of β-hydroxy-α-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*-β-hydroxy-α-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

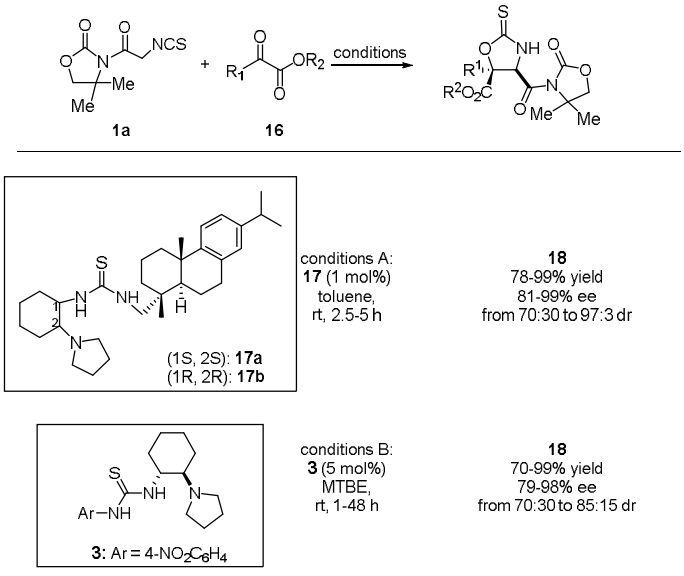
Enantioselective route to the *syn*-configured α,β-diamino acid derivatives **15** was also developed by Seidel and co-workers (Scheme 7).[9] The cascade reaction initiated by the Mannich reaction between dimethyl analogue of α-isothiocyanato-imide **1a** (R=Me) and benzenesulfonyl imines **13** employing 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 α-isothiocyanato-imide **1** (R=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.[10]



Scheme 7

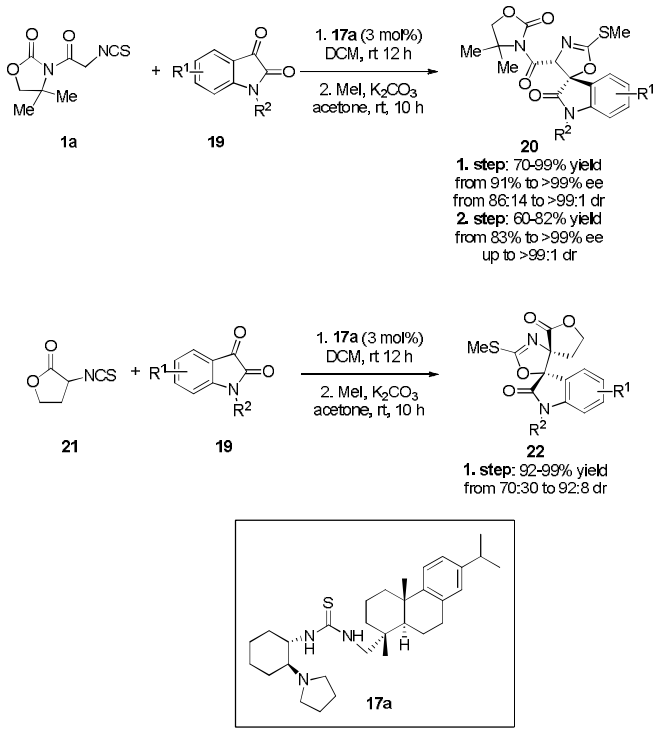
In 2010, two groups independently reported enantioselective aldol reaction of α-isothiocyanato-imides **1a** with α-ketoesters **16** leading to the formation of β-hydroxy-α-amino acids **18** bearing a chiral quaternary stereogenic center (Scheme 8).[11] In the first report, Wang and co-workers have developed an asymmetric approach for the synthesis of cyclic thiocarbamates **18** that utilized tertiary amine organocatalysts.[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.[11b] Subsequently, a broad range of *α*-ketoesters **16** were utilized under optimized reaction conditions.



Scheme 8

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.

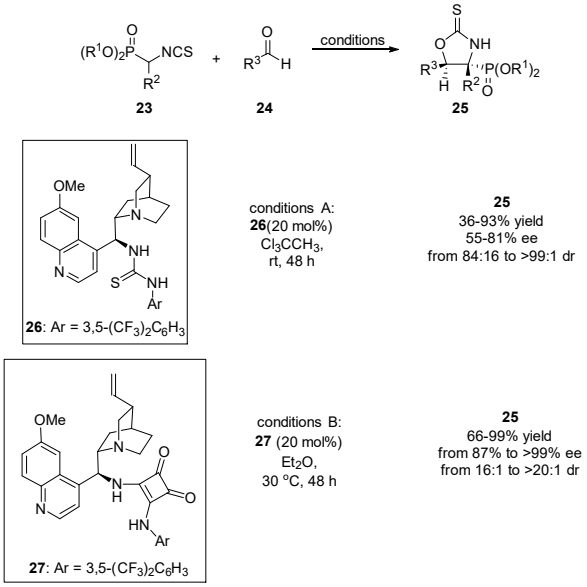
The Wang group has also reported studies on the reaction between α-isothiocyanato-imides **1** and electron-deficient isatins **19** (Scheme 9).[12] In the first organocatalytic step, spirocyclic thiocarbamate was formed using tertiary amine-thiourea **17a** as a catalyst. Subsequent methylation step 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]



Scheme 9

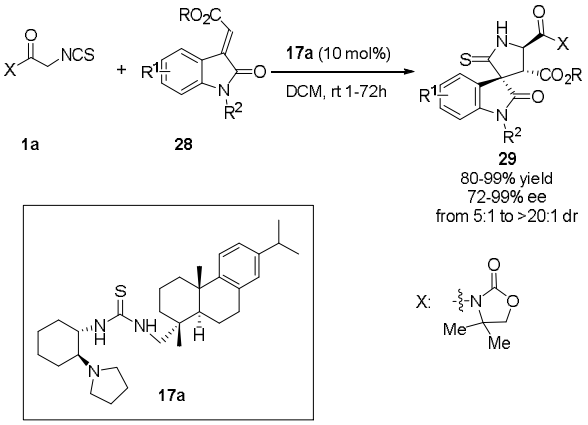
Two research groups independently developed enantioselective approach for the synthesis of β-hydroxy-α-amino phosphonic acid derivatives **25** (Scheme 10). The reaction between α-isothiocyanato-phosphonates **23** and aldehydes **24** occurred in a cascade involving aldol reaction followed by a cyclization 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 CH_3CCl_3 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^1=Ph; R^2=Ph)with benzaldehyde **24a** (R^3=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%).



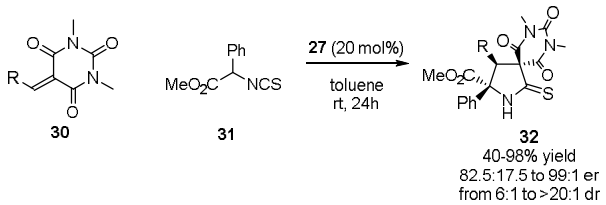
Scheme 10

In 2011 Wang research group established an efficient protocol for the synthesis of spirooxindoles using previously utilized imidoisothiocynates **1a** and electron deficient 3-alkylideneoxindoles **28** (Scheme 11).[16] 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.



Scheme 11

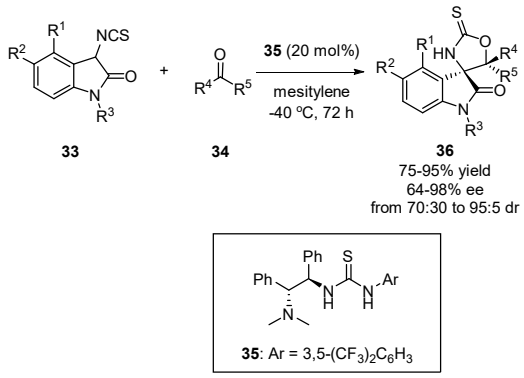
In 2018 Albrecht and co-workers developed a reaction cascade between phenylglycine derived isothiocyanates **13** and alkylidene barbiturates **30** catalyzed by squaramide catalyst **27** derived from quinine (Scheme 12).[17] Authors utilized differently substituted barbiturates derived from either aromatic or alkyl aldehydes. Reaction appeared to be unbiased towards both electron character and position of substitutents 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

3.2. Oxindole-derived isothiocyanates in organocatalytic cascades

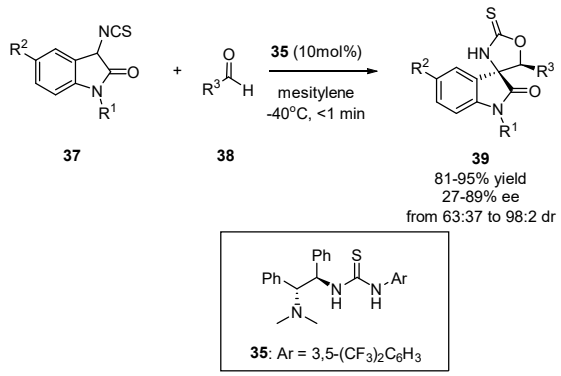
Oxindole-derived isothiocyanates constitute a group of reactants that has been the most commonly employed in asymmetric organocatalytic cascades. In 2011, Yuan and co-workers reported stereocontrolled synthesis of spirooxindoles **36** bearing a quaternary stereogenic center for the first time (Scheme 13).[18] 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

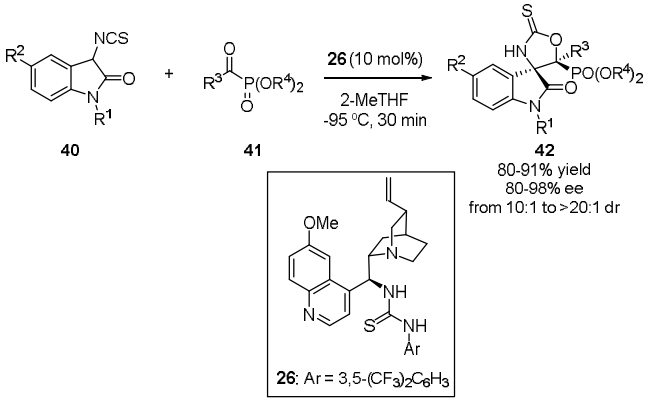
Later on, following the strategy described above, the same research group extended the developed protocol to aldehydes **38** (Scheme 14).[19] After extensive optimization, spiro[oxazolidine-2-thione-oxindoles]

39 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.



Scheme 14

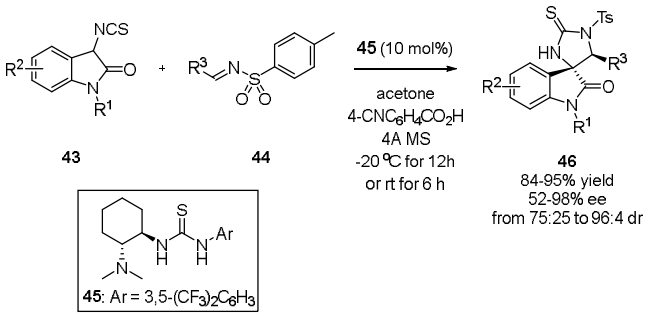
Mukherjee and Kayal reported enantioselective synthesis of β-amino-α-hydroxyphosphonate derivatives **42** bearing an oxindole framework with two quaternary stereogenic centers (Scheme 15).[20] A cascade aldol-cyclization reaction between *N*-benzyl-3-isothiocyanato-oxindole **40** and diethyl acetylphosphonate **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.



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

co-workers in 2014 (Scheme 16).[21] In this work authors utilized aromatic *N*-tosyl imines **44** derived from differently substituted benzaldehydes. Optimization studies identified **45** as the best suited organocatalyst for the reaction and acetone as solvent. With the optimal conditions in hands authors investigated the scope of this reaction, changing the structure of both isothiocyanato-compound **43** and imine **44**. Desired products **46** were obtained in good yields (84-95%) and with good enantio- and diastereoselectivity. Notably, imidazolidine derivatives **46** were successfully transformed into spirobrassinin analogue.[22]

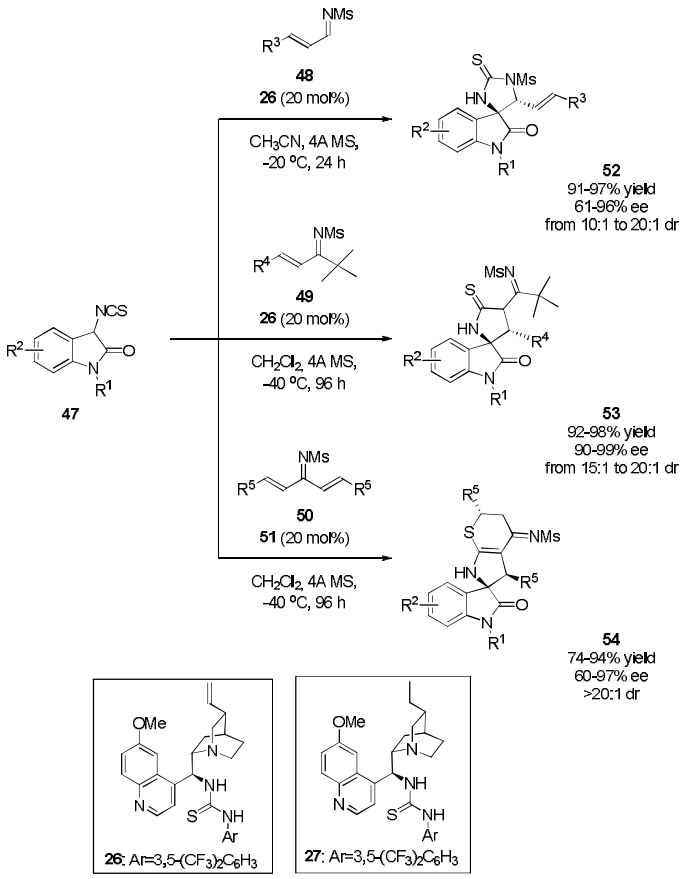


Scheme 16

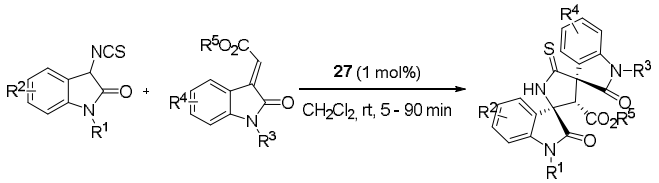
In 2016 Shi and co-workers presented the asymmetric reaction between 3-isothiocyanato-oxindole **47** and *N*-mesylo-α,β-unsaturated imines **48-50** (Scheme 17).[23] The regioselectivity of this process was possible to control by the change of reaction conditions. The possible reaction outcomes include: (1) [3+2]-cycloaddition initiated by the Mannich reaction, which led to thioureas **52**; (2) [3+2]-cycloaddition 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.

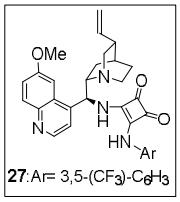
In 2013 Xiao and co-workers reported the enantioselective method of synthesis of bispirooxindole derivatives **57** from 3-isothiocyanato-oxindoles **55** and 3-alkylideneoxindoles **56** (Scheme 18).[24] Mechanism of that reaction involved Michael addition followed by the cyclization. Optimization studies 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.[25]

In 2013 Yuan and co-workers presented a highly enantioselective method of synthesis of dispirocyclic thiopyrrolidinineoxindoles **61** or **62** from 3-isothiocyanato-oxindoles **58** or 4-alkylideneazlactones **59** (Scheme 19).[26] 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 enantio- 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.

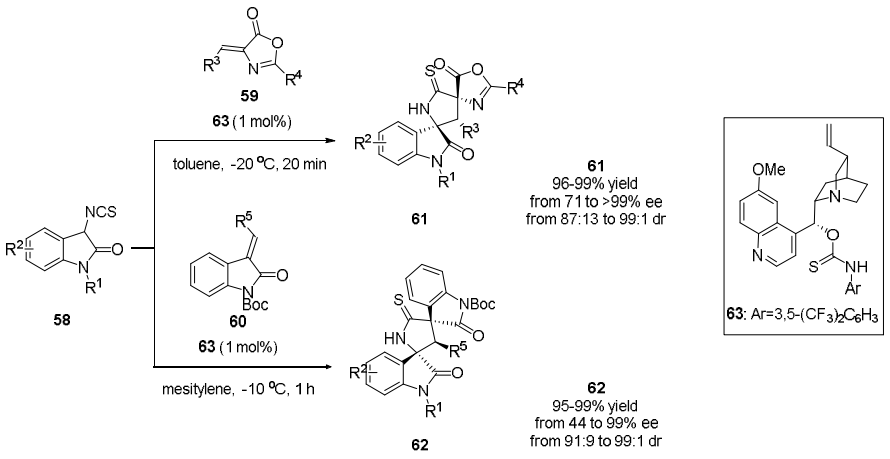


Scheme 17



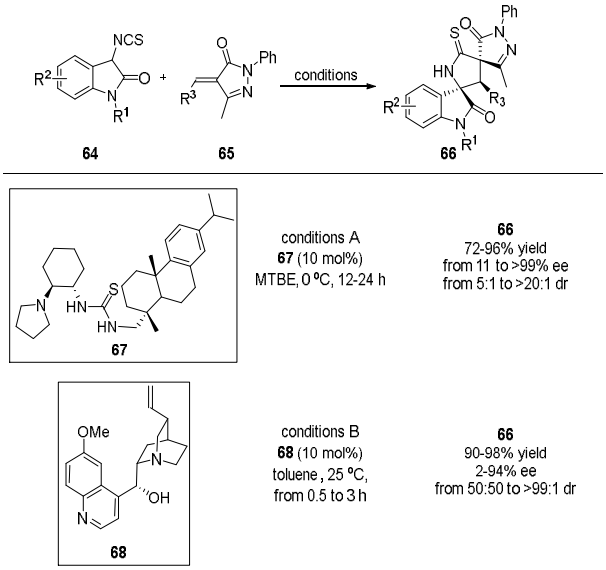


Scheme 18



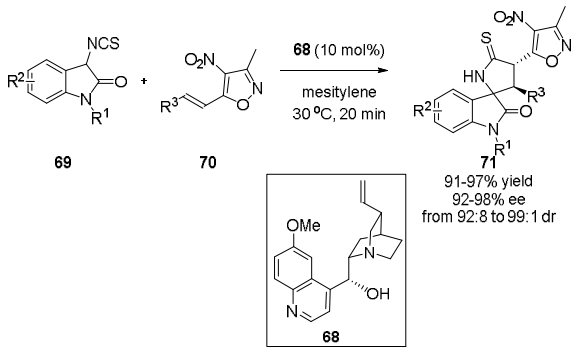
Scheme 19

A related methodology was developed independently by two research groups (Scheme 20).[27,28] In both of the reports the construction of bispirooxindoles **66** in an enantioselective manner using 3-isothiocyanato-oxindoles **64** and α,β-unsaturated pyrazolones **65** was described. In 2013 Wang and co-workers reported that the thiourea catalyst **67** derived from dehydroabietic 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 **68** 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.



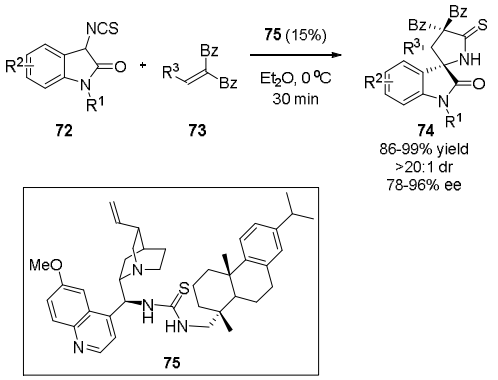
Scheme 20

In 2013 Chinese scientists reported an enantioselective, organocatalytic reaction of isothiocyanato-oxindoles **69** with alkenyl-isoxazoles **70** (Scheme 21).[29] This type of Michael/cyclization cascade yielded 3,3'-pyrrolidynyl spirooxindoles **71**. In the optimization studies the model reactants were 3-isothiocyanato-oxindole **69a** (R_1=Me, R_2=H) and 3-methyl-4-nitro-5-alkenyl-isoxazole **70a** (R_3=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** (R_1=Me, R_2=H, R_3=phenyl) and some transformations have been presented.



Scheme 21

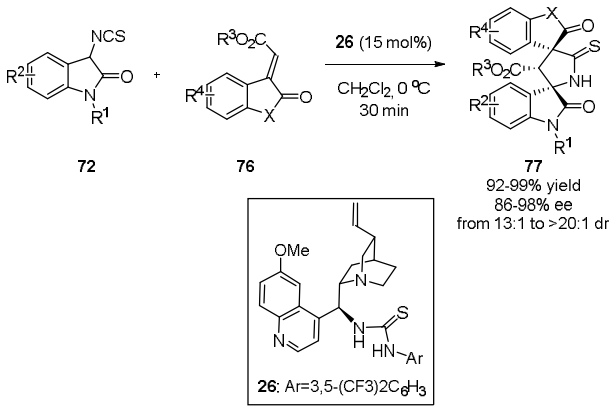
In 2013 Wang and co-workers reported the catalytic asymmetric synthesis of 3,3'-pirrolidynyl mono- and bis-spirooxindoles **74** and **77** (Schemes 22 and 23).[30] 3-Isothiocyanato-oxindole **72a** (R_2=H, R_1=Me) and electron-deficient olefin **73a** (R_3=phenyl) were chosen as model reactants. In 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

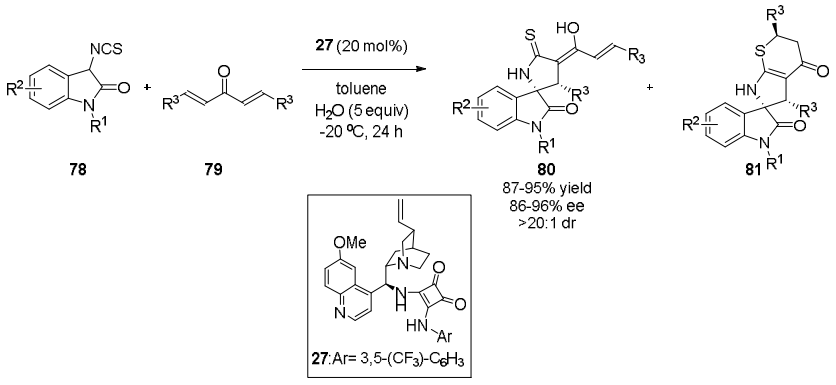
Reaction worked not only for olefinic benzaldehyde **73** derivatives but also for heterocyclic and alkyl olefins. Desired products **74** were obtained in high yields, excellent diastereoisomeric excesses and good enentiomeric excesses.

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.[31]



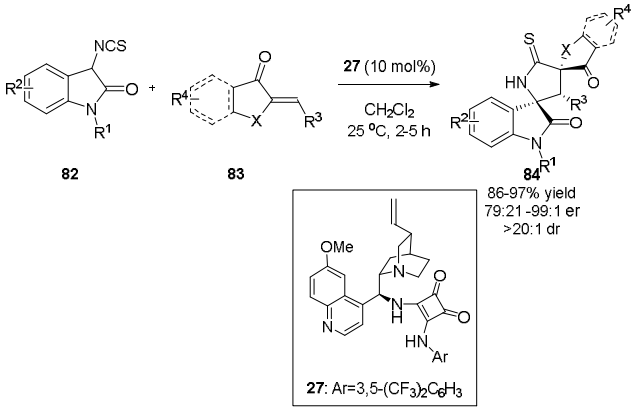
Scheme 23

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).[32] 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.



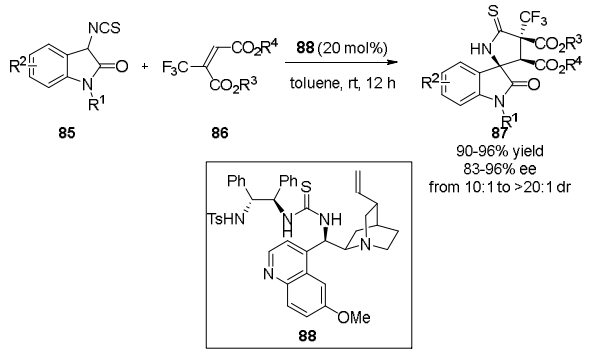
Scheme 24

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).[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.[34]



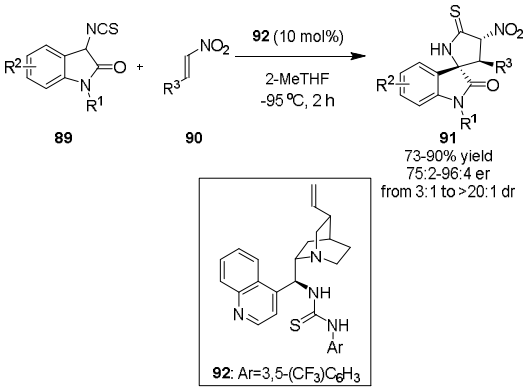
Scheme 25

In 2015, Shi and co-workers reported an enantioselective reaction between 3-isocyanato-oxindoles **85** and trifluoromethylated 2-butenedioic acid diesters **86** (Scheme 26).[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 diastereoselectivites, good to very good enantioselectivities and excellent yields. Selected transformations were performed to demonstrate the synthetic utility of the developed method.[36]



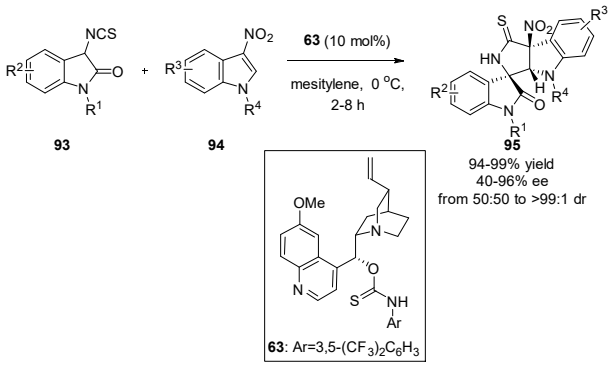
Scheme 26

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).[37] 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.[38]



Scheme 27

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).[39]

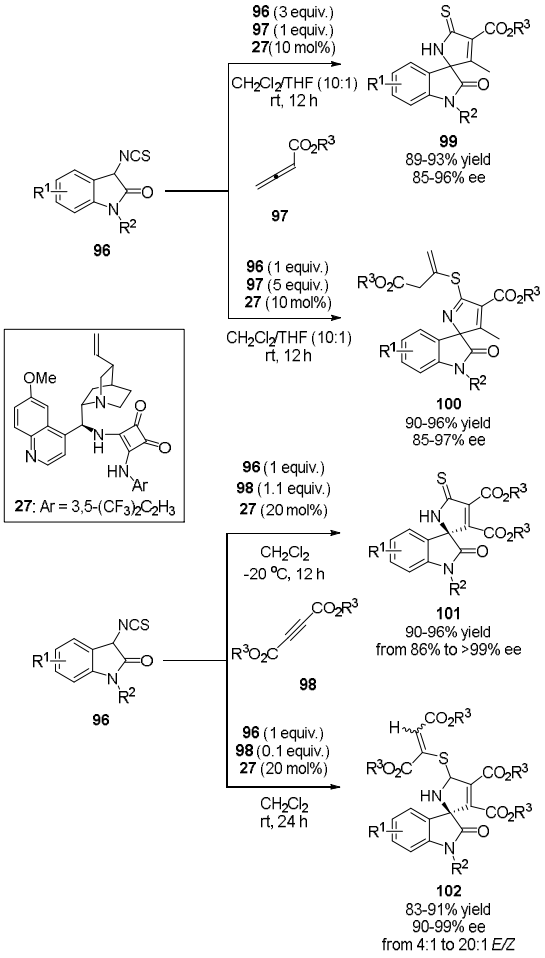


Scheme 28

That approach provided convenient access to polycyclic spirooxindoles **95**. In the optimization studies, **93a** (R_1=methyl, R_2=H) and **94a** (R_3=H, R_4=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).[40]



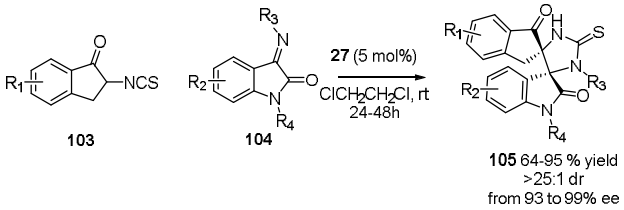
Scheme 29

Enantioselective [3+2]-cycloadditions of 3-isothiocyanato-oxindoles **96** with allenic esters **97** or 2-butynedioic 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 isothiocynato-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-isothiocynates **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

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-strategis will continue to develop and the identification of new, inspiring methodologies are only a matter of time.

Acknowledgements

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