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Catalytic Asymmetric Michael Addition/Cyclization of Isothiocyanato Oxindoles: Highly Efficient and Versatile Approach for the Synthesis of 3,2′-Pyrrolidinyl Mono- and Bi-spirooxindole Frameworks

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The spirooxindole core is a privileged heterocyclic ring system featured in a large number of natural or synthetic compounds with diverse and important biological profiles. It has therefore drawn tremendous interest from synthetic and medicinal chemists.[1] Among the different types of the spirooxindoles,[2] the pyrrolidinyl spirooxindole framework has recently become one of the most important synthetic subjects because of its significant medicinal relevance, and a number of elegant works have been reported for its catalytic asymmetric synthesis.[3] However, most of the synthetic targets are restricted to 3,3′-pyrrolidinyl spirooxindoles, and the catalytic enantioselective synthesis approaches toward the 3,2′-pyrrolidinyl spirooxindoles with a nitrogen atom adjacent to the spiro-carbon atom[4] are very limited.

Compounds with the 3,2′-pyrrolidinyl spirooxindole frameworkhave shown a wide spectrum of considerable bioactivities, such as anti-microbial, anti-tumor, anti-inflammatory, and acetylcholinesterase (AChE) inhibitory activities (Figure 1).[5] Synthetic methods to access these motifs are mainly confined to azomethine ylide cycloaddition of racemic or enantiopure reactants, and this limitation is a large obstacle to medicinal chemistry research development of these compounds.[6] So far only two methods, an azomethine ylide cycloaddition and an N-heterocyclic carbene (NHC)-catalyzed annulation, for the catalytic asymmetric construction of the 3,2′-pyrrolidinyl spirooxindole skeleton have been reported by the groups of Gong and Chi, respectively, and more efficient and accessible methodology towards these synthetic targets is still highly in demand.[7] Herein, we report the development of a new synthetic method for the catalytic asymmetric construction of the 3,2′-pyrrolidinyl spirooxindole framework with high efficiency. Moreover, as oxindole-based bi-spiro motifs have been found to be present in many bioactive compounds, we also identified the validity of this method for the synthesis of this architecture.[2j,l] Gratifyingly, this method was excellent for the construction of a series of complex bi-spirooxindole derivatives with three contiguous stereocenters, including two spiro-quaternary chiral carbon atoms (Scheme 1).

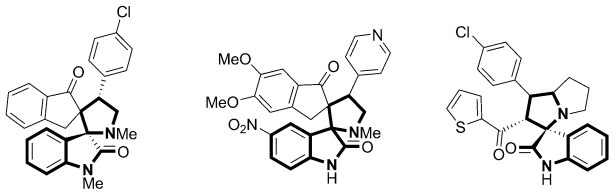
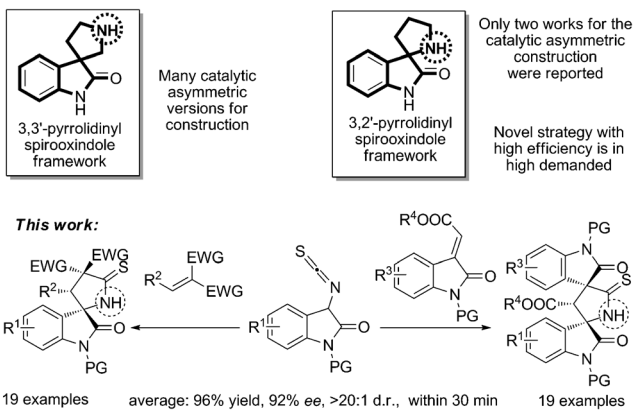


Figure 1. Bioactive compounds containing the 3,2′-pyrrolidinyl spirooxindole framework.



Scheme 1. Previous studies on the construction of the pyrrolidinyl spirooxindole framework, and the cyclization reaction with isothiocyanato oxindole reported herein. EWG = electron-withdrawing group, PG = protecting group.

Recently, α-isothiocyanato compounds were employed not only for the synthesis of chiral β-hydroxy-α-amino acid and α, β-diamino acid derivatives,[8] but also for the enatioselective construction of spirooxindoles.[3d,e,9] Very recently, Shibasaki, Kanai, and co-workers developed an asymmetric

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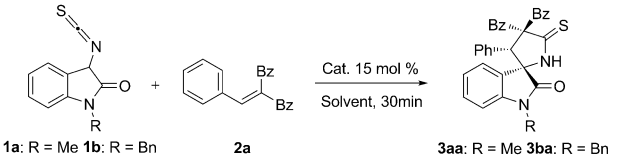
Mannich-type reaction of isothiocyanato oxindoles for the synthesis of the enantiopure imidazoline spirooxindole framework that contains a nitrogen atom at the C3′ position.[4a] However, the Michael-type reaction of isothiocyanato oxindoles has never been reported to our knowledge, although it is a promising route for the construction of the medicinally relevant 3,2′-pyrrolidinyl spirooxindole derivatives. As part of our ongoing work on the development of new methods for chiral spirooxindole synthesis with α-isothiocyanato compounds,[3e,9a] we herein report the first catalytic asymmetric Michael addition/cyclization reaction between isothiocyanato oxindoles and electron-deficient olefins for construction of the 3,2′-pyrrolidinyl spirooxindole framework.

On the basis of our recent success in asymmetric organocatalysis by using bifunctional thiourea catalysts,[10,11] we surmised that this kind of organocatalyst would be suitable for catalyzing the Micheal addition/cyclization in a double-activation manner. The initial investigation began with the reaction between isothiocyanato oxindole **1a** and the electron-deficient olefin **2a** in CH_2Cl_2 at room temperature in the presence of a catalyst at a 15 mol% loading (Table 1). Several cyclohexanediamine-derived bifunctional thiourea catalysts were first screened. Although the catalysts **L1**–**L3** gave the desired product **3aa** with excellent yield and diastereoselectivity, the enantioselective control was poor, indicating that this type of structural scaffold is not suitable for the reaction in terms of stereochemistry (Table 1, entries 1–3). We then tested the cinchona alkaloid-derived thiourea bifunctional catalysts (**L4** and **L5**).[12] To our delight, compared to **L4**, quinidine-derived catalyst **L5**, which contains a bulkier dehydroabietic amine moiety and was developed in our group, gave the product with a much higher enantioselevtivity (*ee*), as well as the same excellent yield and diastereoselectivity (d.r.; Table 1, entries 4–5). Further screening of the solvents revealed that Et_2O was better than other solvents (Table 1, entries 6–8), and lowering the reaction temperature to 0°C resulted in a higher *ee* without obviously sacrificing the reaction rate (89% *ee*, Table 1, entry 9). Variation of the N-protecting group of the isothiocyanato oxindole had slight effect on the enantioselectivity and the N-benzyl substrate **1b** gave a higher *ee* (92% *ee*, Table 1, entry 10).

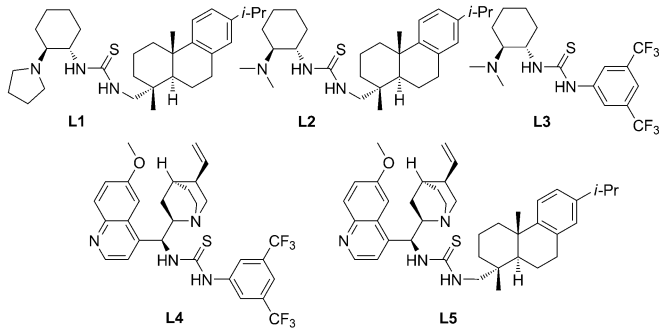
With the optimal reaction conditions established, the generality of the catalytic asymmetric cyclization reaction was next investigated by using a series of electron-deficient olefins **2** and isothiocyanato oxindoles (Table 2). Various olefin derivatives with either electron-withdrawing or electron-donating groups at the *para*-, *meta*-, or even sterically hindered *ortho*-position on the aromatic ring were tolerated and gave the corresponding cycloadducts in excellent chemical yield, excellent diastereoselectivity, and good to excellent enantioselectivity (Table 2, **3ba**–**3bk**). In addition, reactions with substrates **2**, which contain sterically hindered 1-naphthyl, as well as various heteroaromatic rings also proceeded smoothly to give the products with good results (except for **3bn**, which was only obtained with a moderate *ee*). Because the oxindole–indole backbone is found in many medicinally active compounds, an olefin substrate with an indole heterocycle was also tested in this process and, gratifyingly, it gave the products in 99% yield, >20:1 d.r., and 96% *ee* (Table 2, entries 12–15). An aliphatic-substituted substrate also proved to be amenable to this method, and the corresponding product was obtained with an excellent result in terms of yield and stereocontrol (Table 2, entry 16). In addition to **1b**, both the electron-donating and -withdrawing substituted isothiocyanato oxindoles gave the respective cycloadducts with good results (Table 2, entries 18 and 19). The versatile thiocarbonyl group of these products can be easily modified by several different transformations, such as alkylation–sulfur extrusion,[13] reductive desulfuration, oxidization,[3e] and so on.

Encouraged by the successful synthesis of 3,2′-pyrrolidinyl spirooxindole derivatives as described above, we attempted to extend this approach for the construction of more complex bi-spirooxindoles with three contiguous stereocenters, including two spiro-quaternary chiral carbon atoms, that also showed significant medical relevance. The model reaction was performed between isothiocyanato oxindole and

Table 1. Optimization of the reaction.[a]



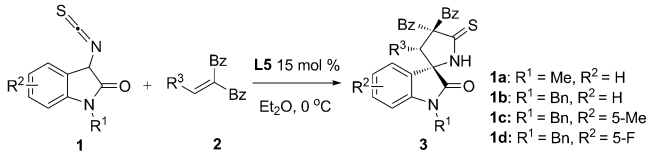
Screened thiourea bifunctional catalyst:



Entry	Cat.	Solvent	*T* [°C]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	**L1**	CH_2Cl_2	RT	**3aa**, 90	>20:1	20
2	**L2**	CH_2Cl_2	RT	**3aa**, 93	>20:1	9
3	**L3**	CH_2Cl_2	RT	**3aa**, 85	12:1	21
4	**L4**	CH_2Cl_2	RT	**3aa**, 95	>20:1	20
5	**L5**	CH_2Cl_2	RT	**3aa**, 92	>20:1	79
6	**L5**	Et_2O	RT	**3aa**, 94	>20:1	84
7	**L5**	PhMe	RT	**3aa**, 94	>20:1	83
8	**L5**	MeCN	RT	**3aa**, 87	20:1	82
9	**L5**	Et_2O	0	**3aa**, 95	>20:1	89
10	**L5**	Et_2O	0	**3ba**, 99	>20:1	92

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1** (1.0 equiv), **2** (1.1 equiv), and catalyst (15 mol%) in solvent (1 mL) for 30 min. [b] Yield of isolated major diastereoisomer of product. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

Table 2. Scope of the catalytic asymmetric synthesis of 3,2′-pyrrolidinyl spirooxindole derivatives.[a]

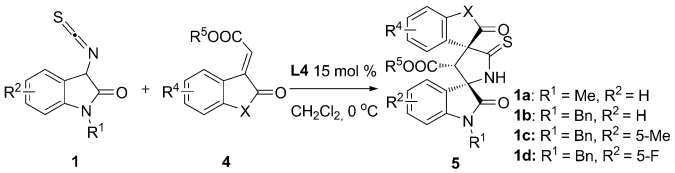


1 2 3

Entry	R^3	1	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	Ph	**1b**	**3ba**, 99	>20:1	92
2	4-F-C_6H_4	**1b**	**3bb**, 99	>20:1	92
3	4-Cl-C_6H_4	**1b**	**3bc**, 99	>20:1	93
4	2,4-diCl-C_6H_4	**1b**	**3bd**, 97	>20:1	93
5	4-Br-C_6H_4	**1b**	**3be**, 96	>20:1	92
6	3-Br-C_6H_4	**1b**	**3bf**, 98	>20:1	89
7	2-Br-C_6H_4	**1b**	**3bg**, 91	>20:1	94
8	4-NO_2-C_6H_4	**1b**	**3bh**, 90	>20:1	93
9	4-MeO-C_6H_4	**1b**	**3bi**, 90	>20:1	93
10	3-MeO-C_6H_4	**1b**	**3bj**, 99	>20:1	90
11[e]	2-Me-C_6H_4	**1b**	**3bk**, 92	>20:1	93
12	1-naphthyl	**1b**	**3bl**, 86	>20:1	89
13	2-thienyl	**1b**	**3bm**, 88	>20:1	89
14	2-furyl	**1b**	**3bn**, 98	>20:1	78
15[f]	3-indolyl	**1b**	**3bo**, 99	>20:1	96
16	$(CH_3)_2CHCH_2$-	**1b**	**3bp**, 94	>20:1	92
17	Ph	**1a**	**3aa**, 95	>20:1	89
18	Ph	**1c**	**3ca**, 99	>20:1	92
19	Ph	**1d**	**3da**, 90	>20:1	90

[a] Unless otherwise specified, the reaction was performed on 0.1 mmol scale with **1** (1.0 equiv), **2** (1.1 equiv), and catalyst **L5** (15 mol%) in Et_2O (1 mL) in an ice bath for 30 min. [b] Yield of isolated major diastereoisomer of product. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The reaction time was 1 h. [f] The reaction time was 4 h.

Table 3. Scope of the catalytic asymmetric synthesis of 3,2′-pyrrolidinyl bi-spirooxindole derivatives with three contiguous stereocenters, including two spiro-quaternary chiral carbons.[a]



1 4 5

Entry	R^4, R^5, X	1	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	H, Et, NMe	**1b**	**5ba**, 99	>20:1	97
2	5-F, Et, NMe	**1b**	**5bb**, 98	>20:1	95
3	7-F, Et, NMe	**1b**	**5bc**, 99	>20:1	93
4	5-Cl, Et, NMe	**1b**	**5bd**, 99	>20:1	92
5	6-Cl, Et, NMe	**1b**	**5be**, 95	>20:1	86
6	7-Cl, Et, NMe	**1b**	**5bf**, 99	>20:1	98
7	5-Br, Et, NMe	**1b**	**5bg**, 92	>20:1	93
8	5-OCF_3, Et, NMe	**1b**	**5bh**, 95	>20:1	93
9	5-Me, Et, NMe	**1b**	**5bi**, 96	13:1	95
10	5-MeO, Et, NMe	**1b**	**5bj**, 96	13:1	94
11	5-Cl 7-Me, Et, NMe	**1b**	**5bk**, 93	>20:1	96
12	H, Bn, NMe	**1b**	**5bl**, 99	>20:1	91
13	H, *t*Bu, NMe	**1b**	**5bm**, 93	>20:1	92
14	H, Et, NBn	**1b**	**5bn**, 96	>20:1	86
15	H, Et, N−Allyl	**1b**	**5bo**, 94	>20:1	94
16	H, Et, S	**1b**	**5bp**, 95	>20:1	90
17	H, Et, NMe	**1a**	**5aa**, 99	>20:1	94
18	H, Et, NMe	**1c**	**5ca**, 95	>20:1	95
19	H, Et, NMe	**1d**	**5da**, 94	>20:1	95

[a] Unless otherwise specified, the reaction was performed on 0.1 mmol scale with **1** (1.0 equiv) **4** (1.1 equiv), and catalyst (15 mol%) in CH_2Cl_2 (2 mL). Compound **1** in 1 mL solvent was added to the reaction over 30 min. The reaction was complete after the addition of **1**. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by ^1H NMR spectroscopic analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

methyleneindolinone, and the reoptimized conditions are shown in Table 3. In contrast, the quinidine-derived thiourea catalyst **L4**, which has a smaller steric moiety than **L5** (see the Scheme in Table 2), was superior for this process, presumably due to the fact that the smaller catalyst **L4** was more compatible for the catalyst–substrate transition state, which has increasing steric hindrance when the bulkier electron-deficient olefin substrate **4** is used. Under the optimized reaction conditions, a variety of bi-spirooxindoles were synthesized and the results are summarized in Table 3. Both electron-donating and electron-withdrawing substituents on methyleneindolinone at different positions on the aromatic ring gave the corresponding products in excellent yield, diastereoselectivity, and good to excellent enantioselectivity (Table 3, entries 1–11). Steric tuning of either the ester group or the nitrogen protecting group on **4** had little effect on the yield and stereoselectivity of the reaction (Table 3, entries 12–15). It is worth noting that when the nitrogen atom of methyleneindolinone was replaced by sulfur, the reaction also proceeded smoothly, providing the product **5bp** with excellent results (Table 3, entries 16). Isothiocyanato oxindoles with different substituents are also tolerated and gave the respective products in excellent yield, d.r., and *ee* (Table 3, entries 17–19). The absolute configuration of product **5aa** was unambiguously determined by X-ray crystallography.[14]

In summary, a highly efficient bifunctional thiourea-catalyzed asymmetric Michael addition/cyclization reaction of isothiocyanato oxindoles has been successfully developed. This versatile process provides a promising approach not only for the enantioselective construction of functionalized 3,2′-pyrrolidinyl spirooxindole derivatives (up to 99% yield, >20:1 d.r., and 96% *ee*), but also for the synthesis of enantiopure bi-spirooxindoles with three contiguous stereocenters, including two spiro-quaternary chiral centers (up to 99% yield, >20:1 d.r., and 98% *ee*). The enantioselective structurally diverse synthesis presented herein offers an unprecedented platform for medicinal chemistry studies of those biologically important 3,2′-pyrrolidinyl spirooxindoles, as well as their bi-spirooxindole derivatives. Further studies on expanding the application of this method and the biological evaluation of these pyrrolidinyl spirooxindole derivatives are in progress.

Experimental Section

General procedure: Catalyst **L4** (0.015 mmol, 15 mol%) and **4a** (0.11 mmol, 1.1 equiv) were dissolved in CH_2Cl_2 (1 mL) in the ice bath. A solution of **1b** (0.10 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) was added to the reaction over 30 min by a constant-flow pump. After the complete addition of **1b**, the mixture was purified by column chromatography on silica gel to obtain desired product.

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Keywords: asymmetric synthesis · heterocycles · organocatalysis · oxindoles · spiro compounds · synthetic methods

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