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Advances of α-activated cyclic isothiocyanate for the enantioselective construction of spirocycles

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The efficient and enantioselective synthesis of pharmaceutically important spirocycles has attracted the focus of organic and medicinal chemists. In this context, with the excellent reactivity of α-activated isothiocyanate as formal 1,3-dipoles in the (3 + 2) cyclization process, the cyclic isothiocyanates featuring important pharmacophores, such as oxindole, pyrazolone, and indanone moieties, have emerged as powerful precursors to access a variety of spirocycles with highly structural diversities. In addition, the facile transformations of these spirocycles have shown potential applications in drug design. This review will cover the recent advances of α-activated cyclic isothiocyanates in the enantioselective construction of spirocycles since 2015, and the applications of corresponding products in organic and medicinal chemistry.

1. Introduction

The wide occurrence of the spirocycle moiety in natural products and bioactive molecules has persistently motivated the emergence of efficient and asymmetric construction of spirocyclic compounds.[1] Recently, the introduction of a spirocycle moiety to rigidify the conformation of the lead compound is one of the useful strategies in drug design.[2] In this regard, a variety of strategies to access optically active spirocycles featuring important pharmacophores were developed. Among these, α-activated isothiocyanates have emerged to be valuable synthons to achieve this goal owing to their excellent reactivities as formal 1,3-dipoles in the (3 + 2) cyclization.[3]

Isothiocyanate derivatives are an important class of natural products and possess many important biological activities.[4] In

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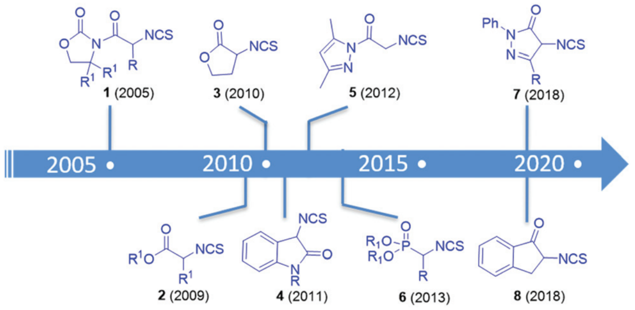
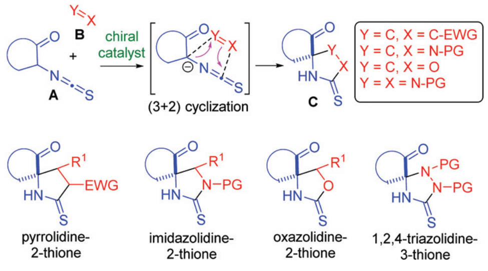


Scheme 1 Time schedule of α-activated isothiocyanate in enantioselective synthesis.

synthetic chemistry, α-activated isothiocyanate (**2** was first described in 1916, Scheme 1) has existed for more than one century.[5] However, the first enantioselective transformation of α-activated isothiocyanate (**1**, Scheme 1) was reported in 2005 by Willis.[6] Since then, various elegant works were reported to expand the utility of α-activated isothiocyanate in asymmetric synthesis.[3,7] The time schedule of the first enantioselective transformations of different kinds of α-activated isothiocyanates is shown in Scheme 1.[6,8,10,11] In contrast to simple isothiocyanate esters or amides, Yuan and co-workers developed 3-isothiocyanato oxindoles **4** for the construction of a spirocycle-fusing important oxindole pharmacophore in 2011.[8d,9] Scheme 2 displays the facile approach to obtain chiral spiro compounds **C** with cyclic α-activated isothiocyanates **A** and electrophiles **B**. With various electrophiles **B**, different medicinal heterocycles, such as pyrrolidine-2-thione, imidazolidine-2-thione, oxazolidine-2-thione, and 1,2,4-triazolidine-3-thione, were synthesized *via* (3 + 2) cyclization.[3]

In 2015, Yuan and co-workers contributed a comprehensive review for α-activated isothiocyanate in catalytic asymmetric reactions.[3a] In the past few years, many efforts have been further devoted in this area. For instance, encouraged by the privilege of α-activated isothiocyanate, the Wang group[10] and Du group[11] designed new synthons **7** and **8** based on pyrazolone[12] and indanone[13] pharmacophores in 2018, respectively (Scheme 1). Thus, it is necessary to review the recent advances in the enantioselective construction of spirocycles from α-activated cyclic isothiocyanate.



Scheme 2 (3 + 2) Cyclization of α-activated cyclic isothiocyanate. EWG = electron-withdrawing group, PG = protecting group.

This review covers the achievements of enantioselective Michael/cyclization, Mannich/cyclization, and other types of cascade reactions after 2015. The Michael/cyclization section was divided into four types, according to the electron-withdrawing group (EWG) of acceptors **B** (EWG = nitro group, ester, ketone, and amide).

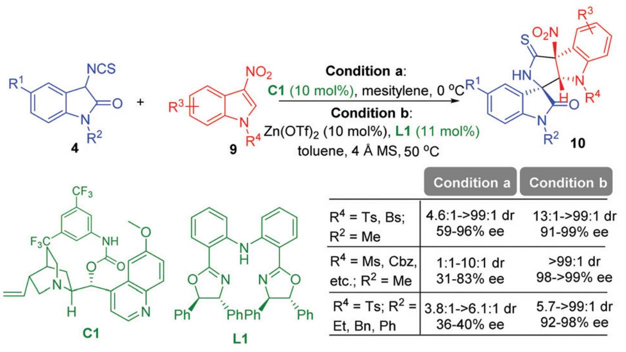
2. Michael/cyclization

Enantioselective Michael addition is an efficient method to construct C–C bond with stereocentres. Undoubtedly, when the Michael acceptor meets the α-activated isothiocyanate in the presence of a chiral catalyst, the (3 + 2) cyclization could easily form the pyrrolidine-2-thione moiety. This process is still the most commonly studied among the chemistry of isothiocyanate.

2.1 Nitro group as EWG

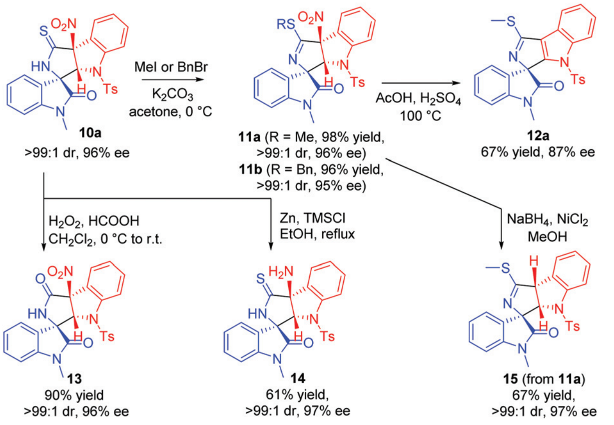
Unlike the simple nitrostyrene, the Yuan group developed an organocatalytic approach of 3-nitroindoles **9** and 3-isothiocyanato oxindoles **4** to obtain polycyclic spirooxindoles **10** in 2015 (Scheme 3, condition a).[14a] The cinchona alkaloid derived amino-thiocarbamate **C1** efficiently induced the diastereo- and enantioselectivities of three contiguous chiral centres *via* Michael/cyclization cascade reaction. Notably, this was an elegant expansion of 3-nitroindoles as Michael acceptors. However, the stereo-outcomes depended on the substituents of the substrates, as the dr and ee ranged from 1 : 1 to 99 : 1 and 31% to 96%, respectively. To overcome these limitations, they developed a transition-metal catalysed method, which showed excellent functional group tolerance (Scheme 3, Condition b).[14b] The chiral/diphenylamine-linked bis(oxazoline) ligand **L1** facilitated this Zn(OTf)$_2$-catalysed (3 + 2) cyclization process to give various polycyclic spirooxindoles **10** in excellent diastereo- and enantioselectivities. It was proposed that the free NH group of the diphenylamine moiety in ligand **L1** was essential for this high stereoselectivity *via* hydrogen bonding.

Various transformations of this polycyclic spirooxindole **10a** under mild conditions verified the synthetic utility of this (3 + 2) process (Scheme 4). In the presence of iodomethane



	Condition a	Condition b
R^4 = Ts, Bs; R^2 = Me	4.6:1->99:1 dr 59-96% ee	13:1->99:1 dr 91-99% ee
R^4 = Ms, Cbz, etc.; R^2 = Me	1:1-10:1 dr 31-83% ee	>99:1 dr 98->99% ee
R^4 = Ts; R^2 = Et, Bn, Ph	3.8:1->6.1:1 dr 36-40% ee	5.7->99:1 dr 92-98% ee

Scheme 3 Asymmetric Michael/cyclization reaction of 3-isothiocyanato oxindoles and 3-nitroindoles.

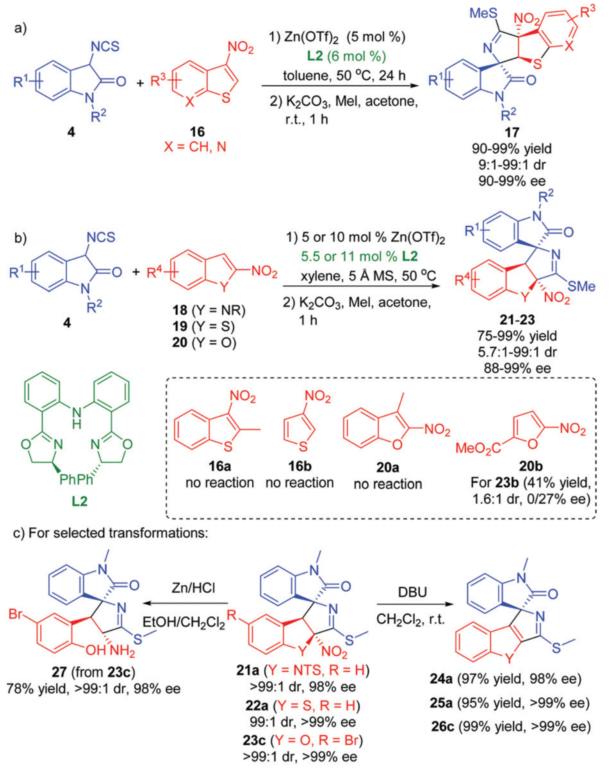


Scheme 4 Synthetic transformations of spirooxindole **10a**.

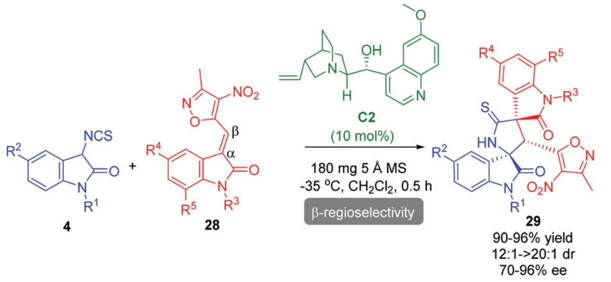
and benzyl bromide as alkylation reagents, the alkylated thiolactam **11a** and **11b** were both obtained in high yields. **11a** could further undergo 1,2-elimination to get spirocyclic oxindole **12a** in 67% yield and 87% ee. The elimination of the nitro group of **11a** with nickel boride reduction formed **15** with high stereoselectivity. In addition, treatment of **10a** with hydrogen peroxide or zinc powder and TMSCl (trimethyl chlorosilane) gave products **13** and **14** without erosion of the stereoselectivities, respectively.

With their achievements of employing the chiral Zn $(OTf)_2$/diphenylamine-linked bis(oxazoline) complex as the catalyst, the authors tested the tolerance of this catalytic system with 3-nitrobenzothiophene derivatives **16** as Michael acceptors instead of 3-nitroindoles **9** in 2018.[15a] Interestingly, with the small modification of ligand **L1** to ligand **L2**, a series of spirocyclic oxindoles **17** featuring 2,3-dihydrobenzothiophene moiety were forged with excellent stereoselectivities in perfect yields through dearomative (3 + 2) cycloaddition (Scheme 5a and b). Unfortunately, the bulky 2-methyl-3-nitrobenzothiophene **16a** and simple 3-nitrothiophene **16b** both failed to undergo the desired process with 3-isothiocyanato oxindoles **4**. At the same time, the catalytic system proved to be suitable to catalyse the dearomative (3 + 2) cycloaddition of 2-nitroindoles **18**, 2-nitrobenzothiophenes **19**, or 2-nitrobenzofurans **20** with 3-isothiocyanato oxindoles **4** (Scheme 5b).[15b,c] As a result, various structurally diverse spiro-oxindoles **21–23** were synthesized in almost quantitative yields. With the potent ability of the Zn(II)/**L2** complex, these interesting spirooxindole derivatives containing three contiguous stereocenters all possessed high diastereo- and enantioselectivities. In addition, the products could be easily transformed into other corresponding complex chiral heterocyclic compounds **24–27** through DBU (1,8-diaza-7-bicyclo-[5.4.0]-undecene) promoted elimination or Zn/HCl-mediated reduction without any erosion of diastereo- and enantioselectivity (Scheme 5c).

Later in 2019, the Liu group employed 3-methyl-4-nitro-5-isoethylene-isoxazoles **28** as the Michael acceptor in the cyclization process with 3-isothiocyanato oxindoles **4** (Scheme 6).[16a] Unlike the normal α-regioselectivity of **28** with the strong electron-withdrawing nitro group,[16b] the simple catalyst quinine **C2** promoted this (3 + 2) cyclization with β-regioselectivity to afford isoxazole-dispirobisoxindoles **29** in high yields and excellent stereo- and enantioselectivities. Various substituents on both partners were well tolerated to give this dispirobisoxindole scaffold. In addition, the steric hindrance in the first Michael addition step between two oxindole skeleton was proposed to inhibit the α-regioselectivity.



Scheme 5 Dearomative (3 + 2) cycloaddition reaction of 3-isothiocyanato oxindoles with five-membered nitro derivatives and their transformations.



Scheme 6 Cyclization of 3-isothiocyanatooxyindoles with 3-methyl-4-nitro-5-isoethylene-isoxazoles.

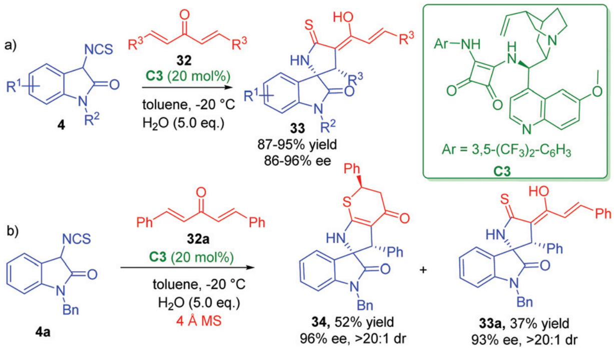
2.2 Ketone as EWG

In 2015, Wang and co-workers developed an excellent formal (3 + 2) cycloaddition between alkynyl ketones **30** and 3-isothiocyanato oxindoles **4** (Scheme 7).[17] The *in situ* generated mag-

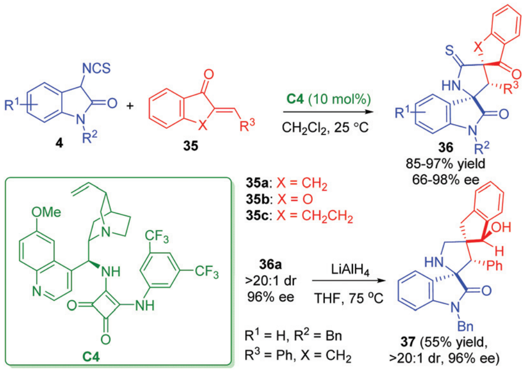
Scheme 7 Cyclization of 3-isothiocyanateoxindoles with alkyne ketones.

nesium catalyst with easily accessible oxazoline–OH type chiral ligand **L3** efficiently catalysed the reaction to give spirooxindoles **31** in good yields and high enantioselectivities. It is worth noting that the phenyl group in the oxazoline ring of ligand **L3** was essential to enhance the enantioselectivity. Moreover, the slow addition of **4** to the mixture of the catalyst and **30** further improved the ee from 68% to 92%. In general, the substituents on the substrates had little influence on the chemical yields and stereoselectivities of this reaction, except that the substitution of **30** with an alkyl (R^3) group led to a slight decrease in the enantioselectivity.

In 2016, a cinchona alkaloid-derived squaramide **C3**-catalysed asymmetric (3 + 2) cyclization of 3-isothiocyanate oxindoles **4** with dibenzylidene ketones **32** was reported by Shi and co-workers to synthesize spiro-oxindoles **33** featuring an enol moiety (Scheme 8a).[18] Interestingly, the reactivity of **32**, which embedded two electron-deficient C=C bonds and one C=O bond, was well studied in this work. Thus, a series of spiro-oxindoles **33** with different substituents were forged in high yields with excellent diastereo- and enantioselectivities. During their initial optimization of the reaction conditions, the (3 + 2)/(4 + 2) cascade was observed to give the tricyclic product **33a** (31% yield in toluene at rt) as the by-product without the addition of water. The addition of water dramatically suppressed the (4 + 2) cyclization, which was further proved by the control experiment in Scheme 8b. The presence of 4 Å molecular sieves finally gave the tricyclic product **34** in 52% yield and 96% ee as the major product.



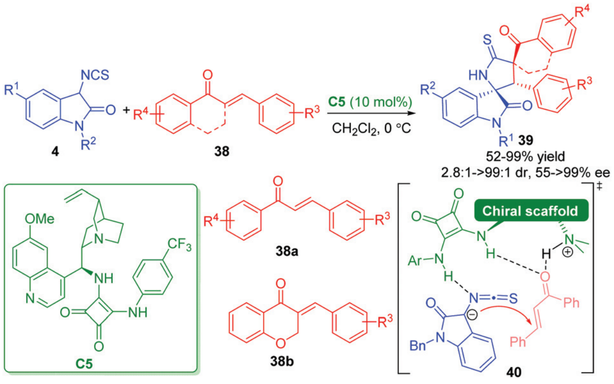
Scheme 8 Cyclization of 3-isothiocyanate oxindoles with dibenzylidene ketones for the synthesis of spirooxindole enols.



Scheme 9 Cyclization of 3-isothiocyanate oxindoles with exocyclic α,β-unsaturated ketones.

The Mukherjee group first developed a simple quinine derived squaramide **C4**-catalysed Michael/cyclization cascade between 3-isothiocyanatooxindoles **4** and exocyclic α,β-unsaturated ketones **35** (Scheme 9).[19] A wide range of 3,2′-pyrrolidinyl bispirooxindoles **36** featuring two spiro-centres and three contiguous stereocentres was furnished in high yields and excellent diastereo- and enantioselectivities. Notably, the unsubstituted β-methylene-α-indanone (R^3 = H, X = CH_2) was also tolerated to afford the desired product in high yield with good enantioselectivity. Also, the (*Z*)-2-benzylidenebenzofuran-3-one (X = O) and β-arylidene-α-tetralone (X = CH_2CH_2) were excellent partners in this process. Importantly, the reduction of **36a** with $LiAlH_4$ afforded the bispiro[indoline-3,2′-pyrrolidine] **37** in 55% yield with over 20 : 1 dr and 96% ee. A preliminary study implied the potential of **37** as a chiral catalyst *via* iminium activation.

With their efforts in the construction of spirooxindoles, the Du group reported a supplementary work to synthesize enantioenriched 3,2′-pyrrolidinyl spirooxindoles. The chiral squaramide **C5** catalysed the (3 + 2) cyclization of 3-isothiocyanatooxindoles **4** and various electron-withdrawing or electron-donating substituted chalcones **38a** to give 3,2′-pyrrolidinyl spirooxindoles **39** in excellent yields and stereoselectivities (Scheme 10).[20a] In addition, the (*E*)-3-benzylidene-chroman-4-ones **38b**, (*E*)-β-arylidene-α-indanones **35a**, and (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **35c** all gave the corresponding spirooxindoles with high diastereo- and enantio-



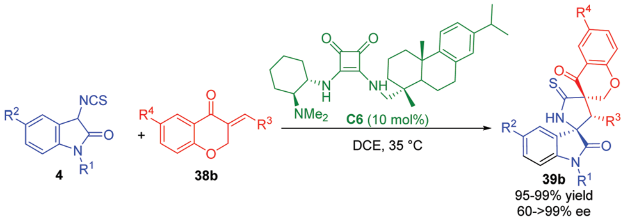
Scheme 10 Cyclization of 3-isothiocyanateoxindoles with chalcones.

selectivities. Accordingly, a unnormal dual activation model was proposed.[20b] As shown in transition state **40**, 3-isothiocyanatooxindole **4a** was deprotonated by the tertiary amine unit of the catalyst **C5**, and then immobilized by the N–H group of squaramide through hydrogen bonding. Simultaneously, the chalcone was activated by both the N–H group of squaramide and the protonated quinuclidine *via* hydrogen bonding.

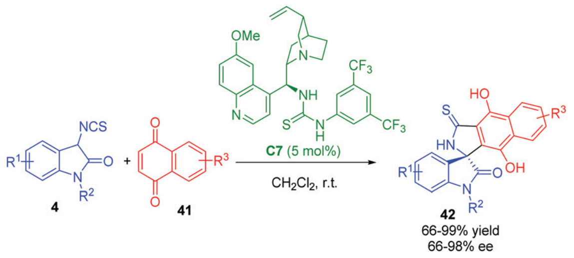
Complementally, the Lin group documented a similar Michael/cyclization cascade reaction of (*E*)-3-benzylidenechroman-4-ones **38b** and 3-isothiocyanatooxindoles **4** (Scheme 11).[21] Interestingly, the newly defined bifunctional catalyst **C6** featuring a rosin-backbone was identified to be the best choice to afford the corresponding spirooxindoles **39b** in high yields with excellent diastereo- and enantioselectivities. A wide array of benzylidenechroman-4-ones **38b**, (*E*)-β-arylidene-α-indanones **35a**, and (*E*)-2-benzylidene-3,4-dihydronaphthalen-1(2*H*)-one **35c** were tolerated under this optimal condition.

Later in 2019, the quinone derivative **41** was used as an electrophile to participate in the Michael/cyclization cascade with 3-isothiocyanato oxindoles **4** by Guo and co-workers (Scheme 12).[22] The commonly used thiourea catalyst **C7** efficiently promoted this asymmetric double arylation process to the end within 15 min in most cases. A variety of spirooxindoles **42** possessing a spiro-centre adjacent to the aromatic ring were established in moderate to high yields and enantioselectivities.

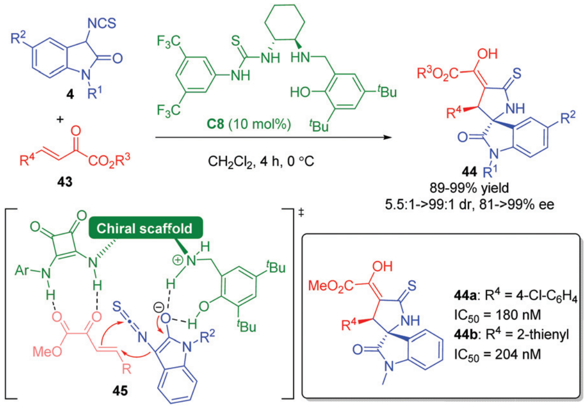
With multi-functional catalyst **C8**, Chen and co-workers described an enantioselective 1,4 addition/cyclization cascade of 3-isothiocyanato oxindoles **4** and β,γ-unsaturated α-keto esters **43** to construct a new class of spirooxindoles **44** with enol structure (Scheme 13).[23] Diverse β,γ-unsaturated α-keto esters **43** were used to give the final spirooxindoles in good yields and high stereoselectivities. However, the alkyl substituent of R^4 and benzyl substituent of R^1 were not applicable. Interestingly, the control experiments showed that the absence of the OH group in catalyst **C8** would dramatically decrease the ee of the product. Thus, the transition state **45** was proposed, in which the 3-isothiocyanato oxindole **4** was activated and fixed by the N–H and OH moieties through hydrogen bonding, and the β,γ-unsaturated α-keto esters **43** was activated by the hydrogen-bonding interaction with the thiourea moiety. Moreover, the anti-inflammatory investigation of compounds **44** on mouse peritoneal macrophage s(RAW264.7) revealed that the IC_{50} values of spirooxindole **44a** and **44b** were only 180 nM and 204 nM, respectively.



Scheme 11 Cyclization of 3-isothiocyanate oxindoles with chroman-4-ones.



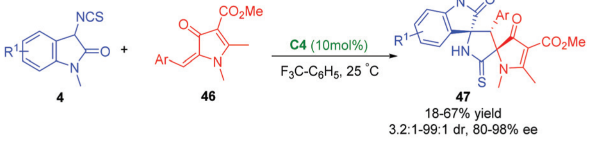
Scheme 12 Cyclization of 3-isothiocyanate oxindoles with quinones.



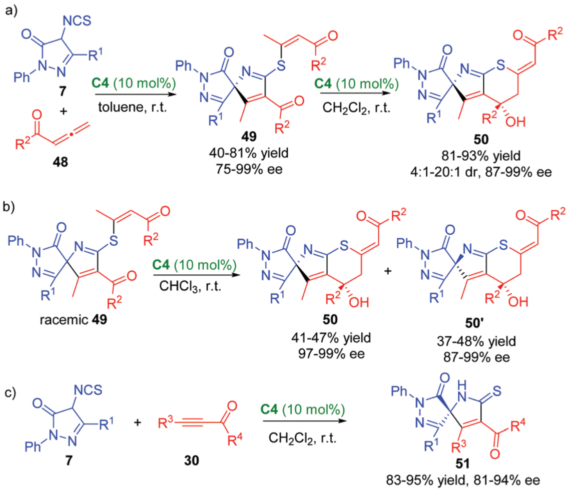
Scheme 13 Cyclization of 3-isothiocyanate oxindoles with β,γ-unsaturated α-keto esters.

Recently, the arylidene-pyrrolin-4-ones **46** were applied by the Grošelj group as an extension of exocyclic α,β-unsaturated ketones in (3 + 2) cyclization with 3-isothiocyanato oxindoles **4** (Scheme 14).[24] With **C4** as the catalyst, a number of spiro-oxindoles **47** featuring two spirocycles were afforded. However, the chemical yield and the stereo-outcome of the product was highly dependent on the property of the substituent on the starting material.

Recently, Wang and co-workers developed a 4-isothiocyanato pyrazolone **7** as a new synthon for the construction of diversity-oriented spirocycles featuring an important pyrazolone pharmacophore.[10] In 2020, the group reported a chiral squaramide **C4**-catalysed Michael/cyclization/thia-Michael sequence of 4-isothiocyanato pyrazolones **7** with two molecules of aryl allenic ketones **48** (Scheme 15a).[25a] A series of spiro[pyrrole-pyrazolone] **49** were furnished in good yields with excellent enantioselectivities. Notably, the intramolecular viny-



Scheme 14 Cyclization of 3-isothiocyanate oxindole with pyrrolidone.

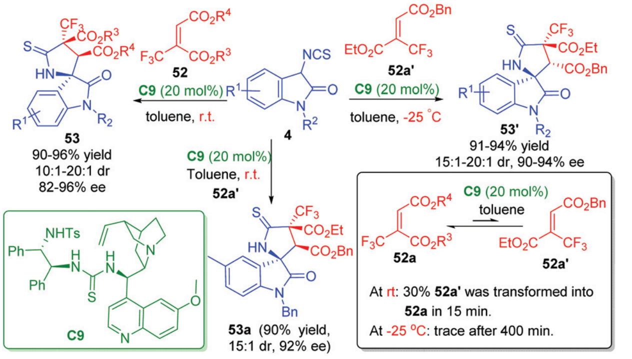


Scheme 15 Cyclization of 4-isothiocyanato pyrazolones with allenic or alkynyl ketones.

logous aldol cyclization product **50** was detected during the initial study. Encouraged by the structure of this intriguing tricyclic molecule, a number of spiro-pyrazolones **50** were synthesized from **49** in the presence of catalyst **C4** with high diastereoselectivity. The investigation of this transformation implied that the stereochemistry of compound **50** was totally controlled by catalyst **C4**. With this catalyst-controlled stereoselective aldol cyclization process, the parallel resolution of racemic **49** to obtain optical products **50** was successfully conducted in the presence of **C4** as the catalyst (Scheme 15b). A few diastereomer pairs of spiro-pyrazolones **50** and **50′** were obtained in good yields with excellent enantioselectivities. Closely, this catalytic system also gave satisfactory stereochemistry control when alkynyl ketones **30** were used as Michael acceptors, affording the desired spiro-pyrazolones **51** in good yields with excellent enantioselectivities (Scheme 15c).[25b]

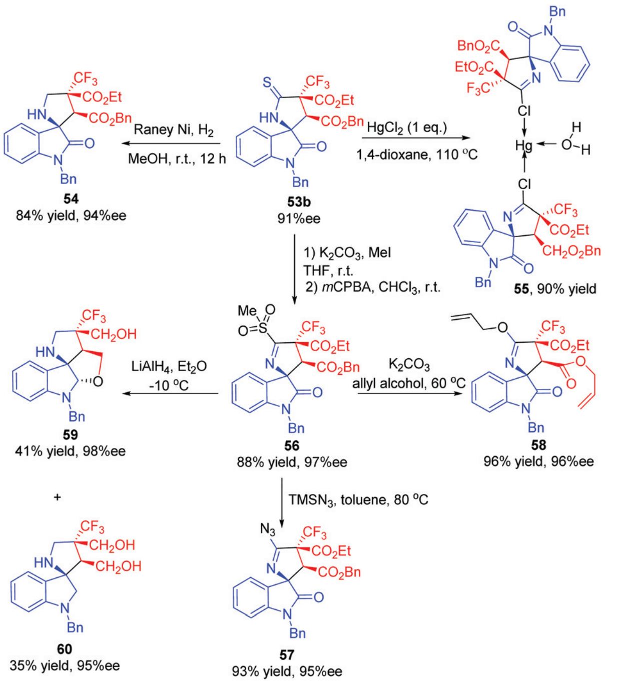
2.3 Ester as EWG

In 2015, considering the importance of the CF$_3$ group in medicinal chemistry, the Shi group developed a highly enantioselective method to construct a wide array of spirooxindoles **53** containing a quaternary carbon stereocenter in high yields (Scheme 16).[26] The multi-functional catalyst **C9** was sufficient to control the stereoselectivity of the Michael/cyclization process between 3-isothiocyanato oxindoles **4** and trifluoromethyl 2-butenedioate **52**. Surprisingly, when 4-benzyl-1-ethyl-2-(trifluoromethyl)-fumarate **52a′** was conducted, the spirooxindole **53a** was also obtained as the major product at rt. After a series of control experiments, the authors found that the diester **52a′** could isomerize to **52a** quickly at rt with the assistance of catalyst **C9**. Interestingly, this trend was tremendously suppressed at −25 °C. This phenomenon gave the opportunity to synthesize product **53′** (epimer of **53**) in good yield with high diastereo- and enantioselectivity at −25 °C. A series of transformations were shown to demonstrate the synthetic utility of these spirooxindoles (Scheme 17). The hydrogenation of **53b** with RANEY® Ni gave pyrrolidine derivative **54** in 84% yield and 94% ee. Interestingly, in the presence of HgCl$_2$, a metal complex **55** was formed from **53b**, and the structure of **55** was well-defined. In addition, the methylation and oxidation cascade of **53b** afforded the sulfonyl-substituted product **56** in 88% yield with 97% ee. Moreover, **56** could be converted to a number of other spirooxindoles **57–60** in good yields with untouched ee with the treatment of TMSN$_3$ (azidotrimethylsilane) in toluene, allyl alcohol in the presence of potassium carbonate, and LiAlH$_4$ in Et$_2$O, respectively.

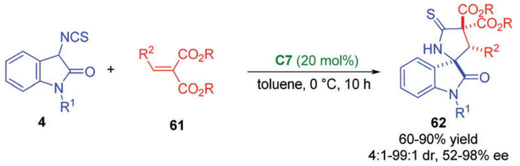


Scheme 16 Cyclization of 3-isothiocyanate oxindoles with trifluoromethylated diesters.

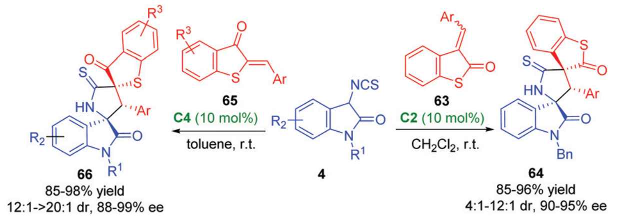
Later in 2016, the Chowdhury group turned their attention to engage the less reactive arylidene malonates **61** as an acceptor in enantioselective Michael/cyclization cased with 3-isothiocyanato oxindoles **4** (Scheme 18).[27] A diverse array of 3,2′-



Scheme 17 Selected transformations of spirooxindole **53b**.



Scheme 18 Cyclization of 3-isothiocyanate oxindoles with aryl malonates.



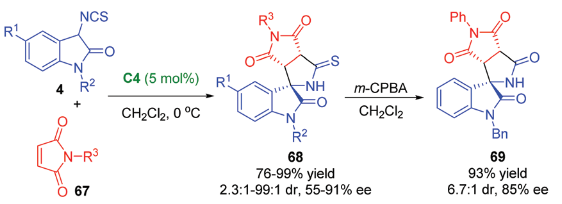
Scheme 19 Cyclization of 3-isothiocyanate oxindoles with thioaurones.

pyrrolidinyl spirooxindoles **62** were then obtained with **C7** as the catalyst in good yield with moderate to high stereoselectivities. The enantioselectivity of this process was inferior when arylidene malonate was replaced by alkylidene malonate. Moreover, with the easily accessible pseudo-enantiomer of the cinchona alkaloid, the use of the pseudo-enantiomer of **C7** as the catalyst efficiently gave the enantiomer of **62**.

Recently, in continuation of their efforts in the synthesis of spirooxindoles, the Shi group extended their interest to the utilization of thioaurone derivatives **63** and **65** as Michael acceptors in the (3 + 2) cyclization with 3-isothiocyanato oxindoles **4** (Scheme 19).[28] With the readily obtained cinchona alkaloids-derived catalyst **C4** or **C2**, a wide range of sulfur-containing spirooxindoles **66** and **64** with three continuous spiral rings were afforded in good yields with moderate to good dr and excellent ee, respectively.

2.4 Amide as EWG

Inspired by the importance of pyrrolidonyl spirooxindoles, the Due group introduced a succinimide moiety into this unique spirocycle scaffold in 2016.[29] With **C4** as the catalyst, the enantioselective Michael/cyclization cascade of 3-isothiocyanato-oxindoles **4** and maleimides **67** gave a variety of desired spirooxindoles **68** in high yields with moderate to high stereoselectivities (Scheme 20). However, the 2-Cl or 2-Br substituted *N*-arylmaleimides also with the *N*-alkylmaleimides would shut down this cascade process. To show the synthetic utility, product **69** featuring the β-carbonyl amide was formed readily from the corresponding precursor.

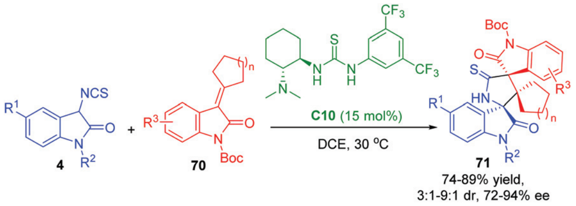


Scheme 20 Cyclization of 3-isothiocyanate oxindoles with maleimides.

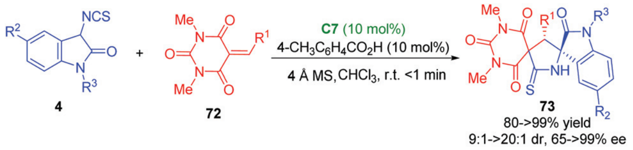
Besides the well-developed methods to construct mono-spirooxindoles and double spirooxindoles, the Qin group first described a Michael/cyclization cascade for the synthesis of triple spirooxindoles. In detail, with the cyclohexane diamine derived thiourea catalyst **C10**, the (3 + 2) cyclization process between 3-isothiocyanato-oxindoles **4** and cyclic methylene indolinones **70** proceeded smoothly (Scheme 21).[30] A wide range of *trans*-configured trispirooxindoles **71** were obtained with different substituents in good yields with moderate to high stereoselectivities.

The barbiturate-based olefins **72** were first employed by the Zhao group for the enantioselective construction of a dispirobarbiturate architecture in cooperation with 3-isothiocyanato-oxindoles **4** (Scheme 22).[31] A large number of dispirobarbiturates **73** possessing an oxindole core were obtained in high yields with high diastereo- and enantioselectivities in the presence of **C7** as the catalyst. The stereooutcome was sensitive to the steric hindrance of the R^1 group of the barbiturate-based olefin **72**. Notably, the reactions all finished within one min, which showed the challenge of this enantioselective transformation. Moreover, the author believed that the addition of $4\text{-MeC}_6H_4CO_2H$ was beneficial for the activation of 3-isothiocyanato-oxindoles **4**, and simultaneously improved the enantioselectivity.

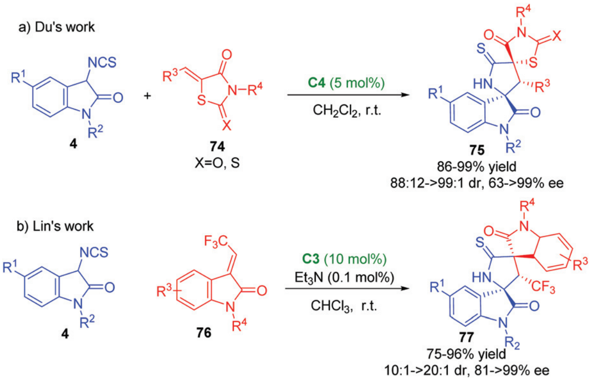
In 2018, the Du group developed a method for the synthesis of spirooxindoles **75** containing a thiazolidinone pharmacophore *via* Michael/cyclization cascade of unsaturated thiazolidinones **74** (X = O) and 3-isothiocyanate oxindoles **4** (Scheme 23a).[32a] With a simple chiral squaramide **C4** as the catalyst, the desired spirooxindoles **75** were furnished in high yields with excellent stereoselectivities. However, the less electronegative sulfur substituted **74** (X = S) gave the desired



Scheme 21 Enantioselective synthesis of triple spirooxindoles.



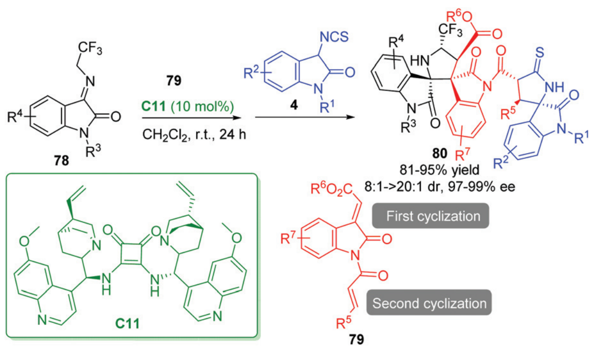
Scheme 22 Enantioselective synthesis of dispirobarbiturate architecture.



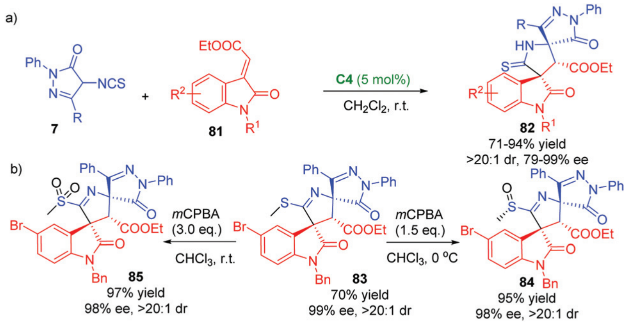
Scheme 23 Cyclization of 3-isothiocyanate oxindoles with thiazolidinones or trifluoroethylidene oxindoles.

product with decreased stereoselectivity. Later, considering the significance of both the CF_3 group and spirooxindole skeleton, Lin and co-workers described an asymmetric (3 + 2) cyclization process between 3-isothiocyanate oxindoles **4** and 3-trifluoroethylidene oxindoles **76**, with the readily squaramide **C3** as the catalyst (Scheme 23b).[32b] The corresponding 3,2′-pyrrolidinyl-bispirooxindoles **77** were forged in high yields with excellent enantioselectivities and diastereoselectivities. Interestingly, the addition of 0.1 mol% of triethylamine efficiently accelerated the reaction and also improved the product yield.

Later, the Du group again revealed an elegant one-pot three-component (3 + 2)/(3 + 2) cyclization process to construct a unique bispirooxindole-spirooxindole scaffold **80** in 2019 Scheme 24.[33] The newly designed cinnamoyl-3-ylideneoxindole **79** possessed two electrophilic sites with different electron deficiency, which was essential to ensure this sequential reaction. First, the bifunctional squaramide **C11** efficiently catalysed the (3 + 2) cyclization of trifluoroethyl isatin ketimines **78** and the more active site (Scheme 24, first cyclization site) of **79**. With their comprehensive investigation, the direct addition of 3-isothiocyanate oxindole **4** to this reaction mixture after 24 h started the second (3 + 2) cyclization process, affording the desired bispirooxindole-spirooxindole derivatives **80** in high yields with excellent diastereo- and enantioselectivities.



Scheme 24 Enantioselective synthesis of bispirooxindole-spirooxindoles.



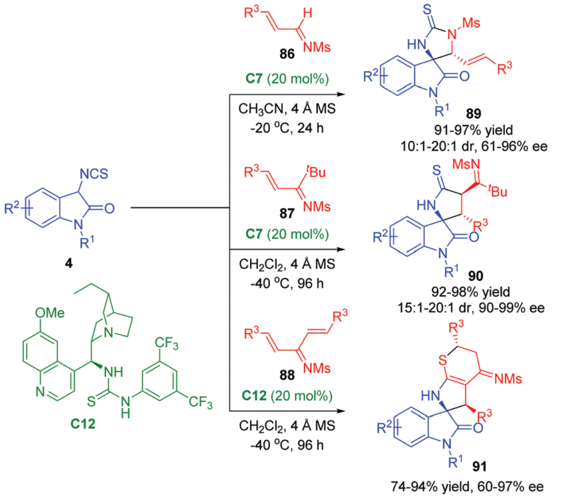
Scheme 25 Cyclization of 4-isothiocyano pyrazolones and 3-ylideneoxindoles.

Recently, with the continued interest in 4-isothiocyanato pyrazolones **7**, the Wang group disclosed a Michael/cyclization process between compounds **7** and 3-ylideneoxindoles **81** (Scheme 25a).[34] In the presence of catalyst **C4**, a series of spirocyclic 4-aminopyrazolone derivatives **82** were obtained efficiently in high yields with excellent diastereo- and enantioselectivities. Notably, the 3-ylideneoxindoles with electron-withdrawing substituents accelerated the reaction dramatically compared to the electron-donating ones. Moreover, a number of synthetic transformations were described to show the utility of this strategy. As illustrated in Scheme 25b, the easily methylated product **83** could convert to sulfoxide **84** and sulphone **85** efficiently by the control of the dosage of *m*-CPBA (3-chloroperbenzoic acid).

3. Mannich/cyclization

With the high reactivity of α-activated isothiocyanate as 1,3-dipoles in the enantioselective synthesis, the Mannich/cyclization of α-activated cyclic isothiocyanate with a suitable partner was an efficient way to construct imidazolidine-2-thione derivatives featuring a spirocycle structure.[3] Besides the previous efforts of chemists, Shi and co-workers successfully developed a series of (3 + 2) or (3 + 2)/(4 + 2) cascade reactions between 3-isothiocyanato oxindoles **4** and α,β-unsaturated methanesulfonamides **86–88** (Scheme 26).[35] With the cinchona alkaloid-derived bifunctional catalysts **C7** and **C12**, the regioselectivity of the reactions was easily controlled. First, with α,β-unsaturated aldimines **86** as the partners, the corresponding spirocyclic oxindoles **89** possessing the imidazolidine-2-thione moiety were synthesized in high yields with excellent stereoselectivities and C═N bond selectivity. In addition, the replacement of the hydrogen of the imine moiety with a bulky tertbutyl group (**87**) led to C═C bond selectivity, affording the spirooxindole **90** with high yield and excellent stereooutcome. Finally, a wide range of S-fused heterocyclic spirooxindoles **91** were obtained with the imines **88** containing three electron-deficient unsaturated bonds as the (3 + 2)/(4 + 2) cascade partner.

Encouraged by the privilege of the combination of pharmacophores in drug design, the Wang group designed and syn-



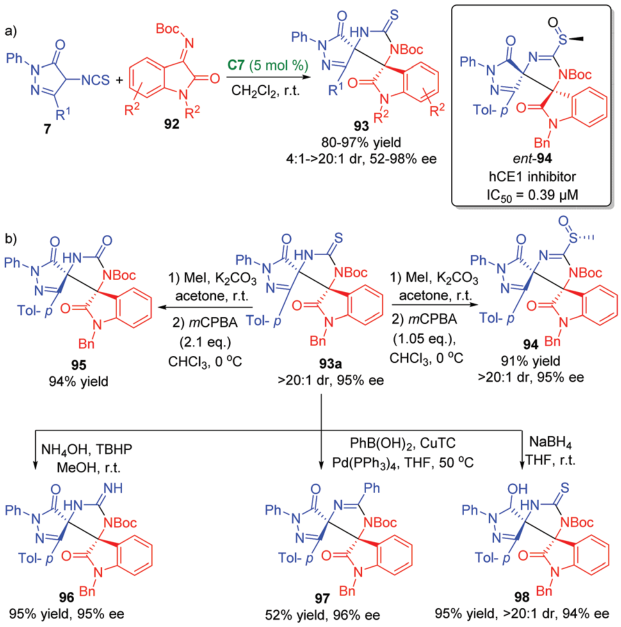
Scheme 26 Regio-and stereoselective cyclization of 3-isothiocyanato oxin-doles with α,β-unsaturated imines.

thesized an intriguing structure featuring pyrazolone, oxindole, and 2-thioxoimidazolidine pharmacophores in 2018.[10] As shown in Scheme 27a, the 4-isothiocyanato pyrazolones **7** were newly designed to reach this goal. With the cinchona alkaloid-derived thiourea catalyst **C7**, the (3 + 2) cyclization of pyrazolones **7** and isatin-derived ketimines **92** delivered the desired dispirotriheterocyclic compounds **93** in high yields with excellent stereoselectivities. However, when the R^1 group of 4-isothiocyanato pyrazolones **7** was replaced with a bulky group or alkyl group, the efficiency of the enantioselectivity control was reduced. To meet the structure diversity requirement of medicinal chemistry, a wide range of synthetic transformations were revealed then (Scheme 27b). Controlling the amount of *m*-CPBA, the methylation and oxidation sequence of compound **93a** could afford chiral sulfoxide **94** and urea derivative **95** in high yields with excellent stereocontrol, respectively. In addition, cyclic guanidine **96**, amidine **97**, and the reduction product **98** were all obtained from the same precursor **93a** with simple operation. Importantly, the investigation showed that the chiral sulfoxide *ent*-**94** exhibited promising inhibitory activity to human carboxylesterase 1 inhibitor (IC_{50} = 0.39 μM), which was 20 times stronger than its enantiomer **94**.

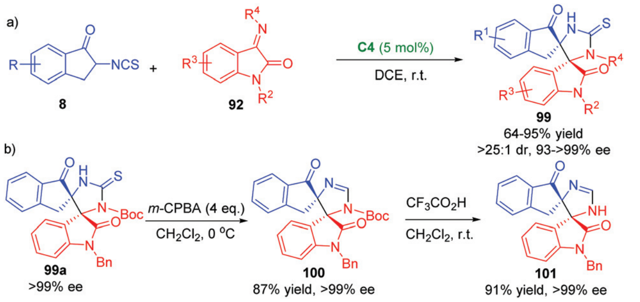
Inspired by the biological and chemical importance of the spiroindanone–oxindole skeleton, the Du group then developed new 1-indanone-derived isothiocyanates **8** (Scheme 28a).[11] With bifunctional squaramide **C4** as the catalyst, the asymmetric Mannich/cyclization cascade reaction of isothiocyanates **8** and isatin-derived ketimines **92** gave a series of spiroindanone–oxindole derivatives **99**. Various substituents on both components were tolerated, affording the desired products in high yields with perfect stereoselectivities. In addition, versatile transformations were conducted to verify the utility. As illustrated in Scheme 28b, the thioimidazolidine moiety of **99a** was converted into an imidazolidine ring in the presence of *m*-CPBA. The corresponding product **100** was synthesized in 87% yield, and the deprotection with trifluoroacetic acid would form the product **101** efficiently.

Later, Shi and co-workers reported a methodology for the construction of spirooxindoles with an aminoquaternary stereogenic centre (Scheme 29).[36] The *in situ* generation of the imine intermediate **102′** *via* the tautomerization of its stable enamine form **102** would cover the instability of the imine moiety. Thus, in the presence of the thiourea catalyst **C13**, several spirooxindoles **103** and **103′** were obtained in moderate yields with moderate to good enantioselectivities. Interestingly, although the diastereoselectivity was poor (1 : 1 or 2 : 1 dr) in the enantioselective version, the racemic ones catalysed by DABCO (1,4-diazabicyclo[2.2.2]octane) displayed high diastereoselectivity (7 : 1–24 : 1 dr).

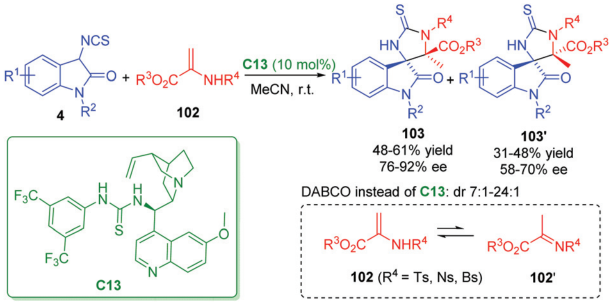
In 2019, the *in situ* generated formaldimines **104′** from 1,3,5-trisubstituted-hexahydro-1,3,5-triazines **104** were applied to the (3 + 2) cyclization process with 3-isothiocyanato oxi-



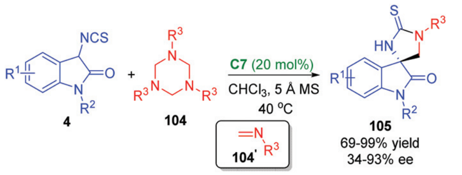
Scheme 27 Asymmetric cyclization of 4-isothiocyanato pyrazolones with isatin-derived ketimines and their synthetic transformations.



Scheme 28 Asymmetric cyclization of 2-isothiocyanato indanones with isatin-derived ketimines and their synthetic transformations.



Scheme 29 Cyclization of 3-isothiocyanato oxindoles with 2-amino acrylates.



Scheme 30 Cyclization of 3-isothiocyanato oxindoles with *in situ* generated formaldimines.

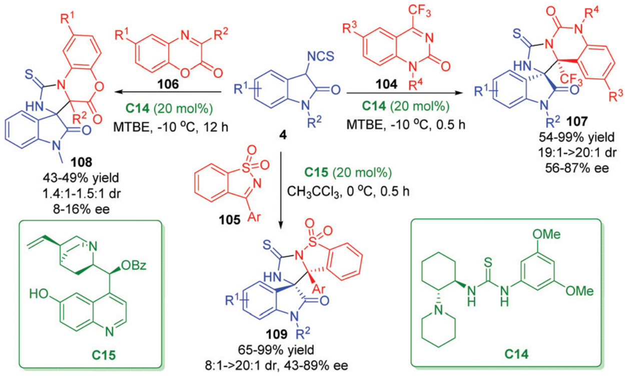
ndoles **4** by Yuan and co-workers (Scheme 30).[37] In the presence of the thiourea catalyst **C7**, a wide range of biologically important spirooxindoles **105** were synthesized efficiently in good yields with high enantioselectivities. It was found that the benzyl-substituted-triazine was not capable to offer the same efficiency of stereoselectivity compared with the aryl-substituted ones.

With their continual efforts on the development of new spirooxindoles with 3-isothiocyanato oxindoles **4**, the same group introduced a series of cyclic ketimines (**104–106**) into the well-developed Mannich/cyclization cascade reaction (Scheme 31).[38] The spiro-fused pentaheterocyclic products **107** were obtained in good yields with moderate to good enantioselectivities *via* the (3 + 2) cyclization of compounds **4** and trifluoromethylketimines **104**. However, when the benzoxazinone derived cyclic ketimines **106** were employed, the corresponding spirocyclic products **108** were afforded with poor stereoselectivities under standard condition. Notably, with the cinchona alkaloid-derived catalyst **C15**, the (3 + 2) cyclization between 3-isothiocyanato oxindoles **4** and saccharin-derived ketimines **105** successfully furnished the polycyclic compounds **109** with moderate to good diastereo- and enantioselectivities.

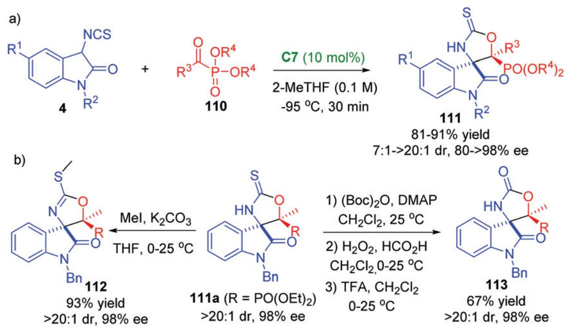
4. Miscellaneous

Compared to the efforts devoted to the development of the Michael/cyclization and Mannich/cyclization cascade reactions involving α-activated cyclic isothiocyanate, other types of enantioselective reaction were rarely investigated since the appearance of Yuan's review.[3] In 2015, Mukherjee and co-workers disclosed an aldol-cyclization cascade reaction between the 3-isothiocyanato oxindoles **4** and α-ketophosphonates **110** (Scheme 32a).[39] With thiourea **C7** as an organocatalyst, a variety of β-amino-α-hydroxyphosphonate derivatives **111** were obtained in high yields with excellent stereoselectivities. In addition, a low temperature and the slow addition of substrates **4** were essential to guarantee the stereoselectivity by suppressing the background reaction. Moreover, the methylation and a three-step protection/oxidation/deprotection sequence of spirooxindole **11a** was conducted to show the synthetic utility, affording oxazoline derivative **112** and oxazolidinyl spirooxindole **113** without loss of enantiopurity, respectively (Scheme 32b).

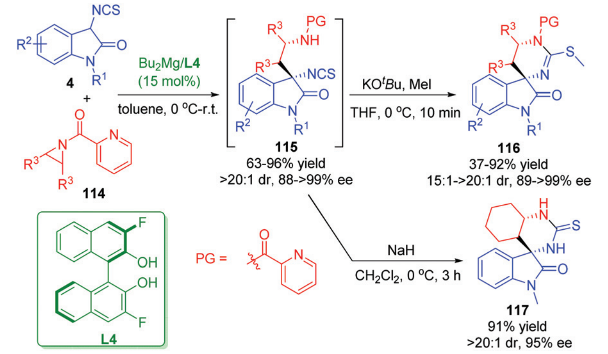
Unlike the uniform (3 + 2) cyclization described above, the Wang group developed a formal (3 + 3) cycloaddition process to construct a six-membered ring (Scheme 33).[40] With the *in situ* generated magnesium catalyst employing the BINOL derivative **L4** as the chiral ligand, the ring-opening of aziridines **114** with 3-isothiocyanato oxindoles **4** afforded the uncyclized products **115** in high yields with excellent enantioselectivities. A series of aziridines with different ring systems and noncyclic aziridines were well-tolerated in the reaction. Notably, without further purification of the crude mixture of **115**, the ring-closure process proceeded efficiently with potass-



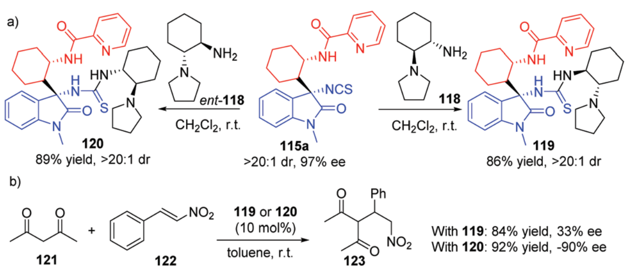
Scheme 31 Cyclization of 3-isothiocyanato oxindoles with cyclic ketimines.



Scheme 32 Aldol-cyclization of 3-isothiocyanato oxindoles with α-ketophosphonates and their synthetic transformations.



Scheme 33 Formal (3 + 3) cycloaddition of 3-isothiocyanato oxindoles with aziridines.



Scheme 34 Catalysts derived from the ring-opening process.

ium *tert*-butoxide and iodomethane, affording pyrimidine derivatives **116** in moderate to high yields with excellent enantioselectivities. Interestingly, treatment of **115** with NaH would directly form the deprotected product **117**. In addition, the ring-opening product **115** was applied to modify amino acids and peptides. Moreover, two novel bifunctional thiourea catalysts **119** and **120** featuring multiple hydrogen-bonding donors were synthesized with the ring-opening product **115a** and the corresponding chiral amine **118** and *ent*-**118**, respectively (Scheme 34a). The investigation of these catalysts with the Michael addition of acetylacetone **121** and nitroalkenes **122** revealed that catalyst **120** matched this reaction well to afford the addition product **123** in 92% yield with 90% ee (Scheme 34b).

5. Conclusions

α-Activated cyclic isothiocyanates have emerged as elegant building blocks to construct spirocycles embedding important pharmacophores. Compared with the well-developed 3-isothiocyanato oxindoles, other α-activated cyclic isothiocyanates, such as 4-isothiocyanato pyrazolones and 2-isothiocyanato indanones, were just developed in recent years, and the related potential reactivities were still under investigation. In addition, the biological activities of these spirocycles synthesized from pharmacophore-based α-activated cyclic isothiocyanates were rarely studied. Thus, in our personal view, the development of new catalytic reactions of α-activated isothiocyanate, as well as new α-activated cyclic isothiocyanate synthons will attract the attention of chemists in the future. Furthermore, the applications of the corresponding new spirocyclic compounds in both organic and medicinal chemistry should be evaluated intensively to show the utility of this chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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