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Catalytic Enantioselective Ring-Opening Reaction of *meso*-Aziridines with α-Isothiocyanato Imides

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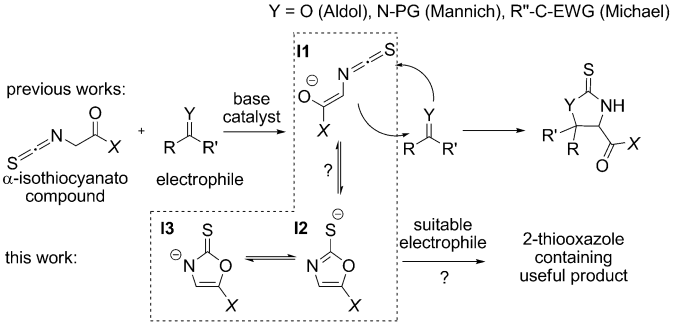
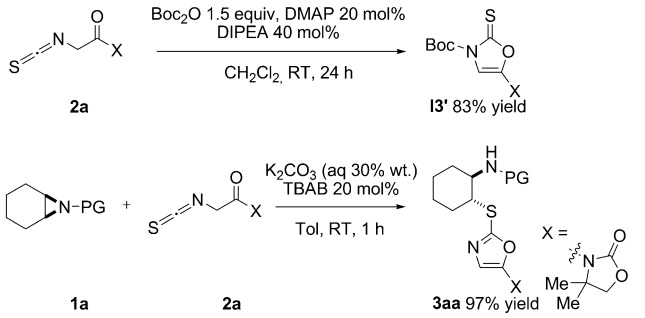
Catalytic asymmetric transformations employing α-isothiocyanato compounds have recently been successful and have captured considerable attention as powerful methods for the synthesis of various kinds of useful chiral compounds. By using this kind of versatile reactant as the nucleophile, the enantioselective Aldol-type,[1] Mannich-type,[2] and Michael addition reactions[3] have been developed to access the highly optically active β-hydroxy/amino-α-amino acid derivatives and spiro compounds. In a general mode of these reactions, the α-isothiocyanato compounds serve both as a nucleophile and electrophile; they are enolized by deprotonation at their α-carbon atom by a base catalyst and then nucleophilic attack at the electron-deficient double bonds (ketone/aldehyde, imine, or olefin). The anion (O, N, or C) generated in the addition process is subsequently quenched by the electron-deficient carbon atom in the isothiocyanate moiety.[4] Based on the above-mentioned reaction course, we hypothesized that the enolized α-isothiocyanato compounds intermediate (Scheme 1, **I1**) might also be able to self-cyclize by trapping the oxygen anions of the enolate by the isothiocyanate. Thus, the enolized intermediate undergoes an equilibrium in α-isothiocyanate–thiooxazole (**I2**, **I3**) tautomerism. As the electrophiles employed in previous work were all restricted to electron-deficient double bonds, which prefer to undergo the nucleophilic attack by the enolate, no adducts of thiols were isolated. We envisaged that if a kind of appropriate electrophile were used to trap the thiooxazole intermediate (**I2**), not only the scope of reaction type of the versatile α-isothiocyanato compounds could be extended, but also a new methodology for



Scheme 1. Proposed reaction mode of α-isothiocyanato compounds.

the synthesis of useful 2-thiooxazole-containing organic molecules could be developed.

To test our hypothesis, α-isothiocyanato imide **2a** was treated with *tert*-butoxycarbonyl (Boc) anhydride and 4-dimethylaminopyridine (DMAP) in the presence of catalytic *N*,*N*-diisopropylethylamine (DIPEA) at room temperature in CH_2Cl_2 (Scheme 2). To our delight, the product **I3′** was isolated in 83% yield, thus demonstrating the existence of the thiooxazole intermediate under the basic conditions. We



Scheme 2. Trapping the thiooxazole intermediate by aziridine ring opening. PG = 3,5-dinitrobenzoyl.

then focused on the development of a suitable reaction that is able to trap the desired intermediate and afford the products with practical significance. Aziridines are considered to be very useful precursors for the production of a variety of chiral amines by the asymmetric nucleophilic ring-opening reaction.[5] Different kinds of nucleophiles were employed in the catalytic enantioselective ring opening of *meso*-aziri-

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dines.[6] Recently, the catalytic asymmetric *meso*-aziridine ring opening with sulfur-based nucleophiles has also been developed,[7] the chiral β-aminosulfur adducts of such reactions have considerable usefulness both in drug development and asymmetric catalysis (chiral ligand synthesis).[8] However, the sulfur-based nucleophiles used in the enantioselective ring-opening reaction are mainly confined to thiophenols and their derivatives, and this substrate scope limitation is a large obstacle of such methodology for the synthesis of diverse chiral β-aminosulfur adducts. We envisioned that an activated *meso*-aziridine would prefer to undergo the sulfur-based nucleophilic attack of the thiooxazole intermediate **I2** rather than the enolate **I1** generated from the α-isothiocyanato imide (see Scheme 1) and such a reaction not only can extend the scope of thiol nucleophiles in the aziridine ring-opening process, but also provides β-aminothiooxazole compounds with significant biological activities (Figure 1).[9] To explore the feasibility of the proposed transformation, aziridine **1a** and α-isothiocyanato imide **2a** were chosen for the model reaction. Gratifyingly, in the presence of K_2CO_3 and catalytic tetra-*n*-butylammonium

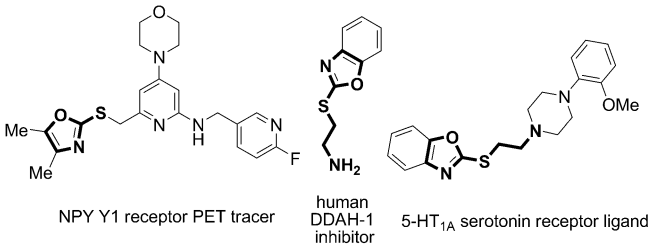
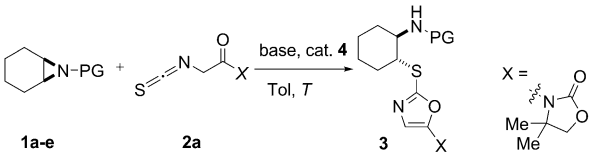


Figure 1. Bioactive 2-thiooxazole or β-aminothiooxazole containing compounds.

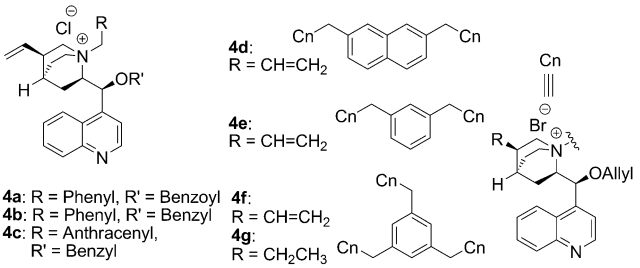
bromide (TBAB), the reaction proceeded smoothly in toluene at room temperature, providing the adduct **3aa** in 97% yield (Scheme 2).[10]

Encouraged by the successful synthesis β-aminothiooxazole adduct **3aa**, we decided to develop an asymmetric version of such a transformation, since the acquirement of optically active products would be vital for its application on the synthesis of bioactive compounds as well as chiral ligands. As it was demonstrated above that the reaction proceeded efficiently by using phase-transfer catalysis (PTC), our initial investigation began with the reaction between *meso*-aziridines **1** and isothiocyanato imide **2a** in PTC conditions at room temperature in the presence of a chiral quaternary ammonium salt at a 20 mol% loading (Table 1).[11,12] To our delight, readily accessible cinchona alkaloid-type catalyst **4a** in combination with solid K_2CO_3 gave the desired product in excellent yield and a promising 50% enantiomeric excess (*ee*) (Table 1, entry 2). However, the further steric tuning of the catalyst **4a** did not achieve a more satisfactory result (entries 3, 4). To address the need for enhanced enatioselectivity, we then screened various cinchona alkaloid-based dimeric or trimeric quaternary ammonium salts, which may

Table 1. Optimization of the asymmetric ring opening.[a]



1a: PG = 3,5-dinitrobenzoyl
1b: PG = 3,5-di-*tert*-butylbenzoyl
1c: PG = 4-*tert*-butylbenzoyl
1d: PG = tosyl
1e: PG = 3,5-bis(trifluoromethyl)benzenesulfonyl



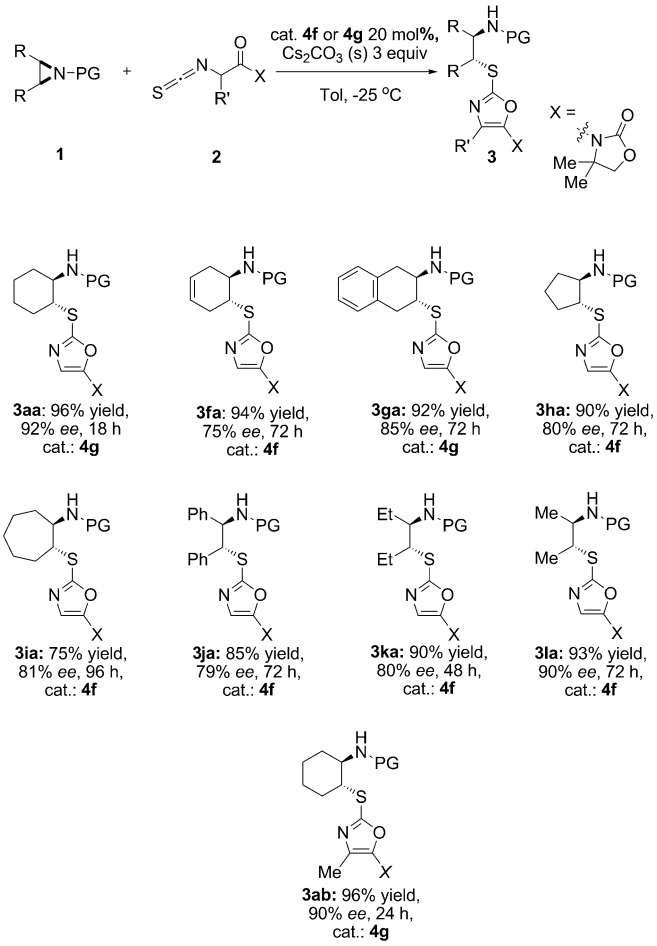
Entry	**1**	Cat.	Base	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	**4a**	K_2CO_3 (aq) 30% wt.	RT	93	40
2	**1a**	**4a**	K_2CO_3 (s)	RT	98	50
3	**1a**	**4b**	K_2CO_3 (s)	RT	99	48
4	**1a**	**4c**	K_2CO_3 (s)	RT	85	43
5	**1a**	**4d**	K_2CO_3 (s)	RT	93	19
6	**1a**	**4e**	K_2CO_3 (s)	RT	95	55
7	**1a**	**4f**	K_2CO_3 (s)	RT	96	66
8	**1b**	**4f**	K_2CO_3 (s)	RT	95	3
9	**1c**	**4f**	K_2CO_3 (s)	RT	94	36
10	**1d**	**4f**	K_2CO_3 (s)	RT	98	47
11	**1e**	**4f**	K_2CO_3 (s)	RT	99	35
12	**1a**	**4f**	Cs_2CO_3 (s)	RT	99	70
13[d]	**1a**	**4f**	Cs_2CO_3 (s)	−40	93	92
14[e]	**1a**	**4g**	Cs_2CO_3 (s)	−25	96	92

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1** (1.1 equiv), **2** (1.0 equiv), base (3.0 equiv), and catalyst (20 mol%) in solvent (4 mL). The reaction time was 1 h. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction time is 72 h. [e] The reaction time is 18 h.

provide a stronger chiral environment for the reaction transition state.[13] It was recognized that the distance between the quaternary ammonium catalytic centers was crucial for the stereocontrol, since although **4d** afforded a very poor result (entry 5), the catalyst **4e** with a relatively shorter distance between ammonium ion gave the product in an increased 55% *ee* (entry 6). The trimeric catalyst **4f** with a bulkier environment gave the product with the best enatioselectivity (66% *ee*, entry 7). Variation of the protecting group on *meso*-aziridines **1** had significant effect on the result in terms of stereochemical control (entries 7–11), and the 3,5-di-*tert*-butylbenzoyl-protected substrate **1b** furnished the product in an almost racemic form (entry 8). It was revealed that the strong electron-withdrawing 3,5-dinitrobenzoyl group was the most suitable one in this process. A further increased *ee* was achieved when Cs_2CO_3 was used (entry 12). Lowering the temperature had a dramatically incremental effect on the enatioselectivity. When the reaction

was conducted at −40 °C, it gave the product in a satisfactory 92 % *ee*, despite the longer time needed for the completion of the reaction (entry 13).[14] Additionally, the dihydrocinchonine-based trimeric catalyst **4g** was also tested in the model reaction, and the product was afforded with the same excellent results as **4f** produced, but in a shorter time with a milder temperature (entry 14).

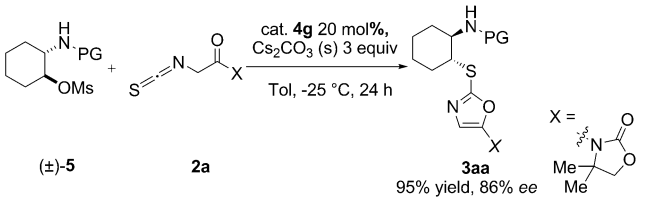
With the optimized reaction conditions in hand, the substrate scope of the catalytic asymmetric ring-opening reaction was next investigated and a series of chiral β-aminothiooxazole compounds were synthesized (Scheme 3). Besides **1a**, other types of six-membered ring *meso*-aziridines



Scheme 3. Synthesis of chiral β-aminothiooxazole compounds. Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1** (1.1 equiv), **2** (1.0 equiv), base (3.0 equiv), and catalyst (20 mol %) in solvent (4 mL) at −25 °C. PG = 3,5-dinitrobenzoyl.

also reacted smoothly, and the corresponding products were obtained in excellent yield and with good enantioselectivity (**3aa**, **3fa**, **3ga**). Different ring sizes of the substrates were tolerated in the presented catalytic system, affording **3ha** and **3ia** with good results (a seven-membered ring substrate is comparably reluctant to undergo this reaction as more than 96 h was needed to complete the transformation). Aziridines containing acyclic aliphatic and aryl substituents also resulted in the formation of the products in excellent yield and with good to excellent *ee* (**3ja**, **3ka**, **3la**). In addition to α-isothiocyanato imide **2a**, α-substituted substrate **2b** also proved to be amendable to this method, giving the 4-methyl 2-thiooxazole containing compound **3ab** with excellent results. The structure of **3aa** was determined by X-ray crystallography and its absolute configuration was determined from a known compound (see the Supporting Information for details).[15]

Since the readily accessible 2-amino ethanol derivative with appropriate protecting group can be transformed to the corresponding aziridine under basic conditions, we surmised that this kind of compound may serve as the precursor of the reactant and generate the aziridine in situ in our established catalytic system. Gratifyingly, the racemic compound **5** reacted smoothly in the process, furnishing the desired product **3aa** in excellent yield and *ee* (Scheme 4). The presented improved method allows the use of more easily available chemical compounds as reactants and thereby increases its practicability.



Scheme 4. Reaction with a 2-amino ethanol derivative. PG = 3,5-dinitrobenzoyl.

In summary, aziridines were discovered to be suitable electrophiles for trapping the 2-thiooxazole intermediate generated from α-isothiocyanato imide under basic conditions, and a catalytic asymmetric ring-opening reaction of α-isothiocyanato imides to *meso*-aziridines was developed. This procedure not only extends the scope of sulfur-based nucleophiles for enantioselective ring opening of *meso*-aziridines, but also provides an efficient methodology for the synthesis of a variety of chiral β-aminothiooxazole compounds with practical significance. Further applications of using α-isothiocyanato compounds in the asymmetric organic synthesis are ongoing.

Experimental Section

Catalyst **4g** (0.020 mmol, 20 mol %), α-isothiocyanato imide **2a** (0.10 mmol, 1.0 equiv), and *meso*-aziridine **1a** (0.11 mmol, 1.1 equiv) were dissolved in dry toluene (4 mL) at −25 °C and then Cs_2CO_3 (0.3 mmol, 3 equiv) was added to the reaction. After 18 h, the mixture was concentrated and applied to silica gel for purification of the desired product **3aa**. Yield is of isolated product, and the enantiomeric excess was determined by HPLC analysis on a chiral stationary phase.

Acknowledgements

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Keywords: asymmetric synthesis · aziridines · isothiocyanato compounds · ring-opening reactions · synthetic methods

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[10] The reactions of isothiocyanato imide **2a** with aldehyde, aldimine, and electron-deficient olefin were performed under PTC conditions, respectively, and only the enolate addition products were isolated. In addition, the reaction of **2a** and **1a** under the previously reported conditions (amine–thiourea catalyst) was also conducted and the same product as under the PTC conditions was obtained, but with poor efficiency (40% yield after 72 h). These results can illustrate better that the specific reactivity reported herein is due to the particular electrophile employed but not the PTC conditions (see the Supporting Information for details).

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[14] When the cinchonidine derived **4f** was employed, the *ent*-**3aa** was obtained with poor enatioselectivity (30% *ee*).

[15] CCDC-920508 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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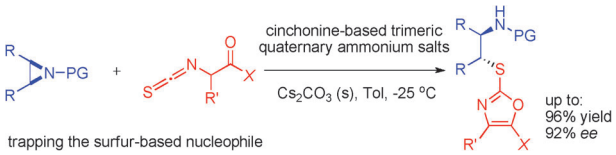
Asymmetric Synthesis



Open up your chemistry! Using cinchonine-based trimeric quaternary ammonium salts as catalysts, *meso*-aziridines can be ring opened, in an enantioselective manner, through nucleophilic addition of the sulfur atom of α-isothiocyanato imides (see scheme; PG = protecting group). This synthetic method provides an efficient way to access useful chiral β-aminothiooxazole compounds.