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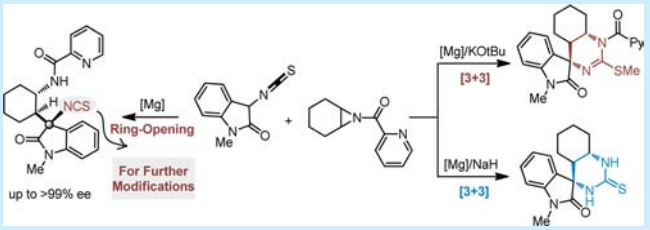
Catalytic Enantioselective Ring-Opening and Ring-Closing Reactions of 3-Isothiocyanato Oxindoles and *N*-(2-Picolinoyl)aziridines

Linqing Wang,† Dongxu Yang,† Dan Li, and Rui Wang*

Key Laboratory of Preclinical Study for New Drugs of Gansu Province, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: 3-Isothiocyanato oxindoles have been successfully applied to an asymmetric formal [3 + 3] cycloaddition reaction with aziridines for the first time. The reaction was efficiently mediated by an in situ generated magnesium catalyst employing (*R*)-3,3′-fluorous-BINOL as a simple chiral ligand. Serials of polycyclic frameworks could be obtained after a ring-closing step. The enantioenriched ring-opening product was also utilized to modified amino acids, peptides, and bifunctional organocatalyst.



In recent years, α-isothiocyanato compounds have emerged as one attractive reactant in asymmetric formal [3 + 2]-cycloaddition reactions resulting in the formation of five-membered heterocyclic rings (Figure 1a). Aldol-, Mannich-, and Michael-cyclization sequences have been successfully applied to the five-membered ring's formation with α-isothiocyanato compounds.[1] However, to the best of our knowledge, other types of asymmetric reactions of α-isothiocyanato compounds have not been successfully investigated. We recently tried the reaction between α-isothiocyanato compounds and aziridines to furnish a formal [3 + 3]-cycloaddition; unfortunately, we only obtained the product through nucleophilc addition of the sulfur atom of α-isothiocyanato compounds.[2] To date, the reactivity and stereoselectivity in the reaction of α-isothiocyanato compounds and aziridines is still challenging and unresolved. On the basis of our recent work on asymmetric ring-opening reactions of *N*-(2-picolinoyl)aziridines,[3,4] herein we report the first example of enantioselective formal [3 + 3]-cycloaddition reactions of α-isothiocyanato compounds with aziridines, and we also tried to apply the enantioenriched ring-opened product in modification of peptides and organocatalyst (Figure 1, b).

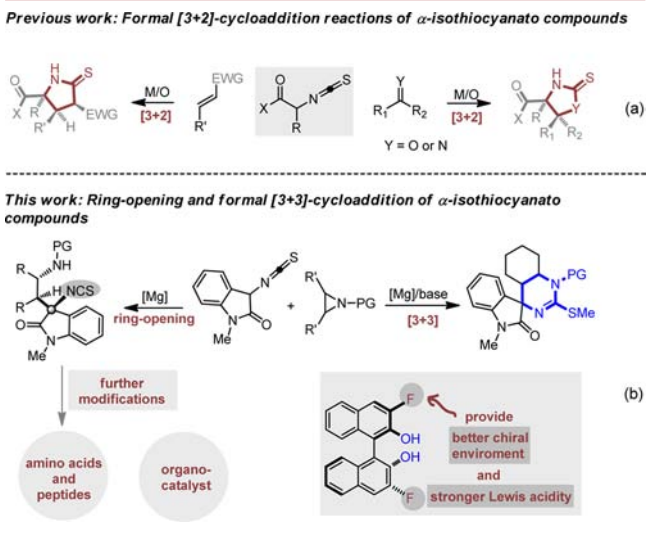
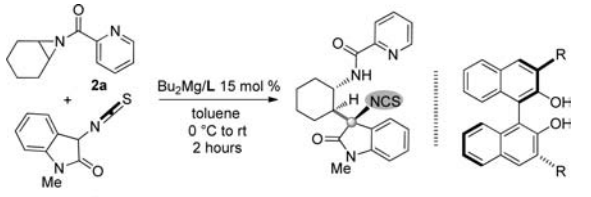


Figure 1. Reaction types of α-isothiocyanato compounds and our development.

Table 1. Optimized Conditions of the Ring-Opening Reactions



entry[a]	L (R)	yield[b] (%)	dr[c]	ee[d] (%)
1	**L1** (H)	39	>20:1	84
2	**L2** (Ph)	24		5
3	**L3** (Br)	57	>20:1	86
4	**L4** (Cl)	86	>20:1	95
5	**L5** (F)	**96**	**>20:1**	**97**
6		complex mixture		

[a]Reactions were performed with **1a** (0.11 mmol) and **2a** (0.10 mmol) in toluene (1.0 mL) in the presence of L and Bu_2Mg (15 mol %) at 0 °C for 1 h and then at rt for 1 h. [b]Isolated yield. [c]Determined by ^1H NMR (300 MHz) of the crude reaction mixtures. [d]Analyzed by chiral stationary-phase HPLC.

Our initial investigation began with the reaction between 3-isothiocyanato oxindoles **1a** and *N*-(2-picolinoyl)aziridine **2a** by

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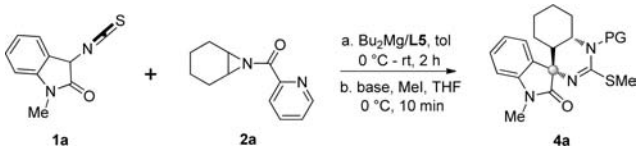
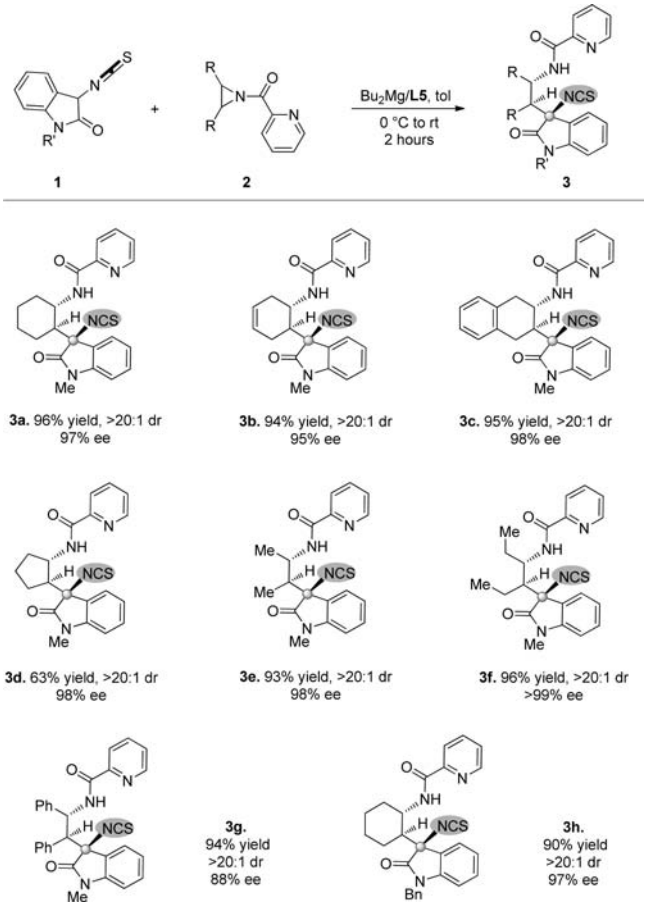
Table 2. Optimized Conditions of the Ring-Closure Step



entry[a]	base	conversion[b] (%)	dr	ee (%)
1	K_2CO_3	0		
2	Et_3N	0		
3	DBU	19		
4	NaO*t*Bu	100 (85)	>20:1	94
5	NaOMe	<10		
6	**KO^{t}Bu**	**100 (92)**	**>20:1**	**94**

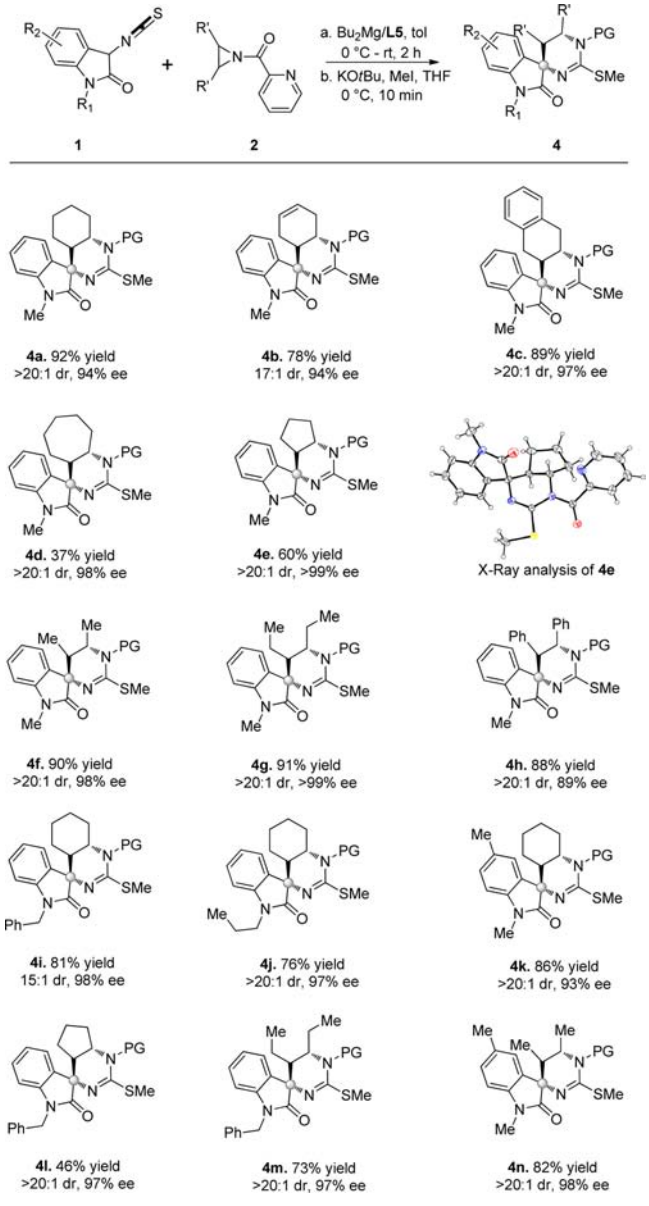
[a]See the Supporting Information for reaction details. [b]Conversions were determined by ^{1}H NMR (300 MHz); due to the ring-closing product **4a**, the mixtures cannot be separated with **3a** by TLC analysis.

Scheme 1. Substrate Scope of the Ring-Opening Reactions[a]



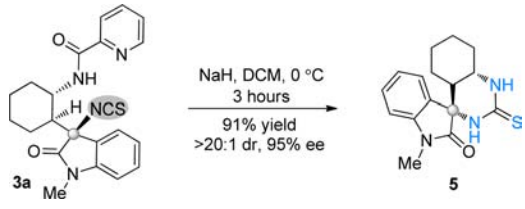
[a]Reactions were performed with **1** (0.22 mmol) and **2** (0.20 mmol) in toluene (2.0 mL) in the presence of **L5** and Bu_2Mg (15 mol %) at 0 °C for 1 h and then at rt for 1 h.

Scheme 2. Substrate Scope of the Formal Cycloaddition Reactions[a]



[a]See the Supporting Information for reaction details.

Scheme 3. Ring-Closure and Deprotection Sequence of the Ring-Opening Product 3a



evaluating the in situ generated magnesium catalyst[5] forming with BINOL derivatives and Bu_2Mg. To our delight, the corresponding ring-opening product **3a** could be generated with an acceptable ee value and moderate yield by employing commercially available (*R*)-BINOL as a simple chiral ligand (Table 1, entry 1). Next, a reasonable trial of (*R*)-3,3′-phenyl-BINOL (**L2**) was carried through the same reaction conditions. However, to our disappointment, both the reactivity and enantioslectivity of the model reaction were dramatically decreased while more unidentified products were obtained (Table 1, entry 2). After analysis of the above results, we envisaged that the normal change of 3,3′-substituted-Binol to more sterically hindered groups might not be a good choice by comparison of the results from chiral ligands equipped with hydrogen and phenyl. Thus, we turned our attention to test

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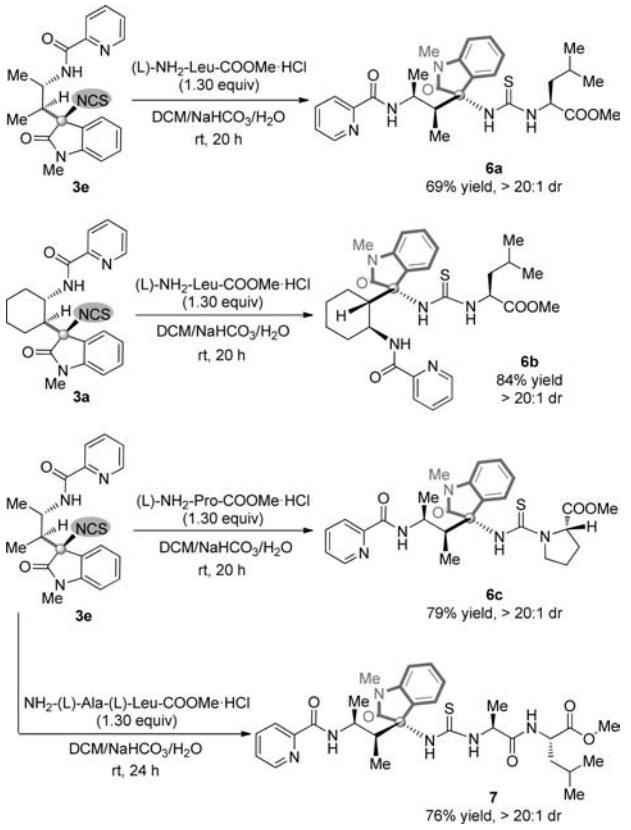
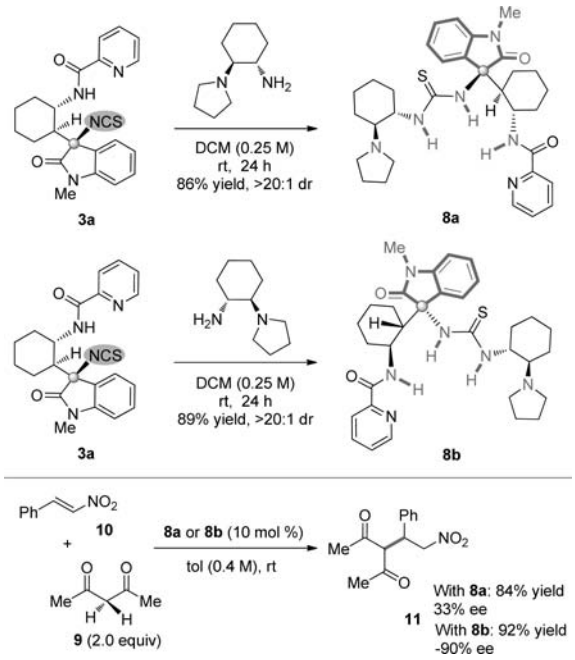
Scheme 4. Modification of Amino Acids and Peptides Using the Ring-Opening Product



Scheme 5. Synthesize of Chial Thioureas Using 3a



3,3′-halogenated-Binol in the current reaction.[6] As shown in Table 1, a promising result was obtained with respect to the chemical yield (57%) and enantioselectivity (86% ee) when (*R*)-3,3′-brominated-BINOL (**L3**) was employed as a chiral ligand. A further screening process following our plan fortunately identified of the optimal fluorous-substituted ligand **L5**. The ee value was strongly increased to 97%. Moreover, we were pleased to find the reactivity of the reaction was also further enhanced, which might be owing to the relative higher Lewis acidity of the fluorous-substituted phenol type ligand.[7]

After building the optimized conditions of the enantioselective ring-opening reactions between 3-isothiocyanato oxindoles **1a** and *N*-(2-picolinoyl) aziridine **2a**, we next focused on accomplishing the cyclization step to generate chiral six-membered heterocyclic rings by evaluating the effect of series of simple bases. As the results summarized in Table 2 show, K_2CO_3, Et_3N, DBU, and NaOMe were found to be less effective at promoting this cyclization step, as often no or only a trace amount of cyclization product was observed by ^1H NMR (Table 2, entries 1, 2, 3, and 5). When NaO^{t}Bu or KO^{t}Bu was used, the cyclization reaction could proceed smoothly at 0 °C to give the formal [3 + 3] cycloaddition product **4a** in excellent yield with slightly decreased ee value (94%) (Table 2, entries 4 and 6).

Having established the optimized methods for both of the enantioselective ring-opening reactions and the ring-closing step, next, the substrate generality of two types of products was investigated. The substrate scope of this catalytic asymmetric ring-opening reaction between 3-isothiocyanato oxindoles and *N*-(2-picolinoyl)aziridines is summarized in Scheme 1. In general, the ring-opening products could be obtained in good chemical yields and excellent enantioselectivities with respect to different ring systems and noncyclic aziridines. However, it is notable that the five-membered aziridine showed lower reac tivity and led to the desired ring-opening product **3d** with a moderate yield (Scheme 1, **3d**).

Next, the results of experiments in which series of enantioenriched pyrimidine derivative rings were synthesized under the optimized reaction conditions were analyzed. The experiments showed that variation of the ring systems of the *N*-(2-picolinoyl)aziridines were generally tolerated, affording the desired ring-closing products with excellent diastereoselectivities and enantioselectivities (94% → 99% ee) in moderate to good yields (Scheme 2, **4a**−**e**). The absolute stereochemistry of the corresponding polycyclic system **4e** was unambiguously determined to be (*S*,*S*,*S*) by an X-ray crystallographic analysis. Noncyclic *N*-(2-picolinoyl)aziridines were also tested in the reaction sequence while affording good to excellent yields and enantioselectivities (**4f**−**h**). Furthermore, some representative 3-isothiocyanato oxindoles were also analyzed in cross reactions with several *N*-(2-picolinoyl)aziridines, affording corresponding cyclization products with excellent eanatioselectivies (**4i**−**n**). Moreover, to our delight, the deprotected product **5** could be easily accessed by treated the ring-opening product **3a** with NaH at mild reaction conditions with slightly decreasing enantioselectivity (Scheme 3).

We then tried to utilize the ring-opening products containing an isothiocyano group to modify amino acids and peptides (Scheme 4). The remaining isothiocyano group in the ring-opening products was easily coupled with the amino group of leucine or proline methyl esters, and a modification example of dipeptide is also shown, thereby achieving the corresponding modified amino acids and peptide with chiral embellished capping at *N*-terminus.[8]

Furthermore, the ring-opening product was utilized to synthesize the organocatalyst. Novel bifunctional amine-thioureas bearing multiple hydrogen-bonding donors[9] were synthesized employing the ring-opening product **3a** (Scheme 5), and the catalytic efficiency of the novel bifunctional

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thioureas **8a** and **8b** was further evaluated by using a model Michael reaction between acetylacetone **9** and nitroalkenes **10**. The relative stereochemistry of the catalyst plays a key role in introducing high enantioselectivities, and the experiments showed that the (*R*,*R*)-cyclohexanediamine moiety was well matched with the ring-opening product **3a** and led to the corresponding conjugate Michael product **11** with remarkably higher ee values.

In summary, we have realized the catalytic enantioselective ring-opening reaction between 3-isothiocyanato oxindoles and aziridines for the first time. Furthermore, this catalytic asymmetric approach was successfully applied to build enantioenriched pyrimidine derivatives by a tandem ring-closing reaction sequence, and the ring-opening product could be utilized to modify amino acids, peptides, and bifunctional organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, X-ray crystal structure, and the CIF files of **4e**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01291.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangrui@lzu.edu.cn.

Author Contributions

†L.W. and D.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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